Dossier zur Nutzenbewertung gemäß § 35a SGB V

Trastuzumab-Deruxtecan (Enhertu®)

Daiichi Sankyo Deutschland GmbH

Modul 4 B (Anhang 4-H)

Behandlung von erwachsenen Patienten mit inoperablem oder metastasiertem HER2-positivem Brustkrebs, die bereits mindestens zwei gegen HER2 gerichtete Vorbehandlungen erhalten haben

Stand: 26.07.2022

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Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Subjects with any TEAE								
Any Grade	50 (100.0)	48 (100.0)	21 (100.0)	129 (99.2)	4 (100.0)	179 (99.4)	183 (99.5)	252 (99.6)
5	2 (4.0)	2 (4.2)	2 (9.5)	8 (6.2)	0	10 (5.6)	10 (5.4)	14 (5.5)
4	2 (4.0)	6 (12.5)	2 (9.5)	5 (3.8)	0	7 (3.9)	7 (3.8)	15 (5.9)
3	29 (58.0)	28 (58.3)	13 (61.9)	67 (51.5)	3 (75.0)	96 (53.3)	99 (53.8)	140 (55.3)
2	15 (30.0)	8 (16.7)	3 (14.3)	41 (31.5)	1 (25.0)	56 (31.1)	57 (31.0)	68 (26.9)
1	2 (4.0)	4 (8.3)	1 (4.8)	8 (6.2)	0	10 (5.6)	10 (5.4)	15 (5.9)
>=3	33 (66.0)	36 (75.0)	17 (81.0)	80 (61.5)	3 (75.0)	113 (62.8)	116 (63.0)	169 (66.8)
Missing	0	0	0	0	0	0	0	0
Infections And Infestations								
Any Grade	22 (44.0)	25 (52.1)	11 (52.4)	75 (57.7)	2 (50.0)	97 (53.9)	99 (53.8)	135 (53.4)
5	0	0	0	2 (1.5)	0	2 (1.1)	2 (1.1)	2 (0.8)
4	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
3	8 (16.0)	2 (4.2)	3 (14.3)	6 (4.6)	0	14 (7.8)	14 (7.6)	19 (7.5)
2	11 (22.0)	12 (25.0)	4 (19.0)	41 (31.5)	2 (50.0)	52 (28.9)	54 (29.3)	70 (27.7)
1	3 (6.0)	11 (22.9)	4 (19.0)	25 (19.2)	0	28 (15.6)	28 (15.2)	43 (17.0)
>=3	8 (16.0)	2 (4.2)	3 (14.3)	9 (6.9)	0	17 (9.4)	17 (9.2)	22 (8.7)
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Upper Respiratory Tract Infection								
Any Grade	7 (14.0)	5 (10.4)	1 (4.8)	17 (13.1)	0	24 (13.3)	24 (13.0)	30 (11.9)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	3 (6.0)	3 (6.3)	1 (4.8)	9 (6.9)	0	12 (6.7)	12 (6.5)	16 (6.3)
1	4 (8.0)	2 (4.2)	0	8 (6.2)	0	12 (6.7)	12 (6.5)	14 (5.5)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Urinary Tract Infection								
Any Grade	5 (10.0)	3 (6.3)	3 (14.3)	16 (12.3)	1 (25.0)	21 (11.7)	22 (12.0)	28 (11.1)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	5 (10.0)	2 (4.2)	3 (14.3)	13 (10.0)	1 (25.0)	18 (10.0)	19 (10.3)	24 (9.5)
1	0	1 (2.1)	0	3 (2.3)	0	3 (1.7)	3 (1.6)	4 (1.6)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
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Nasopharyngitis								
Any Grade	7 (14.0)	3 (6.3)	3 (14.3)	13 (10.0)	0	20 (11.1)	20 (10.9)	26 (10.3)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	2 (4.0)	3 (6.3)	0	3 (2.3)	0	5 (2.8)	5 (2.7)	8 (3.2)
1	5 (10.0)	0	3 (14.3)	10 (7.7)	0	15 (8.3)	15 (8.2)	18 (7.1)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Pneumonia								
Any Grade	4 (8.0)	5 (10.4)	1 (4.8)	6 (4.6)	0	10 (5.6)	10 (5.4)	16 (6.3)
5	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
4	0	0	0	0	0	0	0	0
3	1 (2.0)	1 (2.1)	1 (4.8)	1 (0.8)	0	2 (1.1)	2 (1.1)	4 (1.6)
2	2 (4.0)	1 (2.1)	0	3 (2.3)	0	5 (2.8)	5 (2.7)	6 (2.4)
1	1 (2.0)	3 (6.3)	0	1 (0.8)	0	2 (1.1)	2 (1.1)	5 (2.0)
>=3	1 (2.0)	1 (2.1)	1 (4.8)	2 (1.5)	0	3 (1.7)	3 (1.6)	5 (2.0)
Missing	0	0	0	0	0	0	0	0

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If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

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Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
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Sinusitis								
Any Grade	2 (4.0)	1 (2.1)	0	6 (4.6)	0	8 (4.4)	8 (4.3)	9 (3.6)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	2 (4.0)	1 (2.1)	0	5 (3.8)	0	7 (3.9)	7 (3.8)	8 (3.2)
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Cystitis								
Any Grade	3 (6.0)	2 (4.2)	1 (4.8)	3 (2.3)	1 (25.0)	6 (3.3)	7 (3.8)	10 (4.0)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	3 (6.0)	0	1 (4.8)	1 (0.8)	1 (25.0)	4 (2.2)	5 (2.7)	6 (2.4)
1	0	2 (4.2)	0	2 (1.5)	0	2 (1.1)	2 (1.1)	4 (1.6)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

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Cellulitis								
Any Grade	3 (6.0)	1 (2.1)	0	2 (1.5)	0	5 (2.8)	5 (2.7)	6 (2.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	3 (6.0)	0	0	0	0	3 (1.7)	3 (1.6)	3 (1.2)
2	0	1 (2.1)	0	0	0	0	0	1 (0.4)
1	0	0	0	2 (1.5)	0	2 (1.1)	2 (1.1)	2 (0.8)
>=3	3 (6.0)	0	0	0	0	3 (1.7)	3 (1.6)	3 (1.2)
Missing	0	0	0	0	0	0	0	0
Herpes Zoster								
Any Grade	3 (6.0)	1 (2.1)	0	1 (0.8)	1 (25.0)	4 (2.2)	5 (2.7)	6 (2.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	3 (6.0)	0	0	0	0	3 (1.7)	3 (1.6)	3 (1.2)
1	0	1 (2.1)	0	1 (0.8)	1 (25.0)	1 (0.6)	2 (1.1)	3 (1.2)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

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Bronchitis								
Any Grade	0	1 (2.1)	1 (4.8)	4 (3.1)	0	4 (2.2)	4 (2.2)	6 (2.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	1 (4.8)	0	0	0	0	1 (0.4)
2	0	1 (2.1)	0	2 (1.5)	0	2 (1.1)	2 (1.1)	3 (1.2)
1	0	0	0	2 (1.5)	0	2 (1.1)	2 (1.1)	2 (0.8)
>=3	0	0	1 (4.8)	0	0	0	0	1 (0.4)
Missing	0	0	0	0	0	0	0	0
Candida Infection								
Any Grade	0	2 (4.2)	0	4 (3.1)	0	4 (2.2)	4 (2.2)	6 (2.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	2 (4.2)	0	3 (2.3)	0	3 (1.7)	3 (1.6)	5 (2.0)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

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Conjunctivitis								
Any Grade	0	4 (8.3)	1 (4.8)	4 (3.1)	0	4 (2.2)	4 (2.2)	9 (3.6)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	1 (2.1)	0	1 (0.8)	0	1 (0.6)	1 (0.5)	2 (0.8)
1	0	3 (6.3)	1 (4.8)	3 (2.3)	0	3 (1.7)	3 (1.6)	7 (2.8)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Influenza								
Any Grade	0	2 (4.2)	2 (9.5)	4 (3.1)	0	4 (2.2)	4 (2.2)	8 (3.2)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	1 (4.8)	0	0	0	0	1 (0.4)
2	0	1 (2.1)	1 (4.8)	2 (1.5)	0	2 (1.1)	2 (1.1)	4 (1.6)
1	0	1 (2.1)	0	2 (1.5)	0	2 (1.1)	2 (1.1)	3 (1.2)
>=3	0	0	1 (4.8)	0	0	0	0	1 (0.4)
Missing	0	0	0	0	0	0	0	0

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Lymphangitis								
Any Grade	0	0	0	4 (3.1)	0	4 (2.2)	4 (2.2)	4 (1.6)
5	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	2 (1.5)	0	2 (1.1)	2 (1.1)	2 (0.8)
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
Missing	0	0	0	0	0	0	0	0
Oral Herpes								
Any Grade	2 (4.0)	1 (2.1)	0	2 (1.5)	0	4 (2.2)	4 (2.2)	5 (2.0)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	1 (2.0)	0	0	1 (0.8)	0	2 (1.1)	2 (1.1)	2 (0.8)
1	1 (2.0)	1 (2.1)	0	1 (0.8)	0	2 (1.1)	2 (1.1)	3 (1.2)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

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Safety Analysis Set

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Lower Respiratory Tract Infection								
Any Grade	0	0	0	3 (2.3)	0	3 (1.7)	3 (1.6)	3 (1.2)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	3 (2.3)	0	3 (1.7)	3 (1.6)	3 (1.2)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Periodontitis								
Any Grade	1 (2.0)	1 (2.1)	0	2 (1.5)	0	3 (1.7)	3 (1.6)	4 (1.6)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	1 (2.0)	0	0	2 (1.5)	0	3 (1.7)	3 (1.6)	3 (1.2)
1	0	1 (2.1)	0	0	0	0	0	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

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Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Gastroenteritis								
Any Grade	0	0	0	2 (1.5)	0	2 (1.1)	2 (1.1)	2 (0.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	2 (1.5)	0	2 (1.1)	2 (1.1)	2 (0.8)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Localised Infection								
Any Grade	0	0	0	2 (1.5)	0	2 (1.1)	2 (1.1)	2 (0.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Otitis Media								
Any Grade	0	0	0	2 (1.5)	0	2 (1.1)	2 (1.1)	2 (0.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	2 (1.5)	0	2 (1.1)	2 (1.1)	2 (0.8)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Pharyngitis								
Any Grade	1 (2.0)	3 (6.3)	0	1 (0.8)	0	2 (1.1)	2 (1.1)	5 (2.0)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	1 (2.1)	0	1 (0.8)	0	1 (0.6)	1 (0.5)	2 (0.8)
1	1 (2.0)	1 (2.1)	0	0	0	1 (0.6)	1 (0.5)	2 (0.8)
>=3	0	0	0	0	0	0	0	0
Missing	0	1 (2.1)	0	0	0	0	0	1 (0.4)

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Pyelonephritis								
Any Grade	1 (2.0)	0	0	1 (0.8)	0	2 (1.1)	2 (1.1)	2 (0.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	1 (2.0)	0	0	1 (0.8)	0	2 (1.1)	2 (1.1)	2 (0.8)
2	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0
>=3	1 (2.0)	0	0	1 (0.8)	0	2 (1.1)	2 (1.1)	2 (0.8)
Missing	0	0	0	0	0	0	0	0
Rash Pustular								
Any Grade	0	0	0	2 (1.5)	0	2 (1.1)	2 (1.1)	2 (0.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	2 (1.5)	0	2 (1.1)	2 (1.1)	2 (0.8)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Respiratory Tract Infection								
Any Grade	0	0	0	2 (1.5)	0	2 (1.1)	2 (1.1)	2 (0.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Skin Infection								
Any Grade	1 (2.0)	1 (2.1)	1 (4.8)	1 (0.8)	0	2 (1.1)	2 (1.1)	4 (1.6)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	1 (2.1)	0	1 (0.8)	0	1 (0.6)	1 (0.5)	2 (0.8)
1	1 (2.0)	0	1 (4.8)	0	0	1 (0.6)	1 (0.5)	2 (0.8)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Tooth Abscess								
Any Grade	1 (2.0)	0	0	1 (0.8)	0	2 (1.1)	2 (1.1)	2 (0.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
Missing	0	0	0	0	0	0	0	0
Vaginal Infection								
Any Grade	1 (2.0)	0	0	1 (0.8)	0	2 (1.1)	2 (1.1)	2 (0.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	1 (2.0)	0	0	1 (0.8)	0	2 (1.1)	2 (1.1)	2 (0.8)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Abdominal Abscess								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Acute Hepatitis B								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
2	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0
>=3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Anal Abscess								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Bacterial Infection								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Breast Cellulitis								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Clostridium Difficile Infection								
Any Grade	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
2	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0
>=3	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Diverticulitis								
Any Grade	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Ear Infection								
Any Grade	0	1 (2.1)	0	1 (0.8)	0	1 (0.6)	1 (0.5)	2 (0.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	1 (2.1)	0	0	0	0	0	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Escherichia Sepsis								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
2	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0
>=3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
Missing	0	0	0	0	0	0	0	0
Eye Infection Viral								
Any Grade	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Folliculitis								
Any Grade	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Fungal Infection								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Furuncle								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Gastroenteritis Norovirus								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Gastroenteritis Viral								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Graft Infection								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Herpes Dermatitis								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Herpes Virus Infection								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Klebsiella Infection								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Laryngitis								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Nail Infection								
Any Grade	0	1 (2.1)	0	1 (0.8)	0	1 (0.6)	1 (0.5)	2 (0.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	1 (2.1)	0	0	0	0	0	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Nephritis Bacterial								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Oral Candidiasis								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Osteomyelitis								
Any Grade	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
2	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0
>=3	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Paronychia								
Any Grade	0	1 (2.1)	1 (4.8)	1 (0.8)	0	1 (0.6)	1 (0.5)	3 (1.2)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	1 (2.1)	1 (4.8)	0	0	0	0	2 (0.8)
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Parotitis								
Any Grade	1 (2.0)	1 (2.1)	0	0	0	1 (0.6)	1 (0.5)	2 (0.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	1 (2.0)	1 (2.1)	0	0	0	1 (0.6)	1 (0.5)	2 (0.8)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Periorbital Infection								
Any Grade	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Pneumonia Bacterial								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
2	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0
>=3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Pulmonary Sepsis								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
2	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0
>=3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
Missing	0	0	0	0	0	0	0	0
Rhinitis								
Any Grade	0	1 (2.1)	0	1 (0.8)	0	1 (0.6)	1 (0.5)	2 (0.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	1 (2.1)	0	0	0	0	0	1 (0.4)
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Sialoadenitis								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Staphylococcal Infection								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0
>=3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Tonsillitis								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Tooth Infection								
Any Grade	0	0	0	0	1 (25.0)	0	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	0	1 (25.0)	0	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Tracheitis								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Urosepsis								
Any Grade	0	1 (2.1)	0	1 (0.8)	0	1 (0.6)	1 (0.5)	2 (0.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	1 (2.1)	0	1 (0.8)	0	1 (0.6)	1 (0.5)	2 (0.8)
2	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0
>=3	0	1 (2.1)	0	1 (0.8)	0	1 (0.6)	1 (0.5)	2 (0.8)
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Viral Infection								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Wound Infection								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Aspergillus Infection								
Any Grade	0	1 (2.1)	0	0	0	0	0	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	1 (2.1)	0	0	0	0	0	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Herpes Ophthalmic								
Any Grade	0	2 (4.2)	0	0	0	0	0	2 (0.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	1 (2.1)	0	0	0	0	0	1 (0.4)
2	0	0	0	0	0	0	0	0
1	0	1 (2.1)	0	0	0	0	0	1 (0.4)
>=3	0	1 (2.1)	0	0	0	0	0	1 (0.4)
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Herpes Simplex								
Any Grade	0	1 (2.1)	0	0	0	0	0	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	1 (2.1)	0	0	0	0	0	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Perichondritis								
Any Grade	0	1 (2.1)	0	0	0	0	0	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	1 (2.1)	0	0	0	0	0	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Soft Tissue Infection								
Any Grade	0	0	1 (4.8)	0	0	0	0	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	1 (4.8)	0	0	0	0	1 (0.4)
2	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0
>=3	0	0	1 (4.8)	0	0	0	0	1 (0.4)
Missing	0	0	0	0	0	0	0	0
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)								
Any Grade	1 (2.0)	0	0	3 (2.3)	0	4 (2.2)	4 (2.2)	4 (1.6)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	1 (2.0)	0	0	1 (0.8)	0	2 (1.1)	2 (1.1)	2 (0.8)
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	1 (2.0)	0	0	1 (0.8)	0	2 (1.1)	2 (1.1)	2 (0.8)
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Basal Cell Carcinoma								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
2	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0
>=3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
Missing	0	0	0	0	0	0	0	0
Malignant Pleural Effusion								
Any Grade	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
2	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0
>=3	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Metastases To Skin								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Neoplasm Skin								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Blood And Lymphatic System Disorders								
Any Grade	29 (58.0)	29 (60.4)	15 (71.4)	50 (38.5)	1 (25.0)	79 (43.9)	80 (43.5)	124 (49.0)
5	0	0	0	0	0	0	0	0
4	1 (2.0)	3 (6.3)	1 (4.8)	2 (1.5)	0	3 (1.7)	3 (1.6)	7 (2.8)
3	13 (26.0)	13 (27.1)	3 (14.3)	18 (13.8)	1 (25.0)	31 (17.2)	32 (17.4)	48 (19.0)
2	10 (20.0)	6 (12.5)	8 (38.1)	17 (13.1)	0	27 (15.0)	27 (14.7)	41 (16.2)
1	5 (10.0)	7 (14.6)	3 (14.3)	13 (10.0)	0	18 (10.0)	18 (9.8)	28 (11.1)
>=3	14 (28.0)	16 (33.3)	4 (19.0)	20 (15.4)	1 (25.0)	34 (18.9)	35 (19.0)	55 (21.7)
Missing	0	0	0	0	0	0	0	0
Anaemia								
Any Grade	21 (42.0)	21 (43.8)	10 (47.6)	37 (28.5)	0	58 (32.2)	58 (31.5)	89 (35.2)
5	0	0	0	0	0	0	0	0
4	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
3	8 (16.0)	9 (18.8)	3 (14.3)	8 (6.2)	0	16 (8.9)	16 (8.7)	28 (11.1)
2	8 (16.0)	7 (14.6)	6 (28.6)	14 (10.8)	0	22 (12.2)	22 (12.0)	35 (13.8)
1	5 (10.0)	5 (10.4)	1 (4.8)	14 (10.8)	0	19 (10.6)	19 (10.3)	25 (9.9)
>=3	8 (16.0)	9 (18.8)	3 (14.3)	9 (6.9)	0	17 (9.4)	17 (9.2)	29 (11.5)
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Neutropenia								
Any Grade	10 (20.0)	7 (14.6)	5 (23.8)	16 (12.3)	1 (25.0)	26 (14.4)	27 (14.7)	39 (15.4)
5	0	0	0	0	0	0	0	0
4	1 (2.0)	2 (4.2)	0	1 (0.8)	0	2 (1.1)	2 (1.1)	4 (1.6)
3	6 (12.0)	4 (8.3)	1 (4.8)	9 (6.9)	1 (25.0)	15 (8.3)	16 (8.7)	21 (8.3)
2	3 (6.0)	1 (2.1)	3 (14.3)	5 (3.8)	0	8 (4.4)	8 (4.3)	12 (4.7)
1	0	0	1 (4.8)	1 (0.8)	0	1 (0.6)	1 (0.5)	2 (0.8)
>=3	7 (14.0)	6 (12.5)	1 (4.8)	10 (7.7)	1 (25.0)	17 (9.4)	18 (9.8)	25 (9.9)
Missing	0	0	0	0	0	0	0	0
Thrombocytopenia								
Any Grade	2 (4.0)	5 (10.4)	2 (9.5)	11 (8.5)	1 (25.0)	13 (7.2)	14 (7.6)	21 (8.3)
5	0	0	0	0	0	0	0	0
4	0	2 (4.2)	0	0	0	0	0	2 (0.8)
3	1 (2.0)	1 (2.1)	0	2 (1.5)	0	3 (1.7)	3 (1.6)	4 (1.6)
2	0	0	1 (4.8)	2 (1.5)	1 (25.0)	2 (1.1)	3 (1.6)	4 (1.6)
1	1 (2.0)	2 (4.2)	1 (4.8)	7 (5.4)	0	8 (4.4)	8 (4.3)	11 (4.3)
>=3	1 (2.0)	3 (6.3)	0	2 (1.5)	0	3 (1.7)	3 (1.6)	6 (2.4)
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Lymphopenia								
Any Grade	2 (4.0)	0	0	9 (6.9)	0	11 (6.1)	11 (6.0)	11 (4.3)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	1 (2.0)	0	0	6 (4.6)	0	7 (3.9)	7 (3.8)	7 (2.8)
2	0	0	0	3 (2.3)	0	3 (1.7)	3 (1.6)	3 (1.2)
1	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	1 (2.0)	0	0	6 (4.6)	0	7 (3.9)	7 (3.8)	7 (2.8)
Missing	0	0	0	0	0	0	0	0
Leukopenia								
Any Grade	0	0	1 (4.8)	6 (4.6)	1 (25.0)	6 (3.3)	7 (3.8)	8 (3.2)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	1 (4.8)	1 (0.8)	1 (25.0)	1 (0.6)	2 (1.1)	3 (1.2)
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	4 (3.1)	0	4 (2.2)	4 (2.2)	4 (1.6)
>=3	0	0	1 (4.8)	1 (0.8)	1 (25.0)	1 (0.6)	2 (1.1)	3 (1.2)
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Febrile Neutropenia								
Any Grade	1 (2.0)	0	1 (4.8)	2 (1.5)	0	3 (1.7)	3 (1.6)	4 (1.6)
5	0	0	0	0	0	0	0	0
4	0	0	1 (4.8)	0	0	0	0	1 (0.4)
3	1 (2.0)	0	0	2 (1.5)	0	3 (1.7)	3 (1.6)	3 (1.2)
2	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0
>=3	1 (2.0)	0	1 (4.8)	2 (1.5)	0	3 (1.7)	3 (1.6)	4 (1.6)
Missing	0	0	0	0	0	0	0	0
Lymphadenopathy								
Any Grade	1 (2.0)	0	0	1 (0.8)	0	2 (1.1)	2 (1.1)	2 (0.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	1 (2.0)	0	0	1 (0.8)	0	2 (1.1)	2 (1.1)	2 (0.8)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Iron Deficiency Anaemia								
Any Grade	0	1 (2.1)	0	0	0	0	0	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	1 (2.1)	0	0	0	0	0	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Lymph Node Pain								
Any Grade	0	0	1 (4.8)	0	0	0	0	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	1 (4.8)	0	0	0	0	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Thrombocytosis								
Any Grade	0	1 (2.1)	0	0	0	0	0	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	1 (2.1)	0	0	0	0	0	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Immune System Disorders								
Any Grade	3 (6.0)	1 (2.1)	0	4 (3.1)	0	7 (3.9)	7 (3.8)	8 (3.2)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	3 (6.0)	1 (2.1)	0	4 (3.1)	0	7 (3.9)	7 (3.8)	8 (3.2)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Seasonal Allergy								
Any Grade	2 (4.0)	0	0	3 (2.3)	0	5 (2.8)	5 (2.7)	5 (2.0)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	2 (4.0)	0	0	3 (2.3)	0	5 (2.8)	5 (2.7)	5 (2.0)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Contrast Media Reaction								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Hypersensitivity								
Any Grade	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Contrast Media Allergy								
Any Grade	0	1 (2.1)	0	0	0	0	0	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	1 (2.1)	0	0	0	0	0	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Endocrine Disorders								
Any Grade	1 (2.0)	0	1 (4.8)	1 (0.8)	0	2 (1.1)	2 (1.1)	3 (1.2)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	1 (2.0)	0	1 (4.8)	0	0	1 (0.6)	1 (0.5)	2 (0.8)
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Hypothyroidism								
Any Grade	1 (2.0)	0	0	1 (0.8)	0	2 (1.1)	2 (1.1)	2 (0.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Adrenal Insufficiency								
Any Grade	0	0	1 (4.8)	0	0	0	0	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	1 (4.8)	0	0	0	0	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Metabolism And Nutrition Disorders								
Any Grade	24 (48.0)	27 (56.3)	10 (47.6)	59 (45.4)	1 (25.0)	83 (46.1)	84 (45.7)	121 (47.8)
5	0	0	0	0	0	0	0	0
4	1 (2.0)	0	0	1 (0.8)	0	2 (1.1)	2 (1.1)	2 (0.8)
3	4 (8.0)	5 (10.4)	2 (9.5)	10 (7.7)	0	14 (7.8)	14 (7.6)	21 (8.3)
2	7 (14.0)	5 (10.4)	4 (19.0)	12 (9.2)	0	19 (10.6)	19 (10.3)	28 (11.1)
1	12 (24.0)	17 (35.4)	4 (19.0)	36 (27.7)	1 (25.0)	48 (26.7)	49 (26.6)	70 (27.7)
>=3	5 (10.0)	5 (10.4)	2 (9.5)	11 (8.5)	0	16 (8.9)	16 (8.7)	23 (9.1)
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Decreased Appetite								
Any Grade	17 (34.0)	22 (45.8)	6 (28.6)	41 (31.5)	1 (25.0)	58 (32.2)	59 (32.1)	87 (34.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	1 (2.1)	0	3 (2.3)	0	3 (1.7)	3 (1.6)	4 (1.6)
2	6 (12.0)	4 (8.3)	3 (14.3)	8 (6.2)	0	14 (7.8)	14 (7.6)	21 (8.3)
1	11 (22.0)	17 (35.4)	3 (14.3)	30 (23.1)	1 (25.0)	41 (22.8)	42 (22.8)	62 (24.5)
>=3	0	1 (2.1)	0	3 (2.3)	0	3 (1.7)	3 (1.6)	4 (1.6)
Missing	0	0	0	0	0	0	0	0
Hypokalaemia								
Any Grade	5 (10.0)	5 (10.4)	4 (19.0)	17 (13.1)	0	22 (12.2)	22 (12.0)	31 (12.3)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	1 (2.0)	3 (6.3)	1 (4.8)	5 (3.8)	0	6 (3.3)	6 (3.3)	10 (4.0)
2	1 (2.0)	2 (4.2)	0	0	0	1 (0.6)	1 (0.5)	3 (1.2)
1	3 (6.0)	0	3 (14.3)	12 (9.2)	0	15 (8.3)	15 (8.2)	18 (7.1)
>=3	1 (2.0)	3 (6.3)	1 (4.8)	5 (3.8)	0	6 (3.3)	6 (3.3)	10 (4.0)
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Hypomagnesaemia								
Any Grade	3 (6.0)	0	3 (14.3)	5 (3.8)	0	8 (4.4)	8 (4.3)	11 (4.3)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	3 (6.0)	0	3 (14.3)	5 (3.8)	0	8 (4.4)	8 (4.3)	11 (4.3)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Hypoalbuminaemia								
Any Grade	2 (4.0)	3 (6.3)	4 (19.0)	5 (3.8)	0	7 (3.9)	7 (3.8)	14 (5.5)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	1 (2.0)	1 (2.1)	2 (9.5)	3 (2.3)	0	4 (2.2)	4 (2.2)	7 (2.8)
1	1 (2.0)	2 (4.2)	2 (9.5)	2 (1.5)	0	3 (1.7)	3 (1.6)	7 (2.8)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Dehydration								
Any Grade	2 (4.0)	1 (2.1)	0	4 (3.1)	0	6 (3.3)	6 (3.3)	7 (2.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	1 (2.0)	0	0	1 (0.8)	0	2 (1.1)	2 (1.1)	2 (0.8)
2	1 (2.0)	1 (2.1)	0	2 (1.5)	0	3 (1.7)	3 (1.6)	4 (1.6)
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	1 (2.0)	0	0	1 (0.8)	0	2 (1.1)	2 (1.1)	2 (0.8)
Missing	0	0	0	0	0	0	0	0
Hyperglycaemia								
Any Grade	2 (4.0)	0	0	4 (3.1)	0	6 (3.3)	6 (3.3)	6 (2.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
2	1 (2.0)	0	0	1 (0.8)	0	2 (1.1)	2 (1.1)	2 (0.8)
1	1 (2.0)	0	0	1 (0.8)	0	2 (1.1)	2 (1.1)	2 (0.8)
>=3	0	0	0	2 (1.5)	0	2 (1.1)	2 (1.1)	2 (0.8)
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Hyperkalaemia								
Any Grade	2 (4.0)	0	0	3 (2.3)	0	5 (2.8)	5 (2.7)	5 (2.0)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
2	0	0	0	2 (1.5)	0	2 (1.1)	2 (1.1)	2 (0.8)
1	2 (4.0)	0	0	0	0	2 (1.1)	2 (1.1)	2 (0.8)
>=3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
Missing	0	0	0	0	0	0	0	0
Cell Death								
Any Grade	0	0	0	4 (3.1)	0	4 (2.2)	4 (2.2)	4 (1.6)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	4 (3.1)	0	4 (2.2)	4 (2.2)	4 (1.6)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Hypophosphataemia								
Any Grade	3 (6.0)	1 (2.1)	0	1 (0.8)	0	4 (2.2)	4 (2.2)	5 (2.0)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	2 (4.0)	1 (2.1)	0	0	0	2 (1.1)	2 (1.1)	3 (1.2)
2	1 (2.0)	0	0	1 (0.8)	0	2 (1.1)	2 (1.1)	2 (0.8)
1	0	0	0	0	0	0	0	0
>=3	2 (4.0)	1 (2.1)	0	0	0	2 (1.1)	2 (1.1)	3 (1.2)
Missing	0	0	0	0	0	0	0	0
Hypercalcaemia								
Any Grade	1 (2.0)	1 (2.1)	0	2 (1.5)	0	3 (1.7)	3 (1.6)	4 (1.6)
5	0	0	0	0	0	0	0	0
4	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	1 (2.1)	0	2 (1.5)	0	2 (1.1)	2 (1.1)	3 (1.2)
>=3	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Hyponatraemia								
Any Grade	1 (2.0)	0	1 (4.8)	2 (1.5)	0	3 (1.7)	3 (1.6)	4 (1.6)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	1 (2.0)	0	1 (4.8)	0	0	1 (0.6)	1 (0.5)	2 (0.8)
2	0	0	0	0	0	0	0	0
1	0	0	0	2 (1.5)	0	2 (1.1)	2 (1.1)	2 (0.8)
>=3	1 (2.0)	0	1 (4.8)	0	0	1 (0.6)	1 (0.5)	2 (0.8)
Missing	0	0	0	0	0	0	0	0
Hypocalcaemia								
Any Grade	0	0	1 (4.8)	2 (1.5)	0	2 (1.1)	2 (1.1)	3 (1.2)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	1 (4.8)	2 (1.5)	0	2 (1.1)	2 (1.1)	3 (1.2)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Iron Deficiency								
Any Grade	1 (2.0)	0	0	1 (0.8)	0	2 (1.1)	2 (1.1)	2 (0.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	1 (2.0)	0	0	1 (0.8)	0	2 (1.1)	2 (1.1)	2 (0.8)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Dyslipidaemia								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Electrolyte Imbalance								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Folate Deficiency								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Glucose Tolerance Impaired								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
2	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0
>=3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
Missing	0	0	0	0	0	0	0	0
Hypermagnesaemia								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Hypoglycaemia								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Vitamin D Deficiency								
Any Grade	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Fluid Overload								
Any Grade	0	1 (2.1)	0	0	0	0	0	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	1 (2.1)	0	0	0	0	0	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Psychiatric Disorders								
Any Grade	9 (18.0)	13 (27.1)	7 (33.3)	19 (14.6)	0	28 (15.6)	28 (15.2)	48 (19.0)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	1 (4.8)	0	0	0	0	1 (0.4)
2	6 (12.0)	6 (12.5)	1 (4.8)	9 (6.9)	0	15 (8.3)	15 (8.2)	22 (8.7)
1	3 (6.0)	7 (14.6)	4 (19.0)	10 (7.7)	0	13 (7.2)	13 (7.1)	24 (9.5)
>=3	0	0	1 (4.8)	0	0	0	0	1 (0.4)
Missing	0	0	1 (4.8)	0	0	0	0	1 (0.4)

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Insomnia								
Any Grade	6 (12.0)	5 (10.4)	5 (23.8)	7 (5.4)	0	13 (7.2)	13 (7.1)	23 (9.1)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	4 (8.0)	2 (4.2)	1 (4.8)	1 (0.8)	0	5 (2.8)	5 (2.7)	8 (3.2)
1	2 (4.0)	3 (6.3)	3 (14.3)	6 (4.6)	0	8 (4.4)	8 (4.3)	14 (5.5)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	1 (4.8)	0	0	0	0	1 (0.4)
Anxiety								
Any Grade	3 (6.0)	4 (8.3)	2 (9.5)	9 (6.9)	0	12 (6.7)	12 (6.5)	18 (7.1)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	1 (2.0)	2 (4.2)	0	5 (3.8)	0	6 (3.3)	6 (3.3)	8 (3.2)
1	2 (4.0)	2 (4.2)	2 (9.5)	4 (3.1)	0	6 (3.3)	6 (3.3)	10 (4.0)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Depression								
Any Grade	3 (6.0)	2 (4.2)	1 (4.8)	3 (2.3)	0	6 (3.3)	6 (3.3)	9 (3.6)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	2 (4.0)	1 (2.1)	1 (4.8)	2 (1.5)	0	4 (2.2)	4 (2.2)	6 (2.4)
1	1 (2.0)	1 (2.1)	0	1 (0.8)	0	2 (1.1)	2 (1.1)	3 (1.2)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Alcoholism								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Apathy								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Confusional State								
Any Grade	0	2 (4.2)	0	1 (0.8)	0	1 (0.6)	1 (0.5)	3 (1.2)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	1 (2.1)	0	0	0	0	0	1 (0.4)
1	0	1 (2.1)	0	1 (0.8)	0	1 (0.6)	1 (0.5)	2 (0.8)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Libido Decreased								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Mental Fatigue								
Any Grade	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Mood Altered								
Any Grade	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Delirium								
Any Grade	0	1 (2.1)	0	0	0	0	0	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	1 (2.1)	0	0	0	0	0	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Nervousness								
Any Grade	0	1 (2.1)	0	0	0	0	0	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	1 (2.1)	0	0	0	0	0	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Restlessness								
Any Grade	0	0	1 (4.8)	0	0	0	0	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	1 (4.8)	0	0	0	0	1 (0.4)
2	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0
>=3	0	0	1 (4.8)	0	0	0	0	1 (0.4)
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Nervous System Disorders								
Any Grade	21 (42.0)	23 (47.9)	10 (47.6)	68 (52.3)	2 (50.0)	89 (49.4)	91 (49.5)	124 (49.0)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	1 (4.8)	3 (2.3)	1 (25.0)	3 (1.7)	4 (2.2)	5 (2.0)
2	5 (10.0)	8 (16.7)	3 (14.3)	16 (12.3)	0	21 (11.7)	21 (11.4)	32 (12.6)
1	16 (32.0)	15 (31.3)	6 (28.6)	49 (37.7)	1 (25.0)	65 (36.1)	66 (35.9)	87 (34.4)
>=3	0	0	1 (4.8)	3 (2.3)	1 (25.0)	3 (1.7)	4 (2.2)	5 (2.0)
Missing	0	0	0	0	0	0	0	0
Headache								
Any Grade	7 (14.0)	11 (22.9)	2 (9.5)	31 (23.8)	2 (50.0)	38 (21.1)	40 (21.7)	53 (20.9)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	1 (2.0)	3 (6.3)	0	6 (4.6)	0	7 (3.9)	7 (3.8)	10 (4.0)
1	6 (12.0)	8 (16.7)	2 (9.5)	25 (19.2)	2 (50.0)	31 (17.2)	33 (17.9)	43 (17.0)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Dizziness								
Any Grade	7 (14.0)	5 (10.4)	1 (4.8)	11 (8.5)	1 (25.0)	18 (10.0)	19 (10.3)	25 (9.9)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	1 (2.1)	0	2 (1.5)	0	2 (1.1)	2 (1.1)	3 (1.2)
1	7 (14.0)	4 (8.3)	1 (4.8)	9 (6.9)	1 (25.0)	16 (8.9)	17 (9.2)	22 (8.7)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Peripheral Sensory Neuropathy								
Any Grade	3 (6.0)	4 (8.3)	2 (9.5)	13 (10.0)	0	16 (8.9)	16 (8.7)	22 (8.7)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	2 (4.2)	1 (4.8)	3 (2.3)	0	3 (1.7)	3 (1.6)	6 (2.4)
1	3 (6.0)	2 (4.2)	1 (4.8)	10 (7.7)	0	13 (7.2)	13 (7.1)	16 (6.3)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Dysgeusia								
Any Grade	4 (8.0)	6 (12.5)	1 (4.8)	8 (6.2)	1 (25.0)	12 (6.7)	13 (7.1)	20 (7.9)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	2 (4.2)	1 (4.8)	1 (0.8)	0	1 (0.6)	1 (0.5)	4 (1.6)
1	4 (8.0)	4 (8.3)	0	7 (5.4)	1 (25.0)	11 (6.1)	12 (6.5)	16 (6.3)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Neuropathy Peripheral								
Any Grade	3 (6.0)	1 (2.1)	2 (9.5)	8 (6.2)	1 (25.0)	11 (6.1)	12 (6.5)	15 (5.9)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	1 (25.0)	0	1 (0.5)	1 (0.4)
2	2 (4.0)	0	1 (4.8)	2 (1.5)	0	4 (2.2)	4 (2.2)	5 (2.0)
1	1 (2.0)	1 (2.1)	1 (4.8)	6 (4.6)	0	7 (3.9)	7 (3.8)	9 (3.6)
>=3	0	0	0	0	1 (25.0)	0	1 (0.5)	1 (0.4)
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Paraesthesia								
Any Grade	1 (2.0)	3 (6.3)	0	3 (2.3)	0	4 (2.2)	4 (2.2)	7 (2.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	1 (2.0)	3 (6.3)	0	3 (2.3)	0	4 (2.2)	4 (2.2)	7 (2.8)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Cognitive Disorder								
Any Grade	1 (2.0)	0	0	1 (0.8)	1 (25.0)	2 (1.1)	3 (1.6)	3 (1.2)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	1 (2.0)	0	0	0	1 (25.0)	1 (0.6)	2 (1.1)	2 (0.8)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Lethargy								
Any Grade	0	1 (2.1)	0	3 (2.3)	0	3 (1.7)	3 (1.6)	4 (1.6)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	1 (2.1)	0	2 (1.5)	0	2 (1.1)	2 (1.1)	3 (1.2)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Sciatica								
Any Grade	0	0	0	3 (2.3)	0	3 (1.7)	3 (1.6)	3 (1.2)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	2 (1.5)	0	2 (1.1)	2 (1.1)	2 (0.8)
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	2 (1.5)	0	2 (1.1)	2 (1.1)	2 (0.8)
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Taste Disorder								
Any Grade	1 (2.0)	0	0	2 (1.5)	0	3 (1.7)	3 (1.6)	3 (1.2)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	1 (2.0)	0	0	2 (1.5)	0	3 (1.7)	3 (1.6)	3 (1.2)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Tremor								
Any Grade	1 (2.0)	0	0	2 (1.5)	0	3 (1.7)	3 (1.6)	3 (1.2)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	1 (2.0)	0	0	1 (0.8)	0	2 (1.1)	2 (1.1)	2 (0.8)
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Migraine								
Any Grade	0	2 (4.2)	0	2 (1.5)	0	2 (1.1)	2 (1.1)	4 (1.6)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	1 (2.1)	0	1 (0.8)	0	1 (0.6)	1 (0.5)	2 (0.8)
1	0	1 (2.1)	0	1 (0.8)	0	1 (0.6)	1 (0.5)	2 (0.8)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Somnolence								
Any Grade	0	0	0	2 (1.5)	0	2 (1.1)	2 (1.1)	2 (0.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	2 (1.5)	0	2 (1.1)	2 (1.1)	2 (0.8)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Ageusia								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Ataxia								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Balance Disorder								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Dysarthria								
Any Grade	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Epilepsy								
Any Grade	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Hypoaesthesia								
Any Grade	0	1 (2.1)	0	1 (0.8)	0	1 (0.6)	1 (0.5)	2 (0.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	1 (2.1)	0	0	0	0	0	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Memory Impairment								
Any Grade	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Neurotoxicity								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Parosmia								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Peripheral Motor Neuropathy								
Any Grade	0	1 (2.1)	0	1 (0.8)	0	1 (0.6)	1 (0.5)	2 (0.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	1 (2.1)	0	1 (0.8)	0	1 (0.6)	1 (0.5)	2 (0.8)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Polyneuropathy								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Presyncope								
Any Grade	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Seizure								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Syncope								
Any Grade	0	0	1 (4.8)	1 (0.8)	0	1 (0.6)	1 (0.5)	2 (0.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	1 (4.8)	1 (0.8)	0	1 (0.6)	1 (0.5)	2 (0.8)
2	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0
>=3	0	0	1 (4.8)	1 (0.8)	0	1 (0.6)	1 (0.5)	2 (0.8)
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Akathisia								
Any Grade	0	0	1 (4.8)	0	0	0	0	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	1 (4.8)	0	0	0	0	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Cerebrovascular Accident								
Any Grade	0	1 (2.1)	0	0	0	0	0	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	1 (2.1)	0	0	0	0	0	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Dyskinesia								
Any Grade	0	1 (2.1)	0	0	0	0	0	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	1 (2.1)	0	0	0	0	0	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Restless Legs Syndrome								
Any Grade	0	1 (2.1)	0	0	0	0	0	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	1 (2.1)	0	0	0	0	0	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Trigeminal Nerve Disorder								
Any Grade	0	1 (2.1)	0	0	0	0	0	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	1 (2.1)	0	0	0	0	0	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Eye Disorders								
Any Grade	15 (30.0)	20 (41.7)	5 (23.8)	45 (34.6)	1 (25.0)	60 (33.3)	61 (33.2)	86 (34.0)
5	0	0	0	0	0	0	0	0
4	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
3	0	0	0	0	0	0	0	0
2	2 (4.0)	6 (12.5)	1 (4.8)	9 (6.9)	0	11 (6.1)	11 (6.0)	18 (7.1)
1	13 (26.0)	14 (29.2)	4 (19.0)	35 (26.9)	1 (25.0)	48 (26.7)	49 (26.6)	67 (26.5)
>=3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Dry Eye								
Any Grade	4 (8.0)	7 (14.6)	3 (14.3)	17 (13.1)	0	21 (11.7)	21 (11.4)	31 (12.3)
5	0	0	0	0	0	0	0	0
4	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
3	0	0	0	0	0	0	0	0
2	0	2 (4.2)	0	5 (3.8)	0	5 (2.8)	5 (2.7)	7 (2.8)
1	4 (8.0)	5 (10.4)	3 (14.3)	11 (8.5)	0	15 (8.3)	15 (8.2)	23 (9.1)
>=3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
Missing	0	0	0	0	0	0	0	0
Vision Blurred								
Any Grade	2 (4.0)	2 (4.2)	0	4 (3.1)	0	6 (3.3)	6 (3.3)	8 (3.2)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	2 (4.0)	2 (4.2)	0	4 (3.1)	0	6 (3.3)	6 (3.3)	8 (3.2)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Lacrimation Increased								
Any Grade	1 (2.0)	3 (6.3)	0	4 (3.1)	0	5 (2.8)	5 (2.7)	8 (3.2)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	1 (2.1)	0	0	0	0	0	1 (0.4)
1	1 (2.0)	2 (4.2)	0	4 (3.1)	0	5 (2.8)	5 (2.7)	7 (2.8)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Visual Impairment								
Any Grade	1 (2.0)	2 (4.2)	0	2 (1.5)	1 (25.0)	3 (1.7)	4 (2.2)	6 (2.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	1 (2.1)	0	0	0	0	0	1 (0.4)
1	1 (2.0)	1 (2.1)	0	2 (1.5)	1 (25.0)	3 (1.7)	4 (2.2)	5 (2.0)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Cataract								
Any Grade	0	0	0	3 (2.3)	0	3 (1.7)	3 (1.6)	3 (1.2)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
2	0	0	0	0	0	0	0	0
1	0	0	0	2 (1.5)	0	2 (1.1)	2 (1.1)	2 (0.8)
>=3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
Missing	0	0	0	0	0	0	0	0
Conjunctival Haemorrhage								
Any Grade	1 (2.0)	1 (2.1)	0	2 (1.5)	0	3 (1.7)	3 (1.6)	4 (1.6)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	1 (2.0)	1 (2.1)	0	2 (1.5)	0	3 (1.7)	3 (1.6)	4 (1.6)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Keratitis								
Any Grade	2 (4.0)	3 (6.3)	1 (4.8)	1 (0.8)	0	3 (1.7)	3 (1.6)	7 (2.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	1 (2.0)	2 (4.2)	0	1 (0.8)	0	2 (1.1)	2 (1.1)	4 (1.6)
1	1 (2.0)	1 (2.1)	1 (4.8)	0	0	1 (0.6)	1 (0.5)	3 (1.2)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Photophobia								
Any Grade	0	0	0	3 (2.3)	0	3 (1.7)	3 (1.6)	3 (1.2)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	2 (1.5)	0	2 (1.1)	2 (1.1)	2 (0.8)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Glaucoma								
Any Grade	0	0	0	2 (1.5)	0	2 (1.1)	2 (1.1)	2 (0.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	2 (1.5)	0	2 (1.1)	2 (1.1)	2 (0.8)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Retinal Exudates								
Any Grade	0	0	0	2 (1.5)	0	2 (1.1)	2 (1.1)	2 (0.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	2 (1.5)	0	2 (1.1)	2 (1.1)	2 (0.8)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Visual Acuity Reduced								
Any Grade	0	0	0	2 (1.5)	0	2 (1.1)	2 (1.1)	2 (0.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Asthenopia								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Cataract Cortical								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Chalazion								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Corneal Oedema								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Corneal Thickening								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Diplopia								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Eye Disorder								
Any Grade	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Eye Irritation								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Eye Pain								
Any Grade	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Eyelid Oedema								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Giant Papillary Conjunctivitis								
Any Grade	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Macular Fibrosis								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Ocular Discomfort								
Any Grade	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Ocular Hyperaemia								
Any Grade	0	1 (2.1)	0	1 (0.8)	0	1 (0.6)	1 (0.5)	2 (0.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	1 (2.1)	0	1 (0.8)	0	1 (0.6)	1 (0.5)	2 (0.8)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Optic Disc Haemorrhage								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Optic Nerve Disorder								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Periorbital Oedema								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Pinguecula								
Any Grade	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Punctate Keratitis								
Any Grade	0	1 (2.1)	0	1 (0.8)	0	1 (0.6)	1 (0.5)	2 (0.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	1 (2.1)	0	0	0	0	0	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Retinal Disorder								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Retinal Drusen								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Retinal Haemorrhage								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Ulcerative Keratitis								
Any Grade	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Xerophthalmia								
Any Grade	0	1 (2.1)	0	1 (0.8)	0	1 (0.6)	1 (0.5)	2 (0.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	1 (2.1)	0	1 (0.8)	0	1 (0.6)	1 (0.5)	2 (0.8)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Conjunctival Oedema								
Any Grade	0	1 (2.1)	0	0	0	0	0	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	1 (2.1)	0	0	0	0	0	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Conjunctivitis Allergic								
Any Grade	0	0	1 (4.8)	0	0	0	0	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	1 (4.8)	0	0	0	0	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Corneal Disorder								
Any Grade	0	1 (2.1)	0	0	0	0	0	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	1 (2.1)	0	0	0	0	0	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Corneal Erosion								
Any Grade	0	1 (2.1)	0	0	0	0	0	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	1 (2.1)	0	0	0	0	0	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Retinal Pigmentation								
Any Grade	0	1 (2.1)	0	0	0	0	0	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	1 (2.1)	0	0	0	0	0	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Retinal Tear								
Any Grade	0	1 (2.1)	0	0	0	0	0	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	1 (2.1)	0	0	0	0	0	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Vitreous Floaters								
Any Grade	0	1 (2.1)	0	0	0	0	0	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	1 (2.1)	0	0	0	0	0	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Ear And Labyrinth Disorders								
Any Grade	4 (8.0)	5 (10.4)	1 (4.8)	14 (10.8)	1 (25.0)	18 (10.0)	19 (10.3)	25 (9.9)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	1 (2.0)	1 (2.1)	1 (4.8)	2 (1.5)	0	3 (1.7)	3 (1.6)	5 (2.0)
1	3 (6.0)	4 (8.3)	0	12 (9.2)	1 (25.0)	15 (8.3)	16 (8.7)	20 (7.9)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Tinnitus								
Any Grade	0	0	0	5 (3.8)	1 (25.0)	5 (2.8)	6 (3.3)	6 (2.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	5 (3.8)	1 (25.0)	5 (2.8)	6 (3.3)	6 (2.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Ear Pain								
Any Grade	1 (2.0)	0	0	4 (3.1)	0	5 (2.8)	5 (2.7)	5 (2.0)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	1 (2.0)	0	0	4 (3.1)	0	5 (2.8)	5 (2.7)	5 (2.0)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Vertigo								
Any Grade	2 (4.0)	2 (4.2)	1 (4.8)	3 (2.3)	0	5 (2.8)	5 (2.7)	8 (3.2)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	1 (2.0)	1 (2.1)	1 (4.8)	1 (0.8)	0	2 (1.1)	2 (1.1)	4 (1.6)
1	1 (2.0)	1 (2.1)	0	2 (1.5)	0	3 (1.7)	3 (1.6)	4 (1.6)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Ear Discomfort								
Any Grade	1 (2.0)	1 (2.1)	0	1 (0.8)	0	2 (1.1)	2 (1.1)	3 (1.2)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	1 (2.0)	1 (2.1)	0	1 (0.8)	0	2 (1.1)	2 (1.1)	3 (1.2)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Eustachian Tube Dysfunction								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Hypoacusis								
Any Grade	1 (2.0)	2 (4.2)	0	0	0	1 (0.6)	1 (0.5)	3 (1.2)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	1 (2.0)	2 (4.2)	0	0	0	1 (0.6)	1 (0.5)	3 (1.2)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Inner Ear Inflammation								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Cardiac Disorders								
Any Grade	4 (8.0)	3 (6.3)	2 (9.5)	17 (13.1)	1 (25.0)	21 (11.7)	22 (12.0)	27 (10.7)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	3 (2.3)	0	3 (1.7)	3 (1.6)	3 (1.2)
2	0	1 (2.1)	0	6 (4.6)	0	6 (3.3)	6 (3.3)	7 (2.8)
1	4 (8.0)	2 (4.2)	2 (9.5)	8 (6.2)	1 (25.0)	12 (6.7)	13 (7.1)	17 (6.7)
>=3	0	0	0	3 (2.3)	0	3 (1.7)	3 (1.6)	3 (1.2)
Missing	0	0	0	0	0	0	0	0
Tachycardia								
Any Grade	0	0	0	5 (3.8)	0	5 (2.8)	5 (2.7)	5 (2.0)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	2 (1.5)	0	2 (1.1)	2 (1.1)	2 (0.8)
1	0	0	0	3 (2.3)	0	3 (1.7)	3 (1.6)	3 (1.2)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Atrial Fibrillation								
Any Grade	0	0	0	3 (2.3)	0	3 (1.7)	3 (1.6)	3 (1.2)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
Missing	0	0	0	0	0	0	0	0
Palpitations								
Any Grade	1 (2.0)	1 (2.1)	1 (4.8)	2 (1.5)	0	3 (1.7)	3 (1.6)	5 (2.0)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	1 (2.0)	1 (2.1)	1 (4.8)	2 (1.5)	0	3 (1.7)	3 (1.6)	5 (2.0)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Atrial Flutter								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Bundle Branch Block Right								
Any Grade	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Cardiac Aneurysm								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Cardiac Disorder								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Cardiac Failure								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Cardiac Failure Congestive								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Mitral Valve Incompetence								
Any Grade	0	0	0	0	1 (25.0)	0	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	0	1 (25.0)	0	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Myocardial Infarction								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
2	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0
>=3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Pulmonary Valve Disease								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Sinus Arrest								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
2	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0
>=3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Sinus Tachycardia								
Any Grade	0	0	1 (4.8)	1 (0.8)	0	1 (0.6)	1 (0.5)	2 (0.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	1 (4.8)	0	0	0	0	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Supraventricular Extrasystoles								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Supraventricular Tachycardia								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Tricuspid Valve Incompetence								
Any Grade	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Ventricular Extrasystoles								
Any Grade	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Atrioventricular Block First Degree								
Any Grade	0	1 (2.1)	0	0	0	0	0	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	1 (2.1)	0	0	0	0	0	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Left Ventricular Dysfunction								
Any Grade	0	1 (2.1)	0	0	0	0	0	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	1 (2.1)	0	0	0	0	0	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Vascular Disorders								
Any Grade	8 (16.0)	5 (10.4)	4 (19.0)	18 (13.8)	1 (25.0)	26 (14.4)	27 (14.7)	36 (14.2)
5	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
4	0	0	0	0	0	0	0	0
3	0	1 (2.1)	1 (4.8)	2 (1.5)	1 (25.0)	2 (1.1)	3 (1.6)	5 (2.0)
2	0	1 (2.1)	1 (4.8)	9 (6.9)	0	9 (5.0)	9 (4.9)	11 (4.3)
1	7 (14.0)	3 (6.3)	2 (9.5)	7 (5.4)	0	14 (7.8)	14 (7.6)	19 (7.5)
>=3	1 (2.0)	1 (2.1)	1 (4.8)	2 (1.5)	1 (25.0)	3 (1.7)	4 (2.2)	6 (2.4)
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Lymphoedema								
Any Grade	3 (6.0)	0	1 (4.8)	6 (4.6)	0	9 (5.0)	9 (4.9)	10 (4.0)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	1 (4.8)	4 (3.1)	0	4 (2.2)	4 (2.2)	5 (2.0)
1	3 (6.0)	0	0	2 (1.5)	0	5 (2.8)	5 (2.7)	5 (2.0)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Hypertension								
Any Grade	0	0	0	6 (4.6)	1 (25.0)	6 (3.3)	7 (3.8)	7 (2.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	2 (1.5)	1 (25.0)	2 (1.1)	3 (1.6)	3 (1.2)
2	0	0	0	3 (2.3)	0	3 (1.7)	3 (1.6)	3 (1.2)
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	2 (1.5)	1 (25.0)	2 (1.1)	3 (1.6)	3 (1.2)
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Hot Flush								
Any Grade	2 (4.0)	1 (2.1)	1 (4.8)	2 (1.5)	0	4 (2.2)	4 (2.2)	6 (2.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	2 (4.0)	1 (2.1)	1 (4.8)	2 (1.5)	0	4 (2.2)	4 (2.2)	6 (2.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Hypotension								
Any Grade	0	2 (4.2)	0	3 (2.3)	0	3 (1.7)	3 (1.6)	5 (2.0)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	1 (2.1)	0	0	0	0	0	1 (0.4)
2	0	0	0	2 (1.5)	0	2 (1.1)	2 (1.1)	2 (0.8)
1	0	1 (2.1)	0	1 (0.8)	0	1 (0.6)	1 (0.5)	2 (0.8)
>=3	0	1 (2.1)	0	0	0	0	0	1 (0.4)
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Capillary Fragility								
Any Grade	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Flushing								
Any Grade	1 (2.0)	1 (2.1)	0	0	0	1 (0.6)	1 (0.5)	2 (0.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	1 (2.0)	1 (2.1)	0	0	0	1 (0.6)	1 (0.5)	2 (0.8)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Haematoma								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Orthostatic Hypotension								
Any Grade	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Peripheral Coldness								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Shock Haemorrhagic								
Any Grade	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
5	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0
>=3	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Cyanosis								
Any Grade	0	1 (2.1)	0	0	0	0	0	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	1 (2.1)	0	0	0	0	0	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Deep Vein Thrombosis								
Any Grade	0	0	1 (4.8)	0	0	0	0	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	1 (4.8)	0	0	0	0	1 (0.4)
2	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0
>=3	0	0	1 (4.8)	0	0	0	0	1 (0.4)
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Pallor								
Any Grade	0	1 (2.1)	1 (4.8)	0	0	0	0	2 (0.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	1 (2.1)	1 (4.8)	0	0	0	0	2 (0.8)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Respiratory, Thoracic And Mediastinal Disorders								
Any Grade	27 (54.0)	22 (45.8)	14 (66.7)	76 (58.5)	2 (50.0)	103 (57.2)	105 (57.1)	141 (55.7)
5	1 (2.0)	0	1 (4.8)	3 (2.3)	0	4 (2.2)	4 (2.2)	5 (2.0)
4	0	0	1 (4.8)	0	0	0	0	1 (0.4)
3	2 (4.0)	3 (6.3)	1 (4.8)	8 (6.2)	0	10 (5.6)	10 (5.4)	14 (5.5)
2	11 (22.0)	4 (8.3)	3 (14.3)	22 (16.9)	1 (25.0)	33 (18.3)	34 (18.5)	41 (16.2)
1	13 (26.0)	15 (31.3)	8 (38.1)	43 (33.1)	1 (25.0)	56 (31.1)	57 (31.0)	80 (31.6)
>=3	3 (6.0)	3 (6.3)	3 (14.3)	11 (8.5)	0	14 (7.8)	14 (7.6)	20 (7.9)
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Cough								
Any Grade	12 (24.0)	10 (20.8)	5 (23.8)	32 (24.6)	1 (25.0)	44 (24.4)	45 (24.5)	60 (23.7)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	2 (4.0)	2 (4.2)	1 (4.8)	3 (2.3)	0	5 (2.8)	5 (2.7)	8 (3.2)
1	10 (20.0)	8 (16.7)	4 (19.0)	29 (22.3)	1 (25.0)	39 (21.7)	40 (21.7)	52 (20.6)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Dyspnoea								
Any Grade	6 (12.0)	0	2 (9.5)	25 (19.2)	0	31 (17.2)	31 (16.8)	33 (13.0)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	1 (4.8)	3 (2.3)	0	3 (1.7)	3 (1.6)	4 (1.6)
2	3 (6.0)	0	0	9 (6.9)	0	12 (6.7)	12 (6.5)	12 (4.7)
1	3 (6.0)	0	1 (4.8)	13 (10.0)	0	16 (8.9)	16 (8.7)	17 (6.7)
>=3	0	0	1 (4.8)	3 (2.3)	0	3 (1.7)	3 (1.6)	4 (1.6)
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Epistaxis								
Any Grade	7 (14.0)	3 (6.3)	1 (4.8)	18 (13.8)	1 (25.0)	25 (13.9)	26 (14.1)	30 (11.9)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	1 (2.1)	0	1 (0.8)	0	1 (0.6)	1 (0.5)	2 (0.8)
1	7 (14.0)	2 (4.2)	1 (4.8)	17 (13.1)	1 (25.0)	24 (13.3)	25 (13.6)	28 (11.1)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Pneumonitis								
Any Grade	7 (14.0)	4 (8.3)	3 (14.3)	9 (6.9)	0	16 (8.9)	16 (8.7)	23 (9.1)
5	1 (2.0)	0	1 (4.8)	1 (0.8)	0	2 (1.1)	2 (1.1)	3 (1.2)
4	0	0	0	0	0	0	0	0
3	1 (2.0)	1 (2.1)	0	0	0	1 (0.6)	1 (0.5)	2 (0.8)
2	3 (6.0)	1 (2.1)	1 (4.8)	4 (3.1)	0	7 (3.9)	7 (3.8)	9 (3.6)
1	2 (4.0)	2 (4.2)	1 (4.8)	4 (3.1)	0	6 (3.3)	6 (3.3)	9 (3.6)
>=3	2 (4.0)	1 (2.1)	1 (4.8)	1 (0.8)	0	3 (1.7)	3 (1.6)	5 (2.0)
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Interstitial Lung Disease								
Any Grade	6 (12.0)	5 (10.4)	5 (23.8)	5 (3.8)	0	11 (6.1)	11 (6.0)	21 (8.3)
5	0	0	0	0	0	0	0	0
4	0	0	1 (4.8)	0	0	0	0	1 (0.4)
3	0	1 (2.1)	0	2 (1.5)	0	2 (1.1)	2 (1.1)	3 (1.2)
2	3 (6.0)	1 (2.1)	1 (4.8)	0	0	3 (1.7)	3 (1.6)	5 (2.0)
1	3 (6.0)	3 (6.3)	3 (14.3)	3 (2.3)	0	6 (3.3)	6 (3.3)	12 (4.7)
>=3	0	1 (2.1)	1 (4.8)	2 (1.5)	0	2 (1.1)	2 (1.1)	4 (1.6)
Missing	0	0	0	0	0	0	0	0
Oropharyngeal Pain								
Any Grade	2 (4.0)	0	0	7 (5.4)	0	9 (5.0)	9 (4.9)	9 (3.6)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	1 (2.0)	0	0	2 (1.5)	0	3 (1.7)	3 (1.6)	3 (1.2)
1	1 (2.0)	0	0	5 (3.8)	0	6 (3.3)	6 (3.3)	6 (2.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Dyspnoea Exertional								
Any Grade	1 (2.0)	0	0	5 (3.8)	0	6 (3.3)	6 (3.3)	6 (2.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	1 (2.0)	0	0	4 (3.1)	0	5 (2.8)	5 (2.7)	5 (2.0)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Nasal Congestion								
Any Grade	2 (4.0)	2 (4.2)	0	4 (3.1)	0	6 (3.3)	6 (3.3)	8 (3.2)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	2 (4.0)	2 (4.2)	0	3 (2.3)	0	5 (2.8)	5 (2.7)	7 (2.8)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Pleural Effusion								
Any Grade	2 (4.0)	2 (4.2)	1 (4.8)	4 (3.1)	0	6 (3.3)	6 (3.3)	9 (3.6)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
2	1 (2.0)	2 (4.2)	1 (4.8)	3 (2.3)	0	4 (2.2)	4 (2.2)	7 (2.8)
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
Missing	0	0	0	0	0	0	0	0
Hypoxia								
Any Grade	0	0	1 (4.8)	4 (3.1)	1 (25.0)	4 (2.2)	5 (2.7)	6 (2.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	1 (4.8)	4 (3.1)	0	4 (2.2)	4 (2.2)	5 (2.0)
2	0	0	0	0	1 (25.0)	0	1 (0.5)	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	1 (4.8)	4 (3.1)	0	4 (2.2)	4 (2.2)	5 (2.0)
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Productive Cough								
Any Grade	1 (2.0)	1 (2.1)	0	3 (2.3)	0	4 (2.2)	4 (2.2)	5 (2.0)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	1 (2.0)	1 (2.1)	0	3 (2.3)	0	4 (2.2)	4 (2.2)	5 (2.0)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Rhinorrhoea								
Any Grade	1 (2.0)	1 (2.1)	0	3 (2.3)	0	4 (2.2)	4 (2.2)	5 (2.0)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	1 (2.1)	0	3 (2.3)	0	3 (1.7)	3 (1.6)	4 (1.6)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Pneumothorax								
Any Grade	2 (4.0)	0	1 (4.8)	1 (0.8)	0	3 (1.7)	3 (1.6)	4 (1.6)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	1 (4.8)	1 (0.8)	0	1 (0.6)	1 (0.5)	2 (0.8)
1	2 (4.0)	0	0	0	0	2 (1.1)	2 (1.1)	2 (0.8)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Dysphonia								
Any Grade	0	0	1 (4.8)	2 (1.5)	0	2 (1.1)	2 (1.1)	3 (1.2)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	1 (4.8)	2 (1.5)	0	2 (1.1)	2 (1.1)	3 (1.2)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Lung Opacity								
Any Grade	0	0	0	2 (1.5)	0	2 (1.1)	2 (1.1)	2 (0.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Pulmonary Embolism								
Any Grade	0	1 (2.1)	1 (4.8)	2 (1.5)	0	2 (1.1)	2 (1.1)	4 (1.6)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	1 (2.1)	1 (4.8)	2 (1.5)	0	2 (1.1)	2 (1.1)	4 (1.6)
2	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0
>=3	0	1 (2.1)	1 (4.8)	2 (1.5)	0	2 (1.1)	2 (1.1)	4 (1.6)
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Rhinitis Allergic								
Any Grade	1 (2.0)	0	1 (4.8)	1 (0.8)	0	2 (1.1)	2 (1.1)	3 (1.2)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	1 (2.0)	0	1 (4.8)	1 (0.8)	0	2 (1.1)	2 (1.1)	3 (1.2)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Wheezing								
Any Grade	0	0	0	2 (1.5)	0	2 (1.1)	2 (1.1)	2 (0.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	2 (1.5)	0	2 (1.1)	2 (1.1)	2 (0.8)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Acute Respiratory Failure								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0
>=3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
Missing	0	0	0	0	0	0	0	0
Alveolitis								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Asthma								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Bronchospasm								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Laryngeal Pain								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Nasal Dryness								
Any Grade	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Organising Pneumonia								
Any Grade	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Respiratory Failure								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0
>=3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Sinus Congestion								
Any Grade	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Throat Irritation								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Upper Respiratory Tract Inflammation								
Any Grade	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Aphonia								
Any Grade	0	1 (2.1)	0	0	0	0	0	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	1 (2.1)	0	0	0	0	0	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Laryngeal Inflammation								
Any Grade	0	1 (2.1)	0	0	0	0	0	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	1 (2.1)	0	0	0	0	0	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Pulmonary Hypertension								
Any Grade	0	1 (2.1)	0	0	0	0	0	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	1 (2.1)	0	0	0	0	0	1 (0.4)
2	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0
>=3	0	1 (2.1)	0	0	0	0	0	1 (0.4)
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Gastrointestinal Disorders								
Any Grade	46 (92.0)	45 (93.8)	18 (85.7)	123 (94.6)	4 (100.0)	169 (93.9)	173 (94.0)	236 (93.3)
5	0	1 (2.1)	0	0	0	0	0	1 (0.4)
4	0	0	0	0	0	0	0	0
3	9 (18.0)	5 (10.4)	2 (9.5)	20 (15.4)	1 (25.0)	29 (16.1)	30 (16.3)	37 (14.6)
2	13 (26.0)	21 (43.8)	11 (52.4)	63 (48.5)	1 (25.0)	76 (42.2)	77 (41.8)	109 (43.1)
1	24 (48.0)	18 (37.5)	5 (23.8)	40 (30.8)	2 (50.0)	64 (35.6)	66 (35.9)	89 (35.2)
>=3	9 (18.0)	6 (12.5)	2 (9.5)	20 (15.4)	1 (25.0)	29 (16.1)	30 (16.3)	38 (15.0)
Missing	0	0	0	0	0	0	0	0
Nausea								
Any Grade	38 (76.0)	40 (83.3)	13 (61.9)	103 (79.2)	3 (75.0)	141 (78.3)	144 (78.3)	197 (77.9)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	2 (4.0)	4 (8.3)	2 (9.5)	11 (8.5)	1 (25.0)	13 (7.2)	14 (7.6)	20 (7.9)
2	14 (28.0)	16 (33.3)	5 (23.8)	39 (30.0)	1 (25.0)	53 (29.4)	54 (29.3)	75 (29.6)
1	22 (44.0)	20 (41.7)	6 (28.6)	53 (40.8)	1 (25.0)	75 (41.7)	76 (41.3)	102 (40.3)
>=3	2 (4.0)	4 (8.3)	2 (9.5)	11 (8.5)	1 (25.0)	13 (7.2)	14 (7.6)	20 (7.9)
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Vomiting								
Any Grade	24 (48.0)	20 (41.7)	8 (38.1)	62 (47.7)	2 (50.0)	86 (47.8)	88 (47.8)	116 (45.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	4 (8.0)	2 (4.2)	0	4 (3.1)	0	8 (4.4)	8 (4.3)	10 (4.0)
2	9 (18.0)	6 (12.5)	2 (9.5)	20 (15.4)	0	29 (16.1)	29 (15.8)	37 (14.6)
1	11 (22.0)	12 (25.0)	6 (28.6)	38 (29.2)	2 (50.0)	49 (27.2)	51 (27.7)	69 (27.3)
>=3	4 (8.0)	2 (4.2)	0	4 (3.1)	0	8 (4.4)	8 (4.3)	10 (4.0)
Missing	0	0	0	0	0	0	0	0
Constipation								
Any Grade	16 (32.0)	19 (39.6)	10 (47.6)	48 (36.9)	1 (25.0)	64 (35.6)	65 (35.3)	94 (37.2)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	6 (12.0)	5 (10.4)	3 (14.3)	9 (6.9)	0	15 (8.3)	15 (8.2)	23 (9.1)
1	10 (20.0)	14 (29.2)	7 (33.3)	39 (30.0)	1 (25.0)	49 (27.2)	50 (27.2)	71 (28.1)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Diarrhoea								
Any Grade	15 (30.0)	16 (33.3)	5 (23.8)	42 (32.3)	1 (25.0)	57 (31.7)	58 (31.5)	79 (31.2)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	3 (6.0)	0	0	2 (1.5)	0	5 (2.8)	5 (2.7)	5 (2.0)
2	6 (12.0)	3 (6.3)	2 (9.5)	13 (10.0)	1 (25.0)	19 (10.6)	20 (10.9)	25 (9.9)
1	6 (12.0)	13 (27.1)	3 (14.3)	27 (20.8)	0	33 (18.3)	33 (17.9)	49 (19.4)
>=3	3 (6.0)	0	0	2 (1.5)	0	5 (2.8)	5 (2.7)	5 (2.0)
Missing	0	0	0	0	0	0	0	0
Dyspepsia								
Any Grade	3 (6.0)	5 (10.4)	0	27 (20.8)	1 (25.0)	30 (16.7)	31 (16.8)	36 (14.2)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	1 (2.1)	0	9 (6.9)	1 (25.0)	9 (5.0)	10 (5.4)	11 (4.3)
1	3 (6.0)	4 (8.3)	0	18 (13.8)	0	21 (11.7)	21 (11.4)	25 (9.9)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Stomatitis								
Any Grade	11 (22.0)	16 (33.3)	4 (19.0)	16 (12.3)	2 (50.0)	27 (15.0)	29 (15.8)	49 (19.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	1 (2.0)	0	0	2 (1.5)	0	3 (1.7)	3 (1.6)	3 (1.2)
2	4 (8.0)	6 (12.5)	1 (4.8)	1 (0.8)	0	5 (2.8)	5 (2.7)	12 (4.7)
1	6 (12.0)	10 (20.8)	3 (14.3)	13 (10.0)	2 (50.0)	19 (10.6)	21 (11.4)	34 (13.4)
>=3	1 (2.0)	0	0	2 (1.5)	0	3 (1.7)	3 (1.6)	3 (1.2)
Missing	0	0	0	0	0	0	0	0
Abdominal Pain								
Any Grade	5 (10.0)	3 (6.3)	3 (14.3)	19 (14.6)	1 (25.0)	24 (13.3)	25 (13.6)	31 (12.3)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	2 (1.5)	0	2 (1.1)	2 (1.1)	2 (0.8)
2	3 (6.0)	1 (2.1)	1 (4.8)	5 (3.8)	0	8 (4.4)	8 (4.3)	10 (4.0)
1	2 (4.0)	2 (4.2)	2 (9.5)	12 (9.2)	1 (25.0)	14 (7.8)	15 (8.2)	19 (7.5)
>=3	0	0	0	2 (1.5)	0	2 (1.1)	2 (1.1)	2 (0.8)
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Gastrooesophageal Reflux Disease								
Any Grade	8 (16.0)	4 (8.3)	2 (9.5)	10 (7.7)	0	18 (10.0)	18 (9.8)	24 (9.5)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	2 (4.0)	2 (4.2)	2 (9.5)	4 (3.1)	0	6 (3.3)	6 (3.3)	10 (4.0)
1	6 (12.0)	2 (4.2)	0	6 (4.6)	0	12 (6.7)	12 (6.5)	14 (5.5)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Abdominal Pain Upper								
Any Grade	4 (8.0)	1 (2.1)	0	12 (9.2)	0	16 (8.9)	16 (8.7)	17 (6.7)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	1 (2.0)	0	0	2 (1.5)	0	3 (1.7)	3 (1.6)	3 (1.2)
1	3 (6.0)	1 (2.1)	0	10 (7.7)	0	13 (7.2)	13 (7.1)	14 (5.5)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Haemorrhoids								
Any Grade	4 (8.0)	2 (4.2)	1 (4.8)	6 (4.6)	1 (25.0)	10 (5.6)	11 (6.0)	14 (5.5)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
2	1 (2.0)	2 (4.2)	0	1 (0.8)	0	2 (1.1)	2 (1.1)	4 (1.6)
1	2 (4.0)	0	1 (4.8)	4 (3.1)	1 (25.0)	6 (3.3)	7 (3.8)	8 (3.2)
>=3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
Missing	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
Dry Mouth								
Any Grade	1 (2.0)	2 (4.2)	0	5 (3.8)	0	6 (3.3)	6 (3.3)	8 (3.2)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	2 (4.2)	0	5 (3.8)	0	5 (2.8)	5 (2.7)	7 (2.8)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Abdominal Distension								
Any Grade	3 (6.0)	1 (2.1)	0	2 (1.5)	0	5 (2.8)	5 (2.7)	6 (2.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
1	2 (4.0)	1 (2.1)	0	2 (1.5)	0	4 (2.2)	4 (2.2)	5 (2.0)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Dysphagia								
Any Grade	0	0	2 (9.5)	4 (3.1)	0	4 (2.2)	4 (2.2)	6 (2.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
2	0	0	1 (4.8)	0	0	0	0	1 (0.4)
1	0	0	1 (4.8)	3 (2.3)	0	3 (1.7)	3 (1.6)	4 (1.6)
>=3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Oral Pain								
Any Grade	0	0	0	4 (3.1)	0	4 (2.2)	4 (2.2)	4 (1.6)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	2 (1.5)	0	2 (1.1)	2 (1.1)	2 (0.8)
1	0	0	0	2 (1.5)	0	2 (1.1)	2 (1.1)	2 (0.8)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Ascites								
Any Grade	0	3 (6.3)	1 (4.8)	3 (2.3)	0	3 (1.7)	3 (1.6)	7 (2.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	2 (1.5)	0	2 (1.1)	2 (1.1)	2 (0.8)
2	0	1 (2.1)	1 (4.8)	1 (0.8)	0	1 (0.6)	1 (0.5)	3 (1.2)
1	0	2 (4.2)	0	0	0	0	0	2 (0.8)
>=3	0	0	0	2 (1.5)	0	2 (1.1)	2 (1.1)	2 (0.8)
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Flatulence								
Any Grade	1 (2.0)	1 (2.1)	0	2 (1.5)	0	3 (1.7)	3 (1.6)	4 (1.6)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	1 (2.0)	1 (2.1)	0	1 (0.8)	0	2 (1.1)	2 (1.1)	3 (1.2)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Hyperaesthesia Teeth								
Any Grade	0	0	0	3 (2.3)	0	3 (1.7)	3 (1.6)	3 (1.2)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	3 (2.3)	0	3 (1.7)	3 (1.6)	3 (1.2)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Intestinal Obstruction								
Any Grade	0	0	0	3 (2.3)	0	3 (1.7)	3 (1.6)	3 (1.2)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	3 (2.3)	0	3 (1.7)	3 (1.6)	3 (1.2)
2	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0
>=3	0	0	0	3 (2.3)	0	3 (1.7)	3 (1.6)	3 (1.2)
Missing	0	0	0	0	0	0	0	0
Toothache								
Any Grade	3 (6.0)	2 (4.2)	0	0	0	3 (1.7)	3 (1.6)	5 (2.0)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
1	2 (4.0)	2 (4.2)	0	0	0	2 (1.1)	2 (1.1)	4 (1.6)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Dental Caries								
Any Grade	0	1 (2.1)	0	2 (1.5)	0	2 (1.1)	2 (1.1)	3 (1.2)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	1 (2.1)	0	2 (1.5)	0	2 (1.1)	2 (1.1)	3 (1.2)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Gastritis								
Any Grade	0	1 (2.1)	0	2 (1.5)	0	2 (1.1)	2 (1.1)	3 (1.2)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	1 (2.1)	0	2 (1.5)	0	2 (1.1)	2 (1.1)	3 (1.2)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Gastrointestinal Pain								
Any Grade	0	0	0	2 (1.5)	0	2 (1.1)	2 (1.1)	2 (0.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Gingival Bleeding								
Any Grade	1 (2.0)	0	0	1 (0.8)	0	2 (1.1)	2 (1.1)	2 (0.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	1 (2.0)	0	0	1 (0.8)	0	2 (1.1)	2 (1.1)	2 (0.8)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Glossodynia								
Any Grade	0	0	0	2 (1.5)	0	2 (1.1)	2 (1.1)	2 (0.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Mouth Ulceration								
Any Grade	1 (2.0)	0	0	1 (0.8)	0	2 (1.1)	2 (1.1)	2 (0.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Salivary Hypersecretion								
Any Grade	2 (4.0)	0	0	0	0	2 (1.1)	2 (1.1)	2 (0.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	2 (4.0)	0	0	0	0	2 (1.1)	2 (1.1)	2 (0.8)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Tongue Ulceration								
Any Grade	0	0	0	2 (1.5)	0	2 (1.1)	2 (1.1)	2 (0.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Abdominal Discomfort								
Any Grade	1 (2.0)	0	2 (9.5)	0	0	1 (0.6)	1 (0.5)	3 (1.2)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	1 (2.0)	0	2 (9.5)	0	0	1 (0.6)	1 (0.5)	3 (1.2)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Abdominal Pain Lower								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Abdominal Tenderness								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Anal Haemorrhage								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Angular Cheilitis								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Aphthous Ulcer								
Any Grade	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Cheilitis								
Any Grade	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Colitis								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Enteritis								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Gastric Varices								
Any Grade	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
2	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0
>=3	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Gingival Pain								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Haemorrhoidal Haemorrhage								
Any Grade	1 (2.0)	1 (2.1)	0	0	0	1 (0.6)	1 (0.5)	2 (0.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	1 (2.1)	0	0	0	0	0	1 (0.4)
1	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Hypertrophy Of Tongue Papillae								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Impaired Gastric Emptying								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Lip Dry								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Lip Haemorrhage								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Lip Pain								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Melaena								
Any Grade	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
2	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0
>=3	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Mouth Haemorrhage								
Any Grade	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Periodontal Disease								
Any Grade	1 (2.0)	1 (2.1)	0	0	0	1 (0.6)	1 (0.5)	2 (0.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	1 (2.1)	0	0	0	0	0	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Retching								
Any Grade	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Tongue Erythema								
Any Grade	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Tongue Pigmentation								
Any Grade	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Umbilical Hernia								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Upper Gastrointestinal Haemorrhage								
Any Grade	1 (2.0)	1 (2.1)	0	0	0	1 (0.6)	1 (0.5)	2 (0.8)
5	0	1 (2.1)	0	0	0	0	0	1 (0.4)
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	1 (2.1)	0	0	0	0	0	1 (0.4)
Missing	0	0	0	0	0	0	0	0
White Nipple Sign								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Anal Fissure								
Any Grade	0	2 (4.2)	0	0	0	0	0	2 (0.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	1 (2.1)	0	0	0	0	0	1 (0.4)
1	0	1 (2.1)	0	0	0	0	0	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Chronic Gastritis								
Any Grade	0	1 (2.1)	0	0	0	0	0	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	1 (2.1)	0	0	0	0	0	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Eructation								
Any Grade	0	1 (2.1)	0	0	0	0	0	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	1 (2.1)	0	0	0	0	0	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Faeces Discoloured								
Any Grade	0	1 (2.1)	0	0	0	0	0	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	1 (2.1)	0	0	0	0	0	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Gastrointestinal Disorder								
Any Grade	0	1 (2.1)	0	0	0	0	0	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	1 (2.1)	0	0	0	0	0	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Hiatus Hernia								
Any Grade	0	0	1 (4.8)	0	0	0	0	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	1 (4.8)	0	0	0	0	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Odynophagia								
Any Grade	0	1 (2.1)	0	0	0	0	0	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	1 (2.1)	0	0	0	0	0	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Oesophageal Stenosis								
Any Grade	0	0	1 (4.8)	0	0	0	0	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	1 (4.8)	0	0	0	0	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Oesophagitis								
Any Grade	0	0	1 (4.8)	0	0	0	0	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	1 (4.8)	0	0	0	0	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Pancreatitis								
Any Grade	0	1 (2.1)	1 (4.8)	0	0	0	0	2 (0.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	1 (2.1)	0	0	0	0	0	1 (0.4)
2	0	0	1 (4.8)	0	0	0	0	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	1 (2.1)	0	0	0	0	0	1 (0.4)
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Proctalgia								
Any Grade	0	1 (2.1)	0	0	0	0	0	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	1 (2.1)	0	0	0	0	0	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Rectal Haemorrhage								
Any Grade	0	2 (4.2)	0	0	0	0	0	2 (0.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	2 (4.2)	0	0	0	0	0	2 (0.8)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Tongue Rough								
Any Grade	0	0	1 (4.8)	0	0	0	0	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	1 (4.8)	0	0	0	0	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Hepatobiliary Disorders								
Any Grade	0	2 (4.2)	2 (9.5)	10 (7.7)	0	10 (5.6)	10 (5.4)	14 (5.5)
5	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
4	0	0	0	0	0	0	0	0
3	0	0	1 (4.8)	4 (3.1)	0	4 (2.2)	4 (2.2)	5 (2.0)
2	0	0	0	0	0	0	0	0
1	0	2 (4.2)	1 (4.8)	5 (3.8)	0	5 (2.8)	5 (2.7)	8 (3.2)
>=3	0	0	1 (4.8)	5 (3.8)	0	5 (2.8)	5 (2.7)	6 (2.4)
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Cholestasis								
Any Grade	0	0	0	3 (2.3)	0	3 (1.7)	3 (1.6)	3 (1.2)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	3 (2.3)	0	3 (1.7)	3 (1.6)	3 (1.2)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Hepatic Cytolysis								
Any Grade	0	1 (2.1)	0	2 (1.5)	0	2 (1.1)	2 (1.1)	3 (1.2)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
2	0	0	0	0	0	0	0	0
1	0	1 (2.1)	0	1 (0.8)	0	1 (0.6)	1 (0.5)	2 (0.8)
>=3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Acute Hepatic Failure								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0
>=3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
Missing	0	0	0	0	0	0	0	0
Alcoholic Liver Disease								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
2	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0
>=3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Cholecystitis								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
2	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0
>=3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
Missing	0	0	0	0	0	0	0	0
Cholelithiasis								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Hepatotoxicity								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Hyperbilirubinaemia								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Jaundice								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Venoocclusive Liver Disease								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
2	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0
>=3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Cholangitis								
Any Grade	0	0	1 (4.8)	0	0	0	0	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	1 (4.8)	0	0	0	0	1 (0.4)
2	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0
>=3	0	0	1 (4.8)	0	0	0	0	1 (0.4)
Missing	0	0	0	0	0	0	0	0
Hepatic Cirrhosis								
Any Grade	0	1 (2.1)	0	0	0	0	0	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	1 (2.1)	0	0	0	0	0	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Hepatic Function Abnormal								
Any Grade	0	0	1 (4.8)	0	0	0	0	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	1 (4.8)	0	0	0	0	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Portal Hypertension								
Any Grade	0	1 (2.1)	0	0	0	0	0	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	1 (2.1)	0	0	0	0	0	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Skin And Subcutaneous Tissue Disorders								
Any Grade	30 (60.0)	37 (77.1)	13 (61.9)	82 (63.1)	4 (100.0)	112 (62.2)	116 (63.0)	166 (65.6)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	1 (2.1)	0	3 (2.3)	0	3 (1.7)	3 (1.6)	4 (1.6)
2	9 (18.0)	9 (18.8)	6 (28.6)	19 (14.6)	0	28 (15.6)	28 (15.2)	43 (17.0)
1	21 (42.0)	27 (56.3)	7 (33.3)	60 (46.2)	4 (100.0)	81 (45.0)	85 (46.2)	119 (47.0)
>=3	0	1 (2.1)	0	3 (2.3)	0	3 (1.7)	3 (1.6)	4 (1.6)
Missing	0	0	0	0	0	0	0	0
Alopecia								
Any Grade	25 (50.0)	29 (60.4)	8 (38.1)	62 (47.7)	2 (50.0)	87 (48.3)	89 (48.4)	126 (49.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
2	6 (12.0)	9 (18.8)	5 (23.8)	15 (11.5)	0	21 (11.7)	21 (11.4)	35 (13.8)
1	19 (38.0)	20 (41.7)	3 (14.3)	46 (35.4)	2 (50.0)	65 (36.1)	67 (36.4)	90 (35.6)
>=3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Rash								
Any Grade	4 (8.0)	8 (16.7)	1 (4.8)	14 (10.8)	1 (25.0)	18 (10.0)	19 (10.3)	28 (11.1)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	2 (4.0)	0	0	2 (1.5)	0	4 (2.2)	4 (2.2)	4 (1.6)
1	2 (4.0)	8 (16.7)	1 (4.8)	12 (9.2)	1 (25.0)	14 (7.8)	15 (8.2)	24 (9.5)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Dry Skin								
Any Grade	2 (4.0)	3 (6.3)	1 (4.8)	9 (6.9)	0	11 (6.1)	11 (6.0)	15 (5.9)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	2 (4.0)	3 (6.3)	1 (4.8)	8 (6.2)	0	10 (5.6)	10 (5.4)	14 (5.5)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Nail Disorder								
Any Grade	2 (4.0)	0	0	8 (6.2)	0	10 (5.6)	10 (5.4)	10 (4.0)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	2 (4.0)	0	0	8 (6.2)	0	10 (5.6)	10 (5.4)	10 (4.0)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Pruritus								
Any Grade	1 (2.0)	4 (8.3)	0	8 (6.2)	0	9 (5.0)	9 (4.9)	13 (5.1)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	4 (8.3)	0	8 (6.2)	0	8 (4.4)	8 (4.3)	12 (4.7)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Skin Hyperpigmentation								
Any Grade	3 (6.0)	0	2 (9.5)	5 (3.8)	0	8 (4.4)	8 (4.3)	10 (4.0)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	3 (6.0)	0	2 (9.5)	5 (3.8)	0	8 (4.4)	8 (4.3)	10 (4.0)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Rash Maculo-Papular								
Any Grade	0	1 (2.1)	1 (4.8)	7 (5.4)	0	7 (3.9)	7 (3.8)	9 (3.6)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
2	0	1 (2.1)	0	0	0	0	0	1 (0.4)
1	0	0	1 (4.8)	6 (4.6)	0	6 (3.3)	6 (3.3)	7 (2.8)
>=3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Dermatitis Acneiform								
Any Grade	1 (2.0)	2 (4.2)	1 (4.8)	3 (2.3)	0	4 (2.2)	4 (2.2)	7 (2.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	1 (2.0)	2 (4.2)	1 (4.8)	3 (2.3)	0	4 (2.2)	4 (2.2)	7 (2.8)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Skin Lesion								
Any Grade	0	1 (2.1)	1 (4.8)	4 (3.1)	0	4 (2.2)	4 (2.2)	6 (2.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	1 (4.8)	1 (0.8)	0	1 (0.6)	1 (0.5)	2 (0.8)
1	0	1 (2.1)	0	3 (2.3)	0	3 (1.7)	3 (1.6)	4 (1.6)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Urticaria								
Any Grade	2 (4.0)	0	0	2 (1.5)	0	4 (2.2)	4 (2.2)	4 (1.6)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	1 (2.0)	0	0	2 (1.5)	0	3 (1.7)	3 (1.6)	3 (1.2)
1	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Eczema								
Any Grade	0	1 (2.1)	0	2 (1.5)	0	2 (1.1)	2 (1.1)	3 (1.2)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	1 (2.1)	0	2 (1.5)	0	2 (1.1)	2 (1.1)	3 (1.2)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Erythema								
Any Grade	0	0	1 (4.8)	2 (1.5)	0	2 (1.1)	2 (1.1)	3 (1.2)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	1 (4.8)	2 (1.5)	0	2 (1.1)	2 (1.1)	3 (1.2)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Onychomadesis								
Any Grade	0	0	0	2 (1.5)	0	2 (1.1)	2 (1.1)	2 (0.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	2 (1.5)	0	2 (1.1)	2 (1.1)	2 (0.8)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Purpura								
Any Grade	0	0	0	2 (1.5)	0	2 (1.1)	2 (1.1)	2 (0.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	2 (1.5)	0	2 (1.1)	2 (1.1)	2 (0.8)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Skin Discolouration								
Any Grade	0	0	0	1 (0.8)	1 (25.0)	1 (0.6)	2 (1.1)	2 (0.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	1 (25.0)	1 (0.6)	2 (1.1)	2 (0.8)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Acne								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Cutaneous Vasculitis								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Hirsutism								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Hyperkeratosis								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Ingrowing Nail								
Any Grade	1 (2.0)	1 (2.1)	0	0	0	1 (0.6)	1 (0.5)	2 (0.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	1 (2.1)	0	0	0	0	0	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Ingrown Hair								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Madarosis								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Nail Toxicity								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Onychoclasis								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Pain Of Skin								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
2	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0
>=3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Palmar-Plantar Erythrodysaesthesia Syndrome								
Any Grade	0	1 (2.1)	0	1 (0.8)	0	1 (0.6)	1 (0.5)	2 (0.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	1 (2.1)	0	1 (0.8)	0	1 (0.6)	1 (0.5)	2 (0.8)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Photosensitivity Reaction								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Pigmentation Disorder								
Any Grade	0	0	1 (4.8)	1 (0.8)	0	1 (0.6)	1 (0.5)	2 (0.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	1 (4.8)	0	0	0	0	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Rash Papular								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Skin Discomfort								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Skin Fissures								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Skin Mass								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Skin Oedema								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Skin Ulcer								
Any Grade	0	1 (2.1)	0	1 (0.8)	0	1 (0.6)	1 (0.5)	2 (0.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	1 (2.1)	0	0	0	0	0	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Telangiectasia								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Dermatitis Contact								
Any Grade	0	0	1 (4.8)	0	0	0	0	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	1 (4.8)	0	0	0	0	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Miliaria								
Any Grade	0	1 (2.1)	0	0	0	0	0	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	1 (2.1)	0	0	0	0	0	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Nail Dystrophy								
Any Grade	0	0	1 (4.8)	0	0	0	0	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	1 (4.8)	0	0	0	0	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Night Sweats								
Any Grade	0	1 (2.1)	0	0	0	0	0	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	1 (2.1)	0	0	0	0	0	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Skin Haemorrhage								
Any Grade	0	1 (2.1)	0	0	0	0	0	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	1 (2.1)	0	0	0	0	0	1 (0.4)
2	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0
>=3	0	1 (2.1)	0	0	0	0	0	1 (0.4)
Missing	0	0	0	0	0	0	0	0
Musculoskeletal And Connective Tissue Disorders								
Any Grade	15 (30.0)	21 (43.8)	7 (33.3)	55 (42.3)	0	70 (38.9)	70 (38.0)	98 (38.7)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	1 (2.1)	1 (4.8)	2 (1.5)	0	2 (1.1)	2 (1.1)	4 (1.6)
2	6 (12.0)	8 (16.7)	3 (14.3)	18 (13.8)	0	24 (13.3)	24 (13.0)	35 (13.8)
1	9 (18.0)	12 (25.0)	3 (14.3)	34 (26.2)	0	43 (23.9)	43 (23.4)	58 (22.9)
>=3	0	1 (2.1)	1 (4.8)	2 (1.5)	0	2 (1.1)	2 (1.1)	4 (1.6)
Missing	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Arthralgia								
Any Grade	8 (16.0)	6 (12.5)	1 (4.8)	16 (12.3)	0	24 (13.3)	24 (13.0)	31 (12.3)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	2 (4.0)	3 (6.3)	1 (4.8)	8 (6.2)	0	10 (5.6)	10 (5.4)	14 (5.5)
1	6 (12.0)	3 (6.3)	0	8 (6.2)	0	14 (7.8)	14 (7.6)	17 (6.7)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Back Pain								
Any Grade	2 (4.0)	2 (4.2)	3 (14.3)	18 (13.8)	0	20 (11.1)	20 (10.9)	25 (9.9)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
2	0	1 (2.1)	2 (9.5)	3 (2.3)	0	3 (1.7)	3 (1.6)	6 (2.4)
1	2 (4.0)	1 (2.1)	1 (4.8)	14 (10.8)	0	16 (8.9)	16 (8.7)	18 (7.1)
>=3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Myalgia								
Any Grade	5 (10.0)	5 (10.4)	0	13 (10.0)	0	18 (10.0)	18 (9.8)	23 (9.1)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	1 (2.0)	1 (2.1)	0	2 (1.5)	0	3 (1.7)	3 (1.6)	4 (1.6)
1	4 (8.0)	4 (8.3)	0	11 (8.5)	0	15 (8.3)	15 (8.2)	19 (7.5)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Muscle Spasms								
Any Grade	3 (6.0)	3 (6.3)	1 (4.8)	12 (9.2)	0	15 (8.3)	15 (8.2)	19 (7.5)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	1 (2.0)	1 (2.1)	0	1 (0.8)	0	2 (1.1)	2 (1.1)	3 (1.2)
1	2 (4.0)	2 (4.2)	1 (4.8)	11 (8.5)	0	13 (7.2)	13 (7.1)	16 (6.3)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Pain In Extremity								
Any Grade	3 (6.0)	4 (8.3)	2 (9.5)	9 (6.9)	0	12 (6.7)	12 (6.5)	18 (7.1)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	1 (2.1)	1 (4.8)	0	0	0	0	2 (0.8)
2	1 (2.0)	0	1 (4.8)	4 (3.1)	0	5 (2.8)	5 (2.7)	6 (2.4)
1	2 (4.0)	3 (6.3)	0	5 (3.8)	0	7 (3.9)	7 (3.8)	10 (4.0)
>=3	0	1 (2.1)	1 (4.8)	0	0	0	0	2 (0.8)
Missing	0	0	0	0	0	0	0	0
Flank Pain								
Any Grade	1 (2.0)	0	0	3 (2.3)	0	4 (2.2)	4 (2.2)	4 (1.6)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
2	0	0	0	0	0	0	0	0
1	1 (2.0)	0	0	2 (1.5)	0	3 (1.7)	3 (1.6)	3 (1.2)
>=3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Musculoskeletal Stiffness								
Any Grade	1 (2.0)	0	0	3 (2.3)	0	4 (2.2)	4 (2.2)	4 (1.6)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	1 (2.0)	0	0	2 (1.5)	0	3 (1.7)	3 (1.6)	3 (1.2)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Bone Pain								
Any Grade	2 (4.0)	3 (6.3)	0	1 (0.8)	0	3 (1.7)	3 (1.6)	6 (2.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	1 (2.0)	2 (4.2)	0	1 (0.8)	0	2 (1.1)	2 (1.1)	4 (1.6)
1	1 (2.0)	1 (2.1)	0	0	0	1 (0.6)	1 (0.5)	2 (0.8)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Muscular Weakness								
Any Grade	1 (2.0)	3 (6.3)	0	2 (1.5)	0	3 (1.7)	3 (1.6)	6 (2.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	2 (4.2)	0	1 (0.8)	0	1 (0.6)	1 (0.5)	3 (1.2)
1	1 (2.0)	1 (2.1)	0	1 (0.8)	0	2 (1.1)	2 (1.1)	3 (1.2)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Groin Pain								
Any Grade	0	0	1 (4.8)	2 (1.5)	0	2 (1.1)	2 (1.1)	3 (1.2)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	1 (4.8)	1 (0.8)	0	1 (0.6)	1 (0.5)	2 (0.8)
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Musculoskeletal Chest Pain								
Any Grade	0	0	0	2 (1.5)	0	2 (1.1)	2 (1.1)	2 (0.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Neck Pain								
Any Grade	1 (2.0)	1 (2.1)	2 (9.5)	1 (0.8)	0	2 (1.1)	2 (1.1)	5 (2.0)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	1 (4.8)	0	0	0	0	1 (0.4)
1	1 (2.0)	1 (2.1)	1 (4.8)	1 (0.8)	0	2 (1.1)	2 (1.1)	4 (1.6)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Osteoporosis								
Any Grade	0	0	0	2 (1.5)	0	2 (1.1)	2 (1.1)	2 (0.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	2 (1.5)	0	2 (1.1)	2 (1.1)	2 (0.8)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Spinal Pain								
Any Grade	0	0	0	2 (1.5)	0	2 (1.1)	2 (1.1)	2 (0.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
2	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0
>=3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
Missing	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Arthropathy								
Any Grade	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Intervertebral Disc Protrusion								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Joint Stiffness								
Any Grade	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Joint Swelling								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Muscle Atrophy								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Musculoskeletal Pain								
Any Grade	0	1 (2.1)	1 (4.8)	1 (0.8)	0	1 (0.6)	1 (0.5)	3 (1.2)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	1 (4.8)	0	0	0	0	1 (0.4)
1	0	1 (2.1)	0	1 (0.8)	0	1 (0.6)	1 (0.5)	2 (0.8)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Myalgia Intercostal								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Pain In Jaw								
Any Grade	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Pathological Fracture								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Synovial Cyst								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Tendon Disorder								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Tendonitis								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Joint Range Of Motion Decreased								
Any Grade	0	0	1 (4.8)	0	0	0	0	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	1 (4.8)	0	0	0	0	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Musculoskeletal Discomfort								
Any Grade	0	1 (2.1)	0	0	0	0	0	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	1 (2.1)	0	0	0	0	0	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Osteonecrosis								
Any Grade	0	1 (2.1)	0	0	0	0	0	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	1 (2.1)	0	0	0	0	0	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Renal And Urinary Disorders								
Any Grade	6 (12.0)	4 (8.3)	2 (9.5)	11 (8.5)	2 (50.0)	17 (9.4)	19 (10.3)	25 (9.9)
5	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
4	0	0	0	0	0	0	0	0
3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
2	1 (2.0)	1 (2.1)	0	2 (1.5)	1 (25.0)	3 (1.7)	4 (2.2)	5 (2.0)
1	5 (10.0)	3 (6.3)	2 (9.5)	7 (5.4)	1 (25.0)	12 (6.7)	13 (7.1)	18 (7.1)
>=3	0	0	0	2 (1.5)	0	2 (1.1)	2 (1.1)	2 (0.8)
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Haematuria								
Any Grade	0	1 (2.1)	1 (4.8)	3 (2.3)	1 (25.0)	3 (1.7)	4 (2.2)	6 (2.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
2	0	0	0	0	1 (25.0)	0	1 (0.5)	1 (0.4)
1	0	1 (2.1)	1 (4.8)	2 (1.5)	0	2 (1.1)	2 (1.1)	4 (1.6)
>=3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
Missing	0	0	0	0	0	0	0	0
Pollakiuria								
Any Grade	0	0	0	3 (2.3)	1 (25.0)	3 (1.7)	4 (2.2)	4 (1.6)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	2 (1.5)	1 (25.0)	2 (1.1)	3 (1.6)	3 (1.2)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Dysuria								
Any Grade	2 (4.0)	1 (2.1)	1 (4.8)	1 (0.8)	0	3 (1.7)	3 (1.6)	5 (2.0)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	1 (2.0)	1 (2.1)	0	0	0	1 (0.6)	1 (0.5)	2 (0.8)
1	1 (2.0)	0	1 (4.8)	1 (0.8)	0	2 (1.1)	2 (1.1)	3 (1.2)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Urinary Retention								
Any Grade	2 (4.0)	0	0	1 (0.8)	0	3 (1.7)	3 (1.6)	3 (1.2)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	2 (4.0)	0	0	0	0	2 (1.1)	2 (1.1)	2 (0.8)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Acute Kidney Injury								
Any Grade	0	1 (2.1)	0	1 (0.8)	0	1 (0.6)	1 (0.5)	2 (0.8)
5	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	1 (2.1)	0	0	0	0	0	1 (0.4)
>=3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
Missing	0	0	0	0	0	0	0	0
Chromaturia								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Cystitis Noninfective								
Any Grade	0	1 (2.1)	0	1 (0.8)	0	1 (0.6)	1 (0.5)	2 (0.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	1 (2.1)	0	1 (0.8)	0	1 (0.6)	1 (0.5)	2 (0.8)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Micturition Urgency								
Any Grade	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Nephrolithiasis								
Any Grade	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Nocturia								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Urinary Incontinence								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Urinary Tract Pain								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Reproductive System And Breast Disorders								
Any Grade	5 (10.0)	2 (4.2)	0	7 (5.4)	0	12 (6.7)	12 (6.5)	14 (5.5)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
2	1 (2.0)	1 (2.1)	0	2 (1.5)	0	3 (1.7)	3 (1.6)	4 (1.6)
1	4 (8.0)	1 (2.1)	0	4 (3.1)	0	8 (4.4)	8 (4.3)	9 (3.6)
>=3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
Missing	0	0	0	0	0	0	0	0
Breast Pain								
Any Grade	3 (6.0)	1 (2.1)	0	1 (0.8)	0	4 (2.2)	4 (2.2)	5 (2.0)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	1 (2.1)	0	0	0	0	0	1 (0.4)
1	3 (6.0)	0	0	1 (0.8)	0	4 (2.2)	4 (2.2)	4 (1.6)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Menstruation Irregular								
Any Grade	1 (2.0)	0	0	1 (0.8)	0	2 (1.1)	2 (1.1)	2 (0.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	1 (2.0)	0	0	1 (0.8)	0	2 (1.1)	2 (1.1)	2 (0.8)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Bartholin's Cyst								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Genital Haemorrhage								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
2	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0
>=3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
Missing	0	0	0	0	0	0	0	0
Menstrual Disorder								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Pelvic Pain								
Any Grade	0	1 (2.1)	0	1 (0.8)	0	1 (0.6)	1 (0.5)	2 (0.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	1 (2.1)	0	0	0	0	0	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Vulvovaginal Dryness								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Vulvovaginal Pruritus								
Any Grade	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
General Disorders And Administration Site Conditions								
Any Grade	34 (68.0)	41 (85.4)	17 (81.0)	100 (76.9)	3 (75.0)	134 (74.4)	137 (74.5)	195 (77.1)
5	0	1 (2.1)	1 (4.8)	2 (1.5)	0	2 (1.1)	2 (1.1)	4 (1.6)
4	0	0	0	0	0	0	0	0
3	4 (8.0)	13 (27.1)	4 (19.0)	12 (9.2)	0	16 (8.9)	16 (8.7)	33 (13.0)
2	13 (26.0)	12 (25.0)	4 (19.0)	46 (35.4)	1 (25.0)	59 (32.8)	60 (32.6)	76 (30.0)
1	17 (34.0)	15 (31.3)	8 (38.1)	40 (30.8)	2 (50.0)	57 (31.7)	59 (32.1)	82 (32.4)
>=3	4 (8.0)	14 (29.2)	5 (23.8)	14 (10.8)	0	18 (10.0)	18 (9.8)	37 (14.6)
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Fatigue								
Any Grade	21 (42.0)	25 (52.1)	11 (52.4)	69 (53.1)	2 (50.0)	90 (50.0)	92 (50.0)	128 (50.6)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	3 (6.0)	9 (18.8)	5 (23.8)	11 (8.5)	0	14 (7.8)	14 (7.6)	28 (11.1)
2	7 (14.0)	6 (12.5)	3 (14.3)	33 (25.4)	0	40 (22.2)	40 (21.7)	49 (19.4)
1	11 (22.0)	10 (20.8)	3 (14.3)	25 (19.2)	2 (50.0)	36 (20.0)	38 (20.7)	51 (20.2)
>=3	3 (6.0)	9 (18.8)	5 (23.8)	11 (8.5)	0	14 (7.8)	14 (7.6)	28 (11.1)
Missing	0	0	0	0	0	0	0	0
Asthenia								
Any Grade	9 (18.0)	9 (18.8)	0	16 (12.3)	1 (25.0)	25 (13.9)	26 (14.1)	35 (13.8)
5	0	1 (2.1)	0	0	0	0	0	1 (0.4)
4	0	0	0	0	0	0	0	0
3	1 (2.0)	3 (6.3)	0	1 (0.8)	0	2 (1.1)	2 (1.1)	5 (2.0)
2	3 (6.0)	0	0	13 (10.0)	1 (25.0)	16 (8.9)	17 (9.2)	17 (6.7)
1	5 (10.0)	5 (10.4)	0	2 (1.5)	0	7 (3.9)	7 (3.8)	12 (4.7)
>=3	1 (2.0)	4 (8.3)	0	1 (0.8)	0	2 (1.1)	2 (1.1)	6 (2.4)
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Oedema Peripheral								
Any Grade	3 (6.0)	7 (14.6)	0	13 (10.0)	1 (25.0)	16 (8.9)	17 (9.2)	24 (9.5)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	1 (2.1)	0	0	0	0	0	1 (0.4)
2	1 (2.0)	2 (4.2)	0	2 (1.5)	0	3 (1.7)	3 (1.6)	5 (2.0)
1	2 (4.0)	4 (8.3)	0	11 (8.5)	1 (25.0)	13 (7.2)	14 (7.6)	18 (7.1)
>=3	0	1 (2.1)	0	0	0	0	0	1 (0.4)
Missing	0	0	0	0	0	0	0	0
Pyrexia								
Any Grade	4 (8.0)	14 (29.2)	5 (23.8)	13 (10.0)	0	17 (9.4)	17 (9.2)	36 (14.2)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	3 (6.3)	0	2 (1.5)	0	2 (1.1)	2 (1.1)	5 (2.0)
1	4 (8.0)	11 (22.9)	5 (23.8)	11 (8.5)	0	15 (8.3)	15 (8.2)	31 (12.3)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Mucosal Inflammation								
Any Grade	1 (2.0)	4 (8.3)	0	15 (11.5)	0	16 (8.9)	16 (8.7)	20 (7.9)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	3 (2.3)	0	3 (1.7)	3 (1.6)	3 (1.2)
1	1 (2.0)	4 (8.3)	0	12 (9.2)	0	13 (7.2)	13 (7.1)	17 (6.7)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Influenza Like Illness								
Any Grade	2 (4.0)	0	0	10 (7.7)	0	12 (6.7)	12 (6.5)	12 (4.7)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	1 (2.0)	0	0	2 (1.5)	0	3 (1.7)	3 (1.6)	3 (1.2)
1	1 (2.0)	0	0	8 (6.2)	0	9 (5.0)	9 (4.9)	9 (3.6)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Chills								
Any Grade	3 (6.0)	2 (4.2)	0	4 (3.1)	0	7 (3.9)	7 (3.8)	9 (3.6)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	3 (6.0)	2 (4.2)	0	4 (3.1)	0	7 (3.9)	7 (3.8)	9 (3.6)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Non-Cardiac Chest Pain								
Any Grade	0	1 (2.1)	0	4 (3.1)	0	4 (2.2)	4 (2.2)	5 (2.0)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	1 (2.1)	0	2 (1.5)	0	2 (1.1)	2 (1.1)	3 (1.2)
1	0	0	0	2 (1.5)	0	2 (1.1)	2 (1.1)	2 (0.8)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Peripheral Swelling								
Any Grade	0	0	0	4 (3.1)	0	4 (2.2)	4 (2.2)	4 (1.6)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	2 (1.5)	0	2 (1.1)	2 (1.1)	2 (0.8)
1	0	0	0	2 (1.5)	0	2 (1.1)	2 (1.1)	2 (0.8)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Axillary Pain								
Any Grade	0	0	1 (4.8)	3 (2.3)	0	3 (1.7)	3 (1.6)	4 (1.6)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	1 (4.8)	2 (1.5)	0	2 (1.1)	2 (1.1)	3 (1.2)
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Malaise								
Any Grade	2 (4.0)	4 (8.3)	5 (23.8)	1 (0.8)	0	3 (1.7)	3 (1.6)	12 (4.7)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	1 (2.0)	2 (4.2)	3 (14.3)	0	0	1 (0.6)	1 (0.5)	6 (2.4)
1	1 (2.0)	2 (4.2)	2 (9.5)	1 (0.8)	0	2 (1.1)	2 (1.1)	6 (2.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Oedema								
Any Grade	2 (4.0)	0	0	1 (0.8)	0	3 (1.7)	3 (1.6)	3 (1.2)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
1	1 (2.0)	0	0	1 (0.8)	0	2 (1.1)	2 (1.1)	2 (0.8)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Pain								
Any Grade	0	0	1 (4.8)	3 (2.3)	0	3 (1.7)	3 (1.6)	4 (1.6)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	1 (4.8)	1 (0.8)	0	1 (0.6)	1 (0.5)	2 (0.8)
1	0	0	0	2 (1.5)	0	2 (1.1)	2 (1.1)	2 (0.8)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Feeling Cold								
Any Grade	2 (4.0)	0	0	0	0	2 (1.1)	2 (1.1)	2 (0.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	2 (4.0)	0	0	0	0	2 (1.1)	2 (1.1)	2 (0.8)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Illness								
Any Grade	1 (2.0)	0	0	1 (0.8)	0	2 (1.1)	2 (1.1)	2 (0.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	1 (2.0)	0	0	1 (0.8)	0	2 (1.1)	2 (1.1)	2 (0.8)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Xerosis								
Any Grade	1 (2.0)	0	0	1 (0.8)	0	2 (1.1)	2 (1.1)	2 (0.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	1 (2.0)	0	0	1 (0.8)	0	2 (1.1)	2 (1.1)	2 (0.8)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Catheter Site Rash								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Catheter Site Related Reaction								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Catheter Site Thrombosis								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Discomfort								
Any Grade	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Disease Progression								
Any Grade	0	0	1 (4.8)	1 (0.8)	0	1 (0.6)	1 (0.5)	2 (0.8)
5	0	0	1 (4.8)	1 (0.8)	0	1 (0.6)	1 (0.5)	2 (0.8)
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0
>=3	0	0	1 (4.8)	1 (0.8)	0	1 (0.6)	1 (0.5)	2 (0.8)
Missing	0	0	0	0	0	0	0	0
Face Oedema								
Any Grade	0	1 (2.1)	1 (4.8)	1 (0.8)	0	1 (0.6)	1 (0.5)	3 (1.2)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	1 (4.8)	0	0	0	0	1 (0.4)
1	0	1 (2.1)	0	1 (0.8)	0	1 (0.6)	1 (0.5)	2 (0.8)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Feeling Abnormal								
Any Grade	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
General Physical Health Deterioration								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0
>=3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Hyperthermia								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Hypothermia								
Any Grade	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Injection Site Rash								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Injection Site Reaction								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Localised Oedema								
Any Grade	0	0	0	0	1 (25.0)	0	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	0	1 (25.0)	0	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Nodule								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Performance Status Decreased								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
2	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0
>=3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
Missing	0	0	0	0	0	0	0	0
Temperature Intolerance								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Gait Disturbance								
Any Grade	0	1 (2.1)	0	0	0	0	0	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	1 (2.1)	0	0	0	0	0	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Impaired Healing								
Any Grade	0	1 (2.1)	0	0	0	0	0	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	1 (2.1)	0	0	0	0	0	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Inflammation								
Any Grade	0	1 (2.1)	0	0	0	0	0	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	1 (2.1)	0	0	0	0	0	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Investigations								
Any Grade	35 (70.0)	31 (64.6)	17 (81.0)	69 (53.1)	2 (50.0)	104 (57.8)	106 (57.6)	154 (60.9)
5	0	0	0	0	0	0	0	0
4	1 (2.0)	5 (10.4)	3 (14.3)	2 (1.5)	0	3 (1.7)	3 (1.6)	11 (4.3)
3	13 (26.0)	14 (29.2)	7 (33.3)	29 (22.3)	1 (25.0)	42 (23.3)	43 (23.4)	64 (25.3)
2	15 (30.0)	8 (16.7)	6 (28.6)	24 (18.5)	0	39 (21.7)	39 (21.2)	53 (20.9)
1	6 (12.0)	4 (8.3)	1 (4.8)	14 (10.8)	1 (25.0)	20 (11.1)	21 (11.4)	26 (10.3)
>=3	14 (28.0)	19 (39.6)	10 (47.6)	31 (23.8)	1 (25.0)	45 (25.0)	46 (25.0)	75 (29.6)
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Neutrophil Count Decreased								
Any Grade	17 (34.0)	19 (39.6)	13 (61.9)	24 (18.5)	0	41 (22.8)	41 (22.3)	73 (28.9)
5	0	0	0	0	0	0	0	0
4	0	5 (10.4)	1 (4.8)	0	0	0	0	6 (2.4)
3	9 (18.0)	7 (14.6)	5 (23.8)	15 (11.5)	0	24 (13.3)	24 (13.0)	36 (14.2)
2	7 (14.0)	7 (14.6)	5 (23.8)	6 (4.6)	0	13 (7.2)	13 (7.1)	25 (9.9)
1	1 (2.0)	0	2 (9.5)	3 (2.3)	0	4 (2.2)	4 (2.2)	6 (2.4)
>=3	9 (18.0)	12 (25.0)	6 (28.6)	15 (11.5)	0	24 (13.3)	24 (13.0)	42 (16.6)
Missing	0	0	0	0	0	0	0	0
White Blood Cell Count Decreased								
Any Grade	14 (28.0)	17 (35.4)	13 (61.9)	22 (16.9)	0	36 (20.0)	36 (19.6)	66 (26.1)
5	0	0	0	0	0	0	0	0
4	0	0	1 (4.8)	1 (0.8)	0	1 (0.6)	1 (0.5)	2 (0.8)
3	5 (10.0)	6 (12.5)	3 (14.3)	6 (4.6)	0	11 (6.1)	11 (6.0)	20 (7.9)
2	4 (8.0)	9 (18.8)	7 (33.3)	13 (10.0)	0	17 (9.4)	17 (9.2)	33 (13.0)
1	5 (10.0)	2 (4.2)	2 (9.5)	2 (1.5)	0	7 (3.9)	7 (3.8)	11 (4.3)
>=3	5 (10.0)	6 (12.5)	4 (19.0)	7 (5.4)	0	12 (6.7)	12 (6.5)	22 (8.7)
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Aspartate Aminotransferase Increased								
Any Grade	14 (28.0)	7 (14.6)	7 (33.3)	19 (14.6)	0	33 (18.3)	33 (17.9)	47 (18.6)
5	0	0	0	0	0	0	0	0
4	0	0	1 (4.8)	0	0	0	0	1 (0.4)
3	2 (4.0)	2 (4.2)	1 (4.8)	1 (0.8)	0	3 (1.7)	3 (1.6)	6 (2.4)
2	3 (6.0)	1 (2.1)	1 (4.8)	3 (2.3)	0	6 (3.3)	6 (3.3)	8 (3.2)
1	9 (18.0)	4 (8.3)	4 (19.0)	15 (11.5)	0	24 (13.3)	24 (13.0)	32 (12.6)
>=3	2 (4.0)	2 (4.2)	2 (9.5)	1 (0.8)	0	3 (1.7)	3 (1.6)	7 (2.8)
Missing	0	0	0	0	0	0	0	0
Platelet Count Decreased								
Any Grade	11 (22.0)	13 (27.1)	7 (33.3)	19 (14.6)	0	30 (16.7)	30 (16.3)	50 (19.8)
5	0	0	0	0	0	0	0	0
4	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
3	2 (4.0)	2 (4.2)	4 (19.0)	4 (3.1)	0	6 (3.3)	6 (3.3)	12 (4.7)
2	4 (8.0)	5 (10.4)	1 (4.8)	4 (3.1)	0	8 (4.4)	8 (4.3)	14 (5.5)
1	4 (8.0)	6 (12.5)	2 (9.5)	11 (8.5)	0	15 (8.3)	15 (8.2)	23 (9.1)
>=3	3 (6.0)	2 (4.2)	4 (19.0)	4 (3.1)	0	7 (3.9)	7 (3.8)	13 (5.1)
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Alanine Aminotransferase Increased								
Any Grade	8 (16.0)	7 (14.6)	7 (33.3)	13 (10.0)	0	21 (11.7)	21 (11.4)	35 (13.8)
5	0	0	0	0	0	0	0	0
4	0	0	1 (4.8)	0	0	0	0	1 (0.4)
3	0	2 (4.2)	0	3 (2.3)	0	3 (1.7)	3 (1.6)	5 (2.0)
2	1 (2.0)	0	2 (9.5)	1 (0.8)	0	2 (1.1)	2 (1.1)	4 (1.6)
1	7 (14.0)	5 (10.4)	4 (19.0)	9 (6.9)	0	16 (8.9)	16 (8.7)	25 (9.9)
>=3	0	2 (4.2)	1 (4.8)	3 (2.3)	0	3 (1.7)	3 (1.6)	6 (2.4)
Missing	0	0	0	0	0	0	0	0
Lymphocyte Count Decreased								
Any Grade	4 (8.0)	7 (14.6)	2 (9.5)	15 (11.5)	0	19 (10.6)	19 (10.3)	28 (11.1)
5	0	0	0	0	0	0	0	0
4	0	0	1 (4.8)	1 (0.8)	0	1 (0.6)	1 (0.5)	2 (0.8)
3	1 (2.0)	3 (6.3)	1 (4.8)	5 (3.8)	0	6 (3.3)	6 (3.3)	10 (4.0)
2	3 (6.0)	4 (8.3)	0	6 (4.6)	0	9 (5.0)	9 (4.9)	13 (5.1)
1	0	0	0	3 (2.3)	0	3 (1.7)	3 (1.6)	3 (1.2)
>=3	1 (2.0)	3 (6.3)	2 (9.5)	6 (4.6)	0	7 (3.9)	7 (3.8)	12 (4.7)
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Blood Bilirubin Increased								
Any Grade	4 (8.0)	3 (6.3)	5 (23.8)	11 (8.5)	0	15 (8.3)	15 (8.2)	23 (9.1)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	1 (4.8)	0	0	0	0	1 (0.4)
2	3 (6.0)	2 (4.2)	2 (9.5)	6 (4.6)	0	9 (5.0)	9 (4.9)	13 (5.1)
1	1 (2.0)	1 (2.1)	2 (9.5)	5 (3.8)	0	6 (3.3)	6 (3.3)	9 (3.6)
>=3	0	0	1 (4.8)	0	0	0	0	1 (0.4)
Missing	0	0	0	0	0	0	0	0
Weight Decreased								
Any Grade	5 (10.0)	7 (14.6)	5 (23.8)	9 (6.9)	1 (25.0)	14 (7.8)	15 (8.2)	27 (10.7)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	3 (6.0)	3 (6.3)	3 (14.3)	5 (3.8)	0	8 (4.4)	8 (4.3)	14 (5.5)
1	2 (4.0)	4 (8.3)	2 (9.5)	4 (3.1)	1 (25.0)	6 (3.3)	7 (3.8)	13 (5.1)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Blood Alkaline Phosphatase Increased								
Any Grade	2 (4.0)	6 (12.5)	6 (28.6)	9 (6.9)	0	11 (6.1)	11 (6.0)	23 (9.1)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	1 (4.8)	2 (1.5)	0	2 (1.1)	2 (1.1)	3 (1.2)
2	0	1 (2.1)	0	3 (2.3)	0	3 (1.7)	3 (1.6)	4 (1.6)
1	2 (4.0)	5 (10.4)	5 (23.8)	4 (3.1)	0	6 (3.3)	6 (3.3)	16 (6.3)
>=3	0	0	1 (4.8)	2 (1.5)	0	2 (1.1)	2 (1.1)	3 (1.2)
Missing	0	0	0	0	0	0	0	0
Electrocardiogram Qt Prolonged								
Any Grade	6 (12.0)	0	1 (4.8)	4 (3.1)	0	10 (5.6)	10 (5.4)	11 (4.3)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	2 (1.5)	0	2 (1.1)	2 (1.1)	2 (0.8)
2	4 (8.0)	0	1 (4.8)	1 (0.8)	0	5 (2.8)	5 (2.7)	6 (2.4)
1	2 (4.0)	0	0	1 (0.8)	0	3 (1.7)	3 (1.6)	3 (1.2)
>=3	0	0	0	2 (1.5)	0	2 (1.1)	2 (1.1)	2 (0.8)
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Gamma-Glutamyltransferase Increased								
Any Grade	1 (2.0)	6 (12.5)	1 (4.8)	7 (5.4)	0	8 (4.4)	8 (4.3)	15 (5.9)
5	0	0	0	0	0	0	0	0
4	0	0	1 (4.8)	0	0	0	0	1 (0.4)
3	0	3 (6.3)	0	3 (2.3)	0	3 (1.7)	3 (1.6)	6 (2.4)
2	0	1 (2.1)	0	3 (2.3)	0	3 (1.7)	3 (1.6)	4 (1.6)
1	1 (2.0)	2 (4.2)	0	1 (0.8)	0	2 (1.1)	2 (1.1)	4 (1.6)
>=3	0	3 (6.3)	1 (4.8)	3 (2.3)	0	3 (1.7)	3 (1.6)	7 (2.8)
Missing	0	0	0	0	0	0	0	0
Blood Lactate Dehydrogenase Increased								
Any Grade	4 (8.0)	0	3 (14.3)	1 (0.8)	0	5 (2.8)	5 (2.7)	8 (3.2)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
1	3 (6.0)	0	3 (14.3)	1 (0.8)	0	4 (2.2)	4 (2.2)	7 (2.8)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Troponin Increased								
Any Grade	3 (6.0)	1 (2.1)	0	2 (1.5)	0	5 (2.8)	5 (2.7)	6 (2.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	1 (2.0)	1 (2.1)	0	2 (1.5)	0	3 (1.7)	3 (1.6)	4 (1.6)
2	0	0	0	0	0	0	0	0
1	2 (4.0)	0	0	0	0	2 (1.1)	2 (1.1)	2 (0.8)
>=3	1 (2.0)	1 (2.1)	0	2 (1.5)	0	3 (1.7)	3 (1.6)	4 (1.6)
Missing	0	0	0	0	0	0	0	0
Ejection Fraction Decreased								
Any Grade	1 (2.0)	1 (2.1)	0	2 (1.5)	1 (25.0)	3 (1.7)	4 (2.2)	5 (2.0)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	1 (25.0)	0	1 (0.5)	1 (0.4)
2	1 (2.0)	1 (2.1)	0	2 (1.5)	0	3 (1.7)	3 (1.6)	4 (1.6)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	1 (25.0)	0	1 (0.5)	1 (0.4)
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Troponin I Increased								
Any Grade	3 (6.0)	0	0	1 (0.8)	0	4 (2.2)	4 (2.2)	4 (1.6)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	1 (2.0)	0	0	1 (0.8)	0	2 (1.1)	2 (1.1)	2 (0.8)
2	0	0	0	0	0	0	0	0
1	2 (4.0)	0	0	0	0	2 (1.1)	2 (1.1)	2 (0.8)
>=3	1 (2.0)	0	0	1 (0.8)	0	2 (1.1)	2 (1.1)	2 (0.8)
Missing	0	0	0	0	0	0	0	0
Cardiac Murmur								
Any Grade	1 (2.0)	0	0	2 (1.5)	0	3 (1.7)	3 (1.6)	3 (1.2)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	1 (2.0)	0	0	2 (1.5)	0	3 (1.7)	3 (1.6)	3 (1.2)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Blood Magnesium Decreased								
Any Grade	1 (2.0)	0	1 (4.8)	1 (0.8)	0	2 (1.1)	2 (1.1)	3 (1.2)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	1 (4.8)	1 (0.8)	0	1 (0.6)	1 (0.5)	2 (0.8)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Haematocrit Decreased								
Any Grade	0	0	0	2 (1.5)	0	2 (1.1)	2 (1.1)	2 (0.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	2 (1.5)	0	2 (1.1)	2 (1.1)	2 (0.8)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Haemoglobin Decreased								
Any Grade	0	0	1 (4.8)	2 (1.5)	0	2 (1.1)	2 (1.1)	3 (1.2)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	1 (4.8)	1 (0.8)	0	1 (0.6)	1 (0.5)	2 (0.8)
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Liver Function Test Increased								
Any Grade	0	0	0	2 (1.5)	0	2 (1.1)	2 (1.1)	2 (0.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Activated Partial Thromboplastin Time Prolonged								
Any Grade	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Blood Creatinine Increased								
Any Grade	1 (2.0)	0	1 (4.8)	0	0	1 (0.6)	1 (0.5)	2 (0.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	1 (4.8)	0	0	0	0	1 (0.4)
1	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Blood Potassium Increased								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Breath Sounds Abnormal								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Gamma-Glutamyltransferase								
Any Grade	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Influenza A Virus Test Positive								
Any Grade	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
International Normalised Ratio Increased								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
2	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0
>=3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
Missing	0	0	0	0	0	0	0	0
Intraocular Pressure Increased								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Lymphocyte Count Increased								
Any Grade	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Mammogram Abnormal								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Neutrophil Count Increased								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Oxygen Saturation Decreased								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Pulmonary Function Test Abnormal								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Red Blood Cell Count Decreased								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Transaminases Increased								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Vitamin B6 Increased								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Blood Urine Present								
Any Grade	0	1 (2.1)	0	0	0	0	0	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	1 (2.1)	0	0	0	0	0	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
C-Reactive Protein Increased								
Any Grade	0	0	1 (4.8)	0	0	0	0	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	1 (4.8)	0	0	0	0	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Weight Increased								
Any Grade	0	1 (2.1)	0	0	0	0	0	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	1 (2.1)	0	0	0	0	0	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Injury, Poisoning And Procedural Complications								
Any Grade	7 (14.0)	3 (6.3)	4 (19.0)	19 (14.6)	0	26 (14.4)	26 (14.1)	33 (13.0)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	2 (4.2)	1 (4.8)	3 (2.3)	0	3 (1.7)	3 (1.6)	6 (2.4)
2	4 (8.0)	0	1 (4.8)	6 (4.6)	0	10 (5.6)	10 (5.4)	11 (4.3)
1	3 (6.0)	1 (2.1)	1 (4.8)	10 (7.7)	0	13 (7.2)	13 (7.1)	15 (5.9)
>=3	0	2 (4.2)	1 (4.8)	3 (2.3)	0	3 (1.7)	3 (1.6)	6 (2.4)
Missing	0	0	1 (4.8)	0	0	0	0	1 (0.4)

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Infusion Related Reaction								
Any Grade	3 (6.0)	0	0	1 (0.8)	0	4 (2.2)	4 (2.2)	4 (1.6)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	3 (6.0)	0	0	1 (0.8)	0	4 (2.2)	4 (2.2)	4 (1.6)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Fall								
Any Grade	0	0	1 (4.8)	3 (2.3)	0	3 (1.7)	3 (1.6)	4 (1.6)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	1 (4.8)	2 (1.5)	0	2 (1.1)	2 (1.1)	3 (1.2)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Ligament Sprain								
Any Grade	0	0	0	2 (1.5)	0	2 (1.1)	2 (1.1)	2 (0.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
Missing	0	0	0	0	0	0	0	0
Limb Injury								
Any Grade	0	0	0	2 (1.5)	0	2 (1.1)	2 (1.1)	2 (0.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Accidental Overdose								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Alcohol Poisoning								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
2	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0
>=3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Arthropod Bite								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Clavicle Fracture								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Contusion								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Eschar								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Foot Fracture								
Any Grade	0	1 (2.1)	0	1 (0.8)	0	1 (0.6)	1 (0.5)	2 (0.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	1 (2.1)	0	1 (0.8)	0	1 (0.6)	1 (0.5)	2 (0.8)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Fracture								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Joint Injury								
Any Grade	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Muscle Injury								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Overdose								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Procedural Pain								
Any Grade	1 (2.0)	0	1 (4.8)	0	0	1 (0.6)	1 (0.5)	2 (0.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	1 (4.8)	0	0	0	0	1 (0.4)

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Spinal Compression Fracture								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Thermal Burn								
Any Grade	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Tooth Fracture								
Any Grade	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Tooth Injury								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Vascular Access Complication								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
2	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0
>=3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
Missing	0	0	0	0	0	0	0	0
Wound								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Wrist Fracture								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
2	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0
>=3	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
Missing	0	0	0	0	0	0	0	0
Anaphylactic Transfusion Reaction								
Any Grade	0	1 (2.1)	0	0	0	0	0	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	1 (2.1)	0	0	0	0	0	1 (0.4)
2	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0
>=3	0	1 (2.1)	0	0	0	0	0	1 (0.4)
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Avulsion Fracture								
Any Grade	0	0	1 (4.8)	0	0	0	0	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	1 (4.8)	0	0	0	0	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Femoral Neck Fracture								
Any Grade	0	0	1 (4.8)	0	0	0	0	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	1 (4.8)	0	0	0	0	1 (0.4)
2	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0
>=3	0	0	1 (4.8)	0	0	0	0	1 (0.4)
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Ilium Fracture								
Any Grade	0	1 (2.1)	0	0	0	0	0	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	1 (2.1)	0	0	0	0	0	1 (0.4)
2	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0
>=3	0	1 (2.1)	0	0	0	0	0	1 (0.4)
Missing	0	0	0	0	0	0	0	0
Lumbar Vertebral Fracture								
Any Grade	0	0	1 (4.8)	0	0	0	0	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	1 (4.8)	0	0	0	0	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Surgical And Medical Procedures								
Any Grade	1 (2.0)	1 (2.1)	0	3 (2.3)	0	4 (2.2)	4 (2.2)	5 (2.0)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	2 (1.5)	0	2 (1.1)	2 (1.1)	2 (0.8)
>=3	0	0	0	0	0	0	0	0
Missing	1 (2.0)	1 (2.1)	0	0	0	1 (0.6)	1 (0.5)	2 (0.8)
Allergy Prophylaxis								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Catheterisation Venous								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Intra-Uterine Contraceptive Device Insertion								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Mammoplasty								
Any Grade	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
Cataract Operation								
Any Grade	0	1 (2.1)	0	0	0	0	0	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0
>=3	0	0	0	0	0	0	0	0
Missing	0	1 (2.1)	0	0	0	0	0	1 (0.4)

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Uncoded System Organ Class								
Any Grade	1 (2.0)	0	0	1 (0.8)	0	2 (1.1)	2 (1.1)	2 (0.8)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	1 (2.0)	0	0	1 (0.8)	0	2 (1.1)	2 (1.1)	2 (0.8)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Uncoded Preferred Term: Diziness								
Any Grade	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	1 (2.0)	0	0	0	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 14.3.1.2.1: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst CTCAE Grade
Safety Analysis Set

System Organ Class Preferred Term Worst CTCAE Grade	Part 1: PK Stage + Dose Finding Stage 5.4 mg/kg (N=50)	 6.4 mg/kg (N=48)	 7.4 mg/kg (N=21)	Part 2a 5.4 mg/kg (N=130)	Part 2b 5.4 mg/kg (N=4)	(Part 1+ Part 2a) 5.4 mg/kg (N=180)	Overall 5.4 mg/kg (N=184)	Overall All Doses (N=253)
Uncoded Preferred Term: Skin Toxicity With Macules On Lower Extremities And Face								
Any Grade	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
5	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	1 (0.8)	0	1 (0.6)	1 (0.5)	1 (0.4)
>=3	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

Notes: Percents are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 23.0.
If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade.
If a subject has more than one event per system organ class (or preferred term) level, the subject is counted once at each level of summation.

Source Data: adam.adae; Listing 16.2.7.1

Table 11 Overall survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Estrogen receptors:		
Positive (N=93)		
	Overall survival, months	
	Subjects with events (%)	55 (59.1)
	Subjects censored (%)	38 (40.9)
	25th percentile [a]	16.2
	95% CI	(12.6 , 21.1)
	Median [a]	27.0
	95% CI	(22.5 , 30.9)
	Overall survival rates [a]	
	At 6 months (%)	93.5
	95% CI [b]	(86.1 , 97.0)
	At 12 months (%)	85.8
	95% CI [b]	(76.8 , 91.5)
	At 24 months (%)	58.3
	95% CI [b]	(47.5 , 67.6)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 11 Overall survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Estrogen receptors:		
Negative (N=88)		
	Overall survival, months	
	Subjects with events (%)	38 (43.2)
	Subjects censored (%)	50 (56.8)
	25th percentile [a]	18.5
	95% CI	(12.2 , 22.2)
	Median [a]	36.1
	95% CI	(23.3 , NE)
	Overall survival rates [a]	
	At 6 months (%)	95.3
	95% CI [b]	(88.0 , 98.2)
	At 12 months (%)	85.7
	95% CI [b]	(76.2 , 91.6)
	At 24 months (%)	59.7
	95% CI [b]	(48.2 , 69.4)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 11 Overall survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Progesterone receptors:		
Positive (N=51)		
	Overall survival, months	
	Subjects with events (%)	28 (54.9)
	Subjects censored (%)	23 (45.1)
	25th percentile [a]	17.4
	95% CI	(12.2 , 22.2)
	Median [a]	26.9
	95% CI	(21.9 , NE)
	Overall survival rates [a]	
	At 6 months (%)	94.1
	95% CI [b]	(82.7 , 98.1)
	At 12 months (%)	88.1
	95% CI [b]	(75.4 , 94.5)
	At 24 months (%)	60.0
	95% CI [b]	(45.2 , 72.1)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 11 Overall survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Progesterone receptors:		
Negative (N=125)		
	Overall survival, months	
	Subjects with events (%)	62 (49.6)
	Subjects censored (%)	63 (50.4)
	25th percentile [a]	17.7
	95% CI	(13.3 , 20.6)
	Median [a]	30.9
	95% CI	(23.3 , 37.2)
	Overall survival rates [a]	
	At 6 months (%)	94.3
	95% CI [b]	(88.3 , 97.2)
	At 12 months (%)	84.2
	95% CI [b]	(76.3 , 89.6)
	At 24 months (%)	57.6
	95% CI [b]	(48.1 , 65.9)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 11 Overall survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Hormone receptors:		
Positive (N=97)		
	Overall survival, months	
	Subjects with events (%)	57 (58.8)
	Subjects censored (%)	40 (41.2)
	25th percentile [a]	16.2
	95% CI	(12.6 , 21.1)
	Median [a]	27.0
	95% CI	(22.5 , 30.9)
	Overall survival rates [a]	
	At 6 months (%)	93.8
	95% CI [b]	(86.6 , 97.1)
	At 12 months (%)	86.4
	95% CI [b]	(77.7 , 91.9)
	At 24 months (%)	57.9
	95% CI [b]	(47.4 , 67.1)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 11 Overall survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Hormone receptors:		
Negative (N=83)		
	Overall survival, months	
	Subjects with events (%)	35 (42.2)
	Subjects censored (%)	48 (57.8)
	25th percentile [a]	18.5
	95% CI	(10.2 , 22.9)
	Median [a]	36.1
	95% CI	(23.8 , NE)
	Overall survival rates [a]	
	At 6 months (%)	95.0
	95% CI [b]	(87.3 , 98.1)
	At 12 months (%)	84.8
	95% CI [b]	(74.8 , 91.1)
	At 24 months (%)	61.0
	95% CI [b]	(49.1 , 70.9)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 11 Overall survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Lines of prior systemic therapy not including hormone therapy:		
< 3 lines (N=17)		
	Overall survival, months	
	Subjects with events (%)	2 (11.8)
	Subjects censored (%)	15 (88.2)
	25th percentile [a]	
	95% CI	(4.1 , NE)
	Median [a]	NE
	95% CI	(NE, NE)
	Overall survival rates [a]	
	At 6 months (%)	94.1
	95% CI [b]	(65.0 , 99.1)
	At 12 months (%)	94.1
	95% CI [b]	(65.0 , 99.1)
	At 24 months (%)	94.1
	95% CI [b]	(65.0 , 99.1)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 11 Overall survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Lines of prior systemic therapy not including hormone therapy:		
>= 3 lines (N=167)		
	Overall survival, months	
	Subjects with events (%)	93 (55.7)
	Subjects censored (%)	74 (44.3)
	25th percentile [a]	17.4
	95% CI	(13.3 , 19.7)
	Median [a]	27.0
	95% CI	(22.8 , 31.0)
	Overall survival rates [a]	
	At 6 months (%)	93.9
	95% CI [b]	(89.0 , 96.7)
	At 12 months (%)	84.5
	95% CI [b]	(78.0 , 89.3)
	At 24 months (%)	54.7
	95% CI [b]	(46.6 , 62.1)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 11 Overall survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Prior pertuzumab:		
Yes (N=121)		
	Overall survival, months	
	Subjects with events (%)	64 (52.9)
	Subjects censored (%)	57 (47.1)
	25th percentile [a]	18.0
	95% CI	(13.3 , 21.7)
	Median [a]	29.3
	95% CI	(24.6 , 36.1)
	Overall survival rates [a]	
	At 6 months (%)	95.8
	95% CI [b]	(90.2 , 98.2)
	At 12 months (%)	86.3
	95% CI [b]	(78.6 , 91.4)
	At 24 months (%)	60.1
	95% CI [b]	(50.6 , 68.4)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 11 Overall survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Prior pertuzumab:		
No (N=63)		
	Overall survival, months	
	Subjects with events (%)	31 (49.2)
	Subjects censored (%)	32 (50.8)
	25th percentile [a]	16.2
	95% CI	(7.4 , 19.9)
	Median [a]	26.7
	95% CI	(19.9 , NE)
	Overall survival rates [a]	
	At 6 months (%)	90.3
	95% CI [b]	(79.7 , 95.5)
	At 12 months (%)	83.7
	95% CI [b]	(71.9 , 90.9)
	At 24 months (%)	54.8
	95% CI [b]	(41.4 , 66.4)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 11 Overall survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Prior pertuzumab in 1st or 2nd line in advanced/metastatic breast cancer:		
Yes (N=51)		
	Overall survival, months	
	Subjects with events (%)	29 (56.9)
	Subjects censored (%)	22 (43.1)
	25th percentile [a]	17.4
	95% CI	(7.6 , 21.7)
	Median [a]	28.3
	95% CI	(21.7 , NE)
	Overall survival rates [a]	
	At 6 months (%)	92.2
	95% CI [b]	(80.4 , 97.0)
	At 12 months (%)	82.2
	95% CI [b]	(68.6 , 90.3)
	At 24 months (%)	56.1
	95% CI [b]	(41.4 , 68.5)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 11 Overall survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Prior pertuzumab in 1st or 2nd line in advanced/metastatic breast cancer:		
No (N=133)		
	Overall survival, months	
	Subjects with events (%)	66 (49.6)
	Subjects censored (%)	67 (50.4)
	25th percentile [a]	18.0
	95% CI	(13.7 , 20.6)
	Median [a]	29.3
	95% CI	(24.6 , NE)
	Overall survival rates [a]	
	At 6 months (%)	94.6
	95% CI [b]	(89.1 , 97.4)
	At 12 months (%)	86.7
	95% CI [b]	(79.5 , 91.5)
	At 24 months (%)	59.2
	95% CI [b]	(50.0 , 67.2)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 11 Overall survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Renal impairment at baseline:		
Within Normal Range (N=90)		
	Overall survival, months	
	Subjects with events (%)	45 (50)
	Subjects censored (%)	45 (50)
	25th percentile [a]	18.0
	95% CI	(11.6 , 21.7)
	Median [a]	30.8
	95% CI	(24.6 , NE)
	Overall survival rates [a]	
	At 6 months (%)	90.9
	95% CI [b]	(82.7 , 95.4)
	At 12 months (%)	84.0
	95% CI [b]	(74.5 , 90.2)
	At 24 months (%)	62.8
	95% CI [b]	(51.6 , 72.0)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 11 Overall survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Renal impairment at baseline:		
Mild Impairment (N=69)		
	Overall survival, months	
	Subjects with events (%)	33 (47.8)
	Subjects censored (%)	36 (52.2)
	25th percentile [a]	17.6
	95% CI	(13.3 , 21.7)
	Median [a]	31.0
	95% CI	(21.9 , NE)
	Overall survival rates [a]	
	At 6 months (%)	97.1
	95% CI [b]	(88.8 , 99.3)
	At 12 months (%)	89.5
	95% CI [b]	(79.2 , 94.8)
	At 24 months (%)	55.5
	95% CI [b]	(42.6 , 66.6)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 11 Overall survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Renal impairment at baseline:		
Moderate Impairment (N=25)		
	Overall survival, months	
	Subjects with events (%)	17 (68)
	Subjects censored (%)	8 (32)
	25th percentile [a]	16.7
	95% CI	(2.4 , 20.5)
	Median [a]	25.0
	95% CI	(17.7 , 37.2)
	Overall survival rates [a]	
	At 6 months (%)	95.8
	95% CI [b]	(73.9 , 99.4)
	At 12 months (%)	79.2
	95% CI [b]	(57.0 , 90.8)
	At 24 months (%)	50.0
	95% CI [b]	(29.1 , 67.8)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 11 Overall survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Hepatic impairment at baseline:		
Within Normal Range (N=105)		
	Overall survival, months	
	Subjects with events (%)	51 (48.6)
	Subjects censored (%)	54 (51.4)
	25th percentile [a]	21.6
	95% CI	(16.2 , 24.6)
	Median [a]	33.7
	95% CI	(27.5 , 37.2)
	Overall survival rates [a]	
	At 6 months (%)	94.2
	95% CI [b]	(87.5 , 97.3)
	At 12 months (%)	89.2
	95% CI [b]	(81.3 , 93.9)
	At 24 months (%)	66.9
	95% CI [b]	(56.8 , 75.2)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 11 Overall survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Hepatic impairment at baseline:		
Mild Impairment (N=76)		
	Overall survival, months	
	Subjects with events (%)	42 (55.3)
	Subjects censored (%)	34 (44.7)
	25th percentile [a]	14.1
	95% CI	(9.7 , 18.9)
	Median [a]	22.5
	95% CI	(19.7 , NE)
	Overall survival rates [a]	
	At 6 months (%)	94.7
	95% CI [b]	(86.4 , 98.0)
	At 12 months (%)	81.0
	95% CI [b]	(70.0 , 88.3)
	At 24 months (%)	47.5
	95% CI [b]	(35.6 , 58.4)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 11 Overall survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Best response to T-DM1 therapy:		
CR/PR/SD (N=79)		
	Overall survival, months	
	Subjects with events (%)	37 (46.8)
	Subjects censored (%)	42 (53.2)
	25th percentile [a]	20.6
	95% CI	(15.7 , 22.5)
	Median [a]	33.7
	95% CI	(24.6 , NE)
	Overall survival rates [a]	
	At 6 months (%)	97.5
	95% CI [b]	(90.3 , 99.4)
	At 12 months (%)	92.3
	95% CI [b]	(83.7 , 96.5)
	At 24 months (%)	63.4
	95% CI [b]	(51.5 , 73.1)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 11 Overall survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Best response to T-DM1 therapy:		
PD (N=66)		
	Overall survival, months	
	Subjects with events (%)	39 (59.1)
	Subjects censored (%)	27 (40.9)
	25th percentile [a]	17.4
	95% CI	(8.0 , 21.6)
	Median [a]	26.9
	95% CI	(21.7 , 36.1)
	Overall survival rates [a]	
	At 6 months (%)	90.7
	95% CI [b]	(80.4 , 95.7)
	At 12 months (%)	81.0
	95% CI [b]	(68.9 , 88.7)
	At 24 months (%)	56.2
	95% CI [b]	(42.9 , 67.5)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 11 Overall survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Brain metastases:		
Yes (N=24)		
	Overall survival, months	
	Subjects with events (%)	8 (33.3)
	Subjects censored (%)	16 (66.7)
	25th percentile [a]	21.1
	95% CI	(1.9 , NE)
	Median [a]	NE
	95% CI	(21.1 , NE)
	Overall survival rates [a]	
	At 6 months (%)	91.1
	95% CI [b]	(68.8 , 97.7)
	At 12 months (%)	91.1
	95% CI [b]	(68.8 , 97.7)
	At 24 months (%)	65.8
	95% CI [b]	(41.2 , 82.1)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 11 Overall survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Brain metastases:		
No (N=160)		
	Overall survival, months	
	Subjects with events (%)	87 (54.4)
	Subjects censored (%)	73 (45.6)
	25th percentile [a]	17.4
	95% CI	(13.3 , 20.5)
	Median [a]	28.4
	95% CI	(23.5 , 36.1)
	Overall survival rates [a]	
	At 6 months (%)	94.3
	95% CI [b]	(89.4 , 97.0)
	At 12 months (%)	84.7
	95% CI [b]	(78.0 , 89.5)
	At 24 months (%)	57.4
	95% CI [b]	(49.2 , 64.7)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 11 Overall survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Bone metastases:		
Yes (N=53)		
	Overall survival, months	
	Subjects with events (%)	32 (60.4)
	Subjects censored (%)	21 (39.6)
	25th percentile [a]	14.1
	95% CI	(7.4 , 21.6)
	Median [a]	24.6
	95% CI	(21.6 , 30.9)
	Overall survival rates [a]	
	At 6 months (%)	90.2
	95% CI [b]	(78.1 , 95.8)
	At 12 months (%)	78.5
	95% CI [b]	(64.5 , 87.4)
	At 24 months (%)	51.0
	95% CI [b]	(36.6 , 63.7)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 11 Overall survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Bone metastases:		
No (N=131)		
	Overall survival, months	
	Subjects with events (%)	63 (48.1)
	Subjects censored (%)	68 (51.9)
	25th percentile [a]	18.0
	95% CI	(14.1 , 21.1)
	Median [a]	31.0
	95% CI	(25.3 , 37.2)
	Overall survival rates [a]	
	At 6 months (%)	95.4
	95% CI [b]	(90.0 , 97.9)
	At 12 months (%)	88.2
	95% CI [b]	(81.2 , 92.7)
	At 24 months (%)	61.3
	95% CI [b]	(52.1 , 69.3)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 11 Overall survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
History of visceral disease:		
Yes (N=169)		
	Overall survival, months	
	Subjects with events (%)	88 (52.1)
	Subjects censored (%)	81 (47.9)
	25th percentile [a]	17.4
	95% CI	(13.3 , 20.5)
	Median [a]	29.3
	95% CI	(23.8 , 36.1)
	Overall survival rates [a]	
	At 6 months (%)	94.0
	95% CI [b]	(89.1 , 96.7)
	At 12 months (%)	84.8
	95% CI [b]	(78.3 , 89.4)
	At 24 months (%)	58.0
	95% CI [b]	(50.0 , 65.2)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 11 Overall survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
History of visceral disease:		
No (N=15)		
	Overall survival, months	
	Subjects with events (%)	7 (46.7)
	Subjects censored (%)	8 (53.3)
	25th percentile [a]	22.9
	95% CI	(3.9 , 29.1)
	Median [a]	29.1
	95% CI	(19.7 , NE)
	Overall survival rates [a]	
	At 6 months (%)	93.3
	95% CI [b]	(61.3 , 99.0)
	At 12 months (%)	93.3
	95% CI [b]	(61.3 , 99.0)
	At 24 months (%)	62.2
	95% CI [b]	(31.5 , 82.3)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 11 Overall survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Age:		
<65 years (N=140)		
	Overall survival, months	
	Subjects with events (%)	73 (52.1)
	Subjects censored (%)	67 (47.9)
	25th percentile [a]	17.6
	95% CI	(13.2 , 20.6)
	Median [a]	28.1
	95% CI	(23.3 , 36.1)
	Overall survival rates [a]	
	At 6 months (%)	93.5
	95% CI [b]	(87.8 , 96.5)
	At 12 months (%)	84.5
	95% CI [b]	(77.2 , 89.6)
	At 24 months (%)	56.9
	95% CI [b]	(48.0 , 64.8)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 11 Overall survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Age:		
>=65 years (N=44)		
	Overall survival, months	
	Subjects with events (%)	22 (50)
	Subjects censored (%)	22 (50)
	25th percentile [a]	18.0
	95% CI	(10.4 , 26.7)
	Median [a]	30.9
	95% CI	(21.9 , NE)
	Overall survival rates [a]	
	At 6 months (%)	95.3
	95% CI [b]	(82.7 , 98.8)
	At 12 months (%)	88.4
	95% CI [b]	(74.3 , 95.0)
	At 24 months (%)	62.8
	95% CI [b]	(46.6 , 75.3)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 11 Overall survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Region:		
Asia (N=63)		
	Overall survival, months	
	Subjects with events (%)	26 (41.3)
	Subjects censored (%)	37 (58.7)
	25th percentile [a]	20.5
	95% CI	(13.7 , 23.3)
	Median [a]	37.2
	95% CI	(23.8 , NE)
	Overall survival rates [a]	
	At 6 months (%)	98.4
	95% CI [b]	(89.3 , 99.8)
	At 12 months (%)	90.3
	95% CI [b]	(79.8 , 95.5)
	At 24 months (%)	62.5
	95% CI [b]	(49.2 , 73.3)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 11 Overall survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Region:		
North America (N=53)		
	Overall survival, months	
	Subjects with events (%)	28 (52.8)
	Subjects censored (%)	25 (47.2)
	25th percentile [a]	18.0
	95% CI	(10.4 , 23.5)
	Median [a]	28.4
	95% CI	(22.9 , 36.1)
	Overall survival rates [a]	
	At 6 months (%)	92.3
	95% CI [b]	(80.9 , 97.1)
	At 12 months (%)	86.4
	95% CI [b]	(73.7 , 93.3)
	At 24 months (%)	62.3
	95% CI [b]	(47.5 , 74.1)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 11 Overall survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Region:		
EU (N=68)		
	Overall survival, months	
	Subjects with events (%)	41 (60.3)
	Subjects censored (%)	27 (39.7)
	25th percentile [a]	15.4
	95% CI	(7.2 , 18.5)
	Median [a]	24.6
	95% CI	(19.9 , 29.3)
	Overall survival rates [a]	
	At 6 months (%)	90.9
	95% CI [b]	(80.8 , 95.8)
	At 12 months (%)	79.9
	95% CI [b]	(67.8 , 87.8)
	At 24 months (%)	51.1
	95% CI [b]	(38.2 , 62.6)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 11 Overall survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
ECOG performance status:		
0 (N=102)		
	Overall survival, months	
	Subjects with events (%)	45 (44.1)
	Subjects censored (%)	57 (55.9)
	25th percentile [a]	21.3
	95% CI	(18.0 , 24.6)
	Median [a]	36.1
	95% CI	(27.5 , NE)
	Overall survival rates [a]	
	At 6 months (%)	97.0
	95% CI [b]	(91.0 , 99.0)
	At 12 months (%)	90.9
	95% CI [b]	(83.2 , 95.1)
	At 24 months (%)	66.8
	95% CI [b]	(56.5 , 75.3)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 11 Overall survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
ECOG performance status:		
1 (N=81)		
	Overall survival, months	
	Subjects with events (%)	49 (60.5)
	Subjects censored (%)	32 (39.5)
	25th percentile [a]	13.7
	95% CI	(8.0 , 17.4)
	Median [a]	22.8
	95% CI	(18.9 , 28.4)
	Overall survival rates [a]	
	At 6 months (%)	91.2
	95% CI [b]	(82.4 , 95.7)
	At 12 months (%)	79.6
	95% CI [b]	(68.9 , 87.0)
	At 24 months (%)	48.4
	95% CI [b]	(36.9 , 59.0)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 11 Overall survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Baseline sum of diameters of target lesions:		
<5 cm (N=74)		
	Overall survival, months	
	Subjects with events (%)	26 (35.1)
	Subjects censored (%)	48 (64.9)
	25th percentile [a]	21.7
	95% CI	(16.2 , 27.5)
	Median [a]	NE
	95% CI	(29.3 , NE)
	Overall survival rates [a]	
	At 6 months (%)	93.0
	95% CI [b]	(84.0 , 97.0)
	At 12 months (%)	91.6
	95% CI [b]	(82.2 , 96.1)
	At 24 months (%)	70.9
	95% CI [b]	(58.6 , 80.1)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 11 Overall survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Baseline sum of diameters of target lesions:		
>=5 cm (N=96)		
	Overall survival, months	
	Subjects with events (%)	64 (66.7)
	Subjects censored (%)	32 (33.3)
	25th percentile [a]	14.1
	95% CI	(10.2 , 17.6)
	Median [a]	22.5
	95% CI	(19.9 , 26.9)
	Overall survival rates [a]	
	At 6 months (%)	93.7
	95% CI [b]	(86.5 , 97.1)
	At 12 months (%)	79.8
	95% CI [b]	(70.2 , 86.6)
	At 24 months (%)	44.9
	95% CI [b]	(34.6 , 54.7)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 11 Overall survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
DS-8201a immediately following initial T-DM1:		
Yes (N=56)		
	Overall survival, months	
	Subjects with events (%)	16 (28.6)
	Subjects censored (%)	40 (71.4)
	25th percentile [a]	24.6
	95% CI	(17.7 , NE)
	Median [a]	36.1
	95% CI	(36.1 , NE)
	Overall survival rates [a]	
	At 6 months (%)	96.2
	95% CI [b]	(85.7 , 99.0)
	At 12 months (%)	92.3
	95% CI [b]	(80.7 , 97.0)
	At 24 months (%)	76.2
	95% CI [b]	(61.9 , 85.8)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 11 Overall survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
DS-8201a immediately following initial T-DM1:		
No (N=128)		
	Overall survival, months	
	Subjects with events (%)	79 (61.7)
	Subjects censored (%)	49 (38.3)
	25th percentile [a]	15.7
	95% CI	(11.6 , 18.6)
	Median [a]	24.8
	95% CI	(21.6 , 29.3)
	Overall survival rates [a]	
	At 6 months (%)	92.9
	95% CI [b]	(86.9 , 96.3)
	At 12 months (%)	82.6
	95% CI [b]	(74.8 , 88.2)
	At 24 months (%)	51.1
	95% CI [b]	(42.0 , 59.5)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 11 Overall survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
HER2 status:		
IHC3+ (N=154)		
	Overall survival, months	
	Subjects with events (%)	76 (49.4)
	Subjects censored (%)	78 (50.6)
	25th percentile [a]	18.0
	95% CI	(13.4 , 21.1)
	Median [a]	31.0
	95% CI	(24.9 , 37.2)
	Overall survival rates [a]	
	At 6 months (%)	94.7
	95% CI [b]	(89.8 , 97.3)
	At 12 months (%)	86.0
	95% CI [b]	(79.4 , 90.7)
	At 24 months (%)	60.3
	95% CI [b]	(52.0 , 67.7)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 11 Overall survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
HER2 status:		
ISH+ except IHC3+ (N=28)		
	Overall survival, months	
	Subjects with events (%)	18 (64.3)
	Subjects censored (%)	10 (35.7)
	25th percentile [a]	17.4
	95% CI	(5.5 , 21.7)
	Median [a]	22.8
	95% CI	(17.4 , 29.1)
	Overall survival rates [a]	
	At 6 months (%)	92.6
	95% CI [b]	(73.5 , 98.1)
	At 12 months (%)	84.7
	95% CI [b]	(64.2 , 94.0)
	At 24 months (%)	46.6
	95% CI [b]	(26.2 , 64.7)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 9 Progression-free survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Estrogen receptors:		
Positive (N=93)		
	Progression-free survival, months	
	Subjects with events (%)	41 (44.1)
	Progressive disease (PD)	35 (37.6)
	Death	6 (6.5)
	Subjects censored (%)	52 (55.9)
	25th percentile [a]	7.0
	95% CI	(4.8 , 10.5)
	Median [a]	14.1
	95% CI	(12.3 , 24.7)
	Progression-free survival rates [a]	
	At 6 months (%)	79.6
	95% CI [b]	(69.3 , 86.8)
	At 12 months (%)	63.7
	95% CI [b]	(51.6 , 73.5)
	At 24 months (%)	38.8
	95% CI [b]	(26.0 , 51.4)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Progressive disease (PD) was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 9 Progression-free survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Estrogen receptors:		
Negative (N=88)		
	Progression-free survival, months	
	Subjects with events (%)	33 (37.5)
	Progressive disease (PD)	28 (31.8)
	Death	5 (5.7)
	Subjects censored (%)	55 (62.5)
	25th percentile [a]	8.1
	95% CI	(5.4 , 17.6)
	Median [a]	23.5
	95% CI	(18.1 , NE)
	Progression-free survival rates [a]	
	At 6 months (%)	81.9
	95% CI [b]	(71.4 , 88.9)
	At 12 months (%)	70.0
	95% CI [b]	(58.0 , 79.2)
	At 24 months (%)	47.5
	95% CI [b]	(33.4 , 60.4)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Progressive disease (PD) was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 9 Progression-free survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Progesterone receptors:		
Positive (N=51)		
	Progression-free survival, months	
	Subjects with events (%)	23 (45.1)
	Progressive disease (PD)	19 (37.3)
	Death	4 (7.8)
	Subjects censored (%)	28 (54.9)
	25th percentile [a]	8.3
	95% CI	(4.1 , 12.9)
	Median [a]	15.2
	95% CI	(12.7 , NE)
	Progression-free survival rates [a]	
	At 6 months (%)	83.0
	95% CI [b]	(68.9 , 91.1)
	At 12 months (%)	70.4
	95% CI [b]	(54.3 , 81.8)
	At 24 months (%)	39.1
	95% CI [b]	(22.2 , 55.7)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Progressive disease (PD) was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 9 Progression-free survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Progesterone receptors:		
Negative (N=125)		
	Progression-free survival, months	
	Subjects with events (%)	49 (39.2)
	Progressive disease (PD)	42 (33.6)
	Death	7 (5.6)
	Subjects censored (%)	76 (60.8)
	25th percentile [a]	6.8
	95% CI	(5.4 , 10.6)
	Median [a]	22.2
	95% CI	(14.0 , NE)
	Progression-free survival rates [a]	
	At 6 months (%)	79.0
	95% CI [b]	(70.1 , 85.5)
	At 12 months (%)	66.1
	95% CI [b]	(55.9 , 74.4)
	At 24 months (%)	45.4
	95% CI [b]	(33.8 , 56.3)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Progressive disease (PD) was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 9 Progression-free survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Hormone receptors:		
Positive (N=97)		
	Progression-free survival, months	
	Subjects with events (%)	43 (44.3)
	Progressive disease (PD)	37 (38.1)
	Death	6 (6.2)
	Subjects censored (%)	54 (55.7)
	25th percentile [a]	7.0
	95% CI	(4.4 , 10.6)
	Median [a]	15.0
	95% CI	(12.7 , 25.0)
	Progression-free survival rates [a]	
	At 6 months (%)	79.4
	95% CI [b]	(69.3 , 86.5)
	At 12 months (%)	64.3
	95% CI [b]	(52.6 , 73.8)
	At 24 months (%)	40.7
	95% CI [b]	(28.0 , 53.0)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Progressive disease (PD) was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 9 Progression-free survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Hormone receptors:		
Negative (N=83)		
	Progression-free survival, months	
	Subjects with events (%)	31 (37.3)
	Progressive disease (PD)	26 (31.3)
	Death	5 (6)
	Subjects censored (%)	52 (62.7)
	25th percentile [a]	8.1
	95% CI	(5.4 , 17.6)
	Median [a]	22.9
	95% CI	(17.6 , NE)
	Progression-free survival rates [a]	
	At 6 months (%)	82.1
	95% CI [b]	(71.1 , 89.2)
	At 12 months (%)	69.2
	95% CI [b]	(56.6 , 78.8)
	At 24 months (%)	46.1
	95% CI [b]	(31.7 , 59.3)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Progressive disease (PD) was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 9 Progression-free survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Lines of prior systemic therapy not including hormone therapy:		
< 3 lines (N=17)		
	Progression-free survival, months	
	Subjects with events (%)	6 (35.3)
	Progressive disease (PD)	5 (29.4)
	Death	1 (5.9)
	Subjects censored (%)	11 (64.7)
	25th percentile [a]	16.8
	95% CI	(4.1 , NE)
	Median [a]	NE
	95% CI	(16.8 , NE)
	Progression-free survival rates [a]	
	At 6 months (%)	88.2
	95% CI [b]	(60.6 , 96.9)
	At 12 months (%)	88.2
	95% CI [b]	(60.6 , 96.9)
	At 24 months (%)	53.8
	95% CI [b]	(22.8 , 77.1)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Progressive disease (PD) was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 9 Progression-free survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Lines of prior systemic therapy not including hormone therapy:		
>= 3 lines (N=167)		
	Progression-free survival, months	
	Subjects with events (%)	70 (41.9)
	Progressive disease (PD)	59 (35.3)
	Death	11 (6.6)
	Subjects censored (%)	97 (58.1)
	25th percentile [a]	6.8
	95% CI	(5.5 , 9.6)
	Median [a]	17.6
	95% CI	(12.9 , 24.7)
	Progression-free survival rates [a]	
	At 6 months (%)	79.5
	95% CI [b]	(72.0 , 85.2)
	At 12 months (%)	62.8
	95% CI [b]	(53.9 , 70.5)
	At 24 months (%)	40.5
	95% CI [b]	(30.5 , 50.4)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Progressive disease (PD) was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 9 Progression-free survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Prior pertuzumab:		
Yes (N=121)		
	Progression-free survival, months	
	Subjects with events (%)	51 (42.1)
	Progressive disease (PD)	46 (38)
	Death	5 (4.1)
	Subjects censored (%)	70 (57.9)
	25th percentile [a]	8.1
	95% CI	(5.4 , 12.4)
	Median [a]	19.5
	95% CI	(13.8 , NE)
	Progression-free survival rates [a]	
	At 6 months (%)	80.4
	95% CI [b]	(71.5 , 86.8)
	At 12 months (%)	68.5
	95% CI [b]	(58.4 , 76.7)
	At 24 months (%)	40.6
	95% CI [b]	(29.0 , 51.9)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Progressive disease (PD) was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 9 Progression-free survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Prior pertuzumab:		
No (N=63)		
	Progression-free survival, months	
	Subjects with events (%)	25 (39.7)
	Progressive disease (PD)	18 (28.6)
	Death	7 (11.1)
	Subjects censored (%)	38 (60.3)
	25th percentile [a]	7.0
	95% CI	(4.3 , 9.7)
	Median [a]	15.2
	95% CI	(9.7 , NE)
	Progression-free survival rates [a]	
	At 6 months (%)	80.2
	95% CI [b]	(67.1 , 88.6)
	At 12 months (%)	60.2
	95% CI [b]	(44.9 , 72.5)
	At 24 months (%)	46.4
	95% CI [b]	(30.0 , 61.2)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Progressive disease (PD) was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 9 Progression-free survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Prior pertuzumab in 1st or 2nd line in advanced/metastatic breast cancer:		
Yes (N=51)		
	Progression-free survival, months	
	Subjects with events (%)	20 (39.2)
	Progressive disease (PD)	17 (33.3)
	Death	3 (5.9)
	Subjects censored (%)	31 (60.8)
	25th percentile [a]	8.5
	95% CI	(4.2 , 16.8)
	Median [a]	22.2
	95% CI	(12.7 , NE)
	Progression-free survival rates [a]	
	At 6 months (%)	80.2
	95% CI [b]	(65.3 , 89.1)
	At 12 months (%)	72.6
	95% CI [b]	(56.7 , 83.5)
	At 24 months (%)	44.7
	95% CI [b]	(25.5 , 62.2)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Progressive disease (PD) was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 9 Progression-free survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Prior pertuzumab in 1st or 2nd line in advanced/metastatic breast cancer:		
No (N=133)		
	Progression-free survival, months	
	Subjects with events (%)	56 (42.1)
	Progressive disease (PD)	47 (35.3)
	Death	9 (6.8)
	Subjects censored (%)	77 (57.9)
	25th percentile [a]	7.0
	95% CI	(5.6 , 9.7)
	Median [a]	17.8
	95% CI	(12.9 , 25.0)
	Progression-free survival rates [a]	
	At 6 months (%)	80.5
	95% CI [b]	(72.1 , 86.6)
	At 12 months (%)	62.9
	95% CI [b]	(52.9 , 71.5)
	At 24 months (%)	40.7
	95% CI [b]	(29.6 , 51.4)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Progressive disease (PD) was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 9 Progression-free survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Renal impairment at baseline:		
Within Normal Range (N=90)		
	Progression-free survival, months	
	Subjects with events (%)	45 (50)
	Progressive disease (PD)	39 (43.3)
	Death	6 (6.7)
	Subjects censored (%)	45 (50)
	25th percentile [a]	6.3
	95% CI	(4.3 , 8.3)
	Median [a]	17.6
	95% CI	(9.9 , 24.7)
	Progression-free survival rates [a]	
	At 6 months (%)	76.1
	95% CI [b]	(65.5 , 83.9)
	At 12 months (%)	59.1
	95% CI [b]	(47.5 , 69.0)
	At 24 months (%)	38.4
	95% CI [b]	(26.1 , 50.6)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Progressive disease (PD) was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 9 Progression-free survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Renal impairment at baseline:		
Mild Impairment (N=69)		
	Progression-free survival, months	
	Subjects with events (%)	22 (31.9)
	Progressive disease (PD)	18 (26.1)
	Death	4 (5.8)
	Subjects censored (%)	47 (68.1)
	25th percentile [a]	12.7
	95% CI	(6.2 , 16.4)
	Median [a]	25.0
	95% CI	(14.1 , NE)
	Progression-free survival rates [a]	
	At 6 months (%)	86.7
	95% CI [b]	(75.2 , 93.1)
	At 12 months (%)	76.8
	95% CI [b]	(63.2 , 85.9)
	At 24 months (%)	53.3
	95% CI [b]	(36.6 , 67.4)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Progressive disease (PD) was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 9 Progression-free survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Renal impairment at baseline:		
Moderate Impairment (N=25)		
	Progression-free survival, months	
	Subjects with events (%)	9 (36)
	Progressive disease (PD)	7 (28)
	Death	2 (8)
	Subjects censored (%)	16 (64)
	25th percentile [a]	8.5
	95% CI	(2.4 , 12.7)
	Median [a]	12.7
	95% CI	(8.5 , 22.9)
	Progression-free survival rates [a]	
	At 6 months (%)	78.5
	95% CI [b]	(52.0 , 91.4)
	At 12 months (%)	58.1
	95% CI [b]	(26.3 , 80.2)
	At 24 months (%)	15.5
	95% CI [b]	(0.9 , 47.9)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Progressive disease (PD) was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 9 Progression-free survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Hepatic impairment at baseline:		
Within Normal Range (N=105)		
	Progression-free survival, months	
	Subjects with events (%)	41 (39)
	Progressive disease (PD)	34 (32.4)
	Death	7 (6.7)
	Subjects censored (%)	64 (61)
	25th percentile [a]	8.3
	95% CI	(6.2 , 13.8)
	Median [a]	22.1
	95% CI	(15.0 , NE)
	Progression-free survival rates [a]	
	At 6 months (%)	84.1
	95% CI [b]	(75.1 , 90.1)
	At 12 months (%)	69.2
	95% CI [b]	(58.3 , 77.9)
	At 24 months (%)	43.0
	95% CI [b]	(30.2 , 55.2)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Progressive disease (PD) was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 9 Progression-free survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Hepatic impairment at baseline:		
Mild Impairment (N=76)		
	Progression-free survival, months	
	Subjects with events (%)	33 (43.4)
	Progressive disease (PD)	29 (38.2)
	Death	4 (5.3)
	Subjects censored (%)	43 (56.6)
	25th percentile [a]	6.7
	95% CI	(4.3 , 9.7)
	Median [a]	16.4
	95% CI	(9.7 , 25.0)
	Progression-free survival rates [a]	
	At 6 months (%)	77.1
	95% CI [b]	(64.8 , 85.5)
	At 12 months (%)	62.5
	95% CI [b]	(48.9 , 73.4)
	At 24 months (%)	42.8
	95% CI [b]	(28.4 , 56.4)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Progressive disease (PD) was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 9 Progression-free survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Best response to T-DM1 therapy:		
CR/PR/SD (N=79)		
	Progression-free survival, months	
	Subjects with events (%)	35 (44.3)
	Progressive disease (PD)	32 (40.5)
	Death	3 (3.8)
	Subjects censored (%)	44 (55.7)
	25th percentile [a]	8.1
	95% CI	(6.2 , 12.4)
	Median [a]	19.4
	95% CI	(12.4 , 25.0)
	Progression-free survival rates [a]	
	At 6 months (%)	85.9
	95% CI [b]	(75.3 , 92.2)
	At 12 months (%)	65.4
	95% CI [b]	(52.1 , 75.8)
	At 24 months (%)	37.0
	95% CI [b]	(23.1 , 50.9)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Progressive disease (PD) was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 9 Progression-free survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Best response to T-DM1 therapy:		
PD (N=66)		
	Progression-free survival, months	
	Subjects with events (%)	29 (43.9)
	Progressive disease (PD)	23 (34.8)
	Death	6 (9.1)
	Subjects censored (%)	37 (56.1)
	25th percentile [a]	6.6
	95% CI	(4.3 , 9.7)
	Median [a]	17.6
	95% CI	(9.9 , NE)
	Progression-free survival rates [a]	
	At 6 months (%)	75.1
	95% CI [b]	(62.2 , 84.2)
	At 12 months (%)	61.9
	95% CI [b]	(48.0 , 73.2)
	At 24 months (%)	40.6
	95% CI [b]	(25.3 , 55.3)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Progressive disease (PD) was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 9 Progression-free survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Brain metastases:		
Yes (N=24)		
	Progression-free survival, months	
	Subjects with events (%)	11 (45.8)
	Progressive disease (PD)	10 (41.7)
	Death	1 (4.2)
	Subjects censored (%)	13 (54.2)
	25th percentile [a]	6.7
	95% CI	(1.4 , 18.1)
	Median [a]	19.5
	95% CI	(6.7 , NE)
	Progression-free survival rates [a]	
	At 6 months (%)	77.6
	95% CI [b]	(54.3 , 90.0)
	At 12 months (%)	61.8
	95% CI [b]	(37.5 , 79.0)
	At 24 months (%)	33.1
	95% CI [b]	(10.0 , 58.8)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Progressive disease (PD) was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 9 Progression-free survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Brain metastases:		
No (N=160)		
	Progression-free survival, months	
	Subjects with events (%)	65 (40.6)
	Progressive disease (PD)	54 (33.8)
	Death	11 (6.9)
	Subjects censored (%)	95 (59.4)
	25th percentile [a]	7.1
	95% CI	(5.6 , 10.5)
	Median [a]	17.8
	95% CI	(14.0 , NE)
	Progression-free survival rates [a]	
	At 6 months (%)	80.7
	95% CI [b]	(73.1 , 86.4)
	At 12 months (%)	66.4
	95% CI [b]	(57.5 , 73.9)
	At 24 months (%)	43.7
	95% CI [b]	(33.4 , 53.5)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Progressive disease (PD) was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 9 Progression-free survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Bone metastases:		
Yes (N=53)		
	Progression-free survival, months	
	Subjects with events (%)	25 (47.2)
	Progressive disease (PD)	18 (34)
	Death	7 (13.2)
	Subjects censored (%)	28 (52.8)
	25th percentile [a]	7.2
	95% CI	(4.3 , 12.3)
	Median [a]	15.0
	95% CI	(10.6 , 22.2)
	Progression-free survival rates [a]	
	At 6 months (%)	78.3
	95% CI [b]	(63.4 , 87.7)
	At 12 months (%)	63.9
	95% CI [b]	(47.8 , 76.2)
	At 24 months (%)	28.5
	95% CI [b]	(12.6 , 46.7)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Progressive disease (PD) was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 9 Progression-free survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Bone metastases:		
No (N=131)		
	Progression-free survival, months	
	Subjects with events (%)	51 (38.9)
	Progressive disease (PD)	46 (35.1)
	Death	5 (3.8)
	Subjects censored (%)	80 (61.1)
	25th percentile [a]	7.0
	95% CI	(5.4 , 10.5)
	Median [a]	22.9
	95% CI	(15.2 , NE)
	Progression-free survival rates [a]	
	At 6 months (%)	81.3
	95% CI [b]	(72.9 , 87.3)
	At 12 months (%)	66.8
	95% CI [b]	(56.8 , 74.9)
	At 24 months (%)	47.1
	95% CI [b]	(35.7 , 57.8)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Progressive disease (PD) was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 9 Progression-free survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
History of visceral disease:		
Yes (N=169)		
	Progression-free survival, months	
	Subjects with events (%)	71 (42)
	Progressive disease (PD)	60 (35.5)
	Death	11 (6.5)
	Subjects censored (%)	98 (58)
	25th percentile [a]	7.0
	95% CI	(5.4 , 9.7)
	Median [a]	17.8
	95% CI	(14.0 , 25.0)
	Progression-free survival rates [a]	
	At 6 months (%)	79.4
	95% CI [b]	(71.9 , 85.0)
	At 12 months (%)	64.6
	95% CI [b]	(55.9 , 71.9)
	At 24 months (%)	43.0
	95% CI [b]	(33.2 , 52.4)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Progressive disease (PD) was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 9 Progression-free survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
History of visceral disease:		
No (N=15)		
	Progression-free survival, months	
	Subjects with events (%)	5 (33.3)
	Progressive disease (PD)	4 (26.7)
	Death	1 (6.7)
	Subjects censored (%)	10 (66.7)
	25th percentile [a]	12.3
	95% CI	(5.5 , 22.9)
	Median [a]	22.9
	95% CI	(9.7 , NE)
	Progression-free survival rates [a]	
	At 6 months (%)	92.3
	95% CI [b]	(56.6 , 98.9)
	At 12 months (%)	80.8
	95% CI [b]	(41.0 , 95.0)
	At 24 months (%)	33.7
	95% CI [b]	(5.2 , 66.9)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Progressive disease (PD) was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 9 Progression-free survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Age:		
<65 years (N=140)		
	Progression-free survival, months	
	Subjects with events (%)	58 (41.4)
	Progressive disease (PD)	50 (35.7)
	Death	8 (5.7)
	Subjects censored (%)	82 (58.6)
	25th percentile [a]	6.8
	95% CI	(5.4 , 9.7)
	Median [a]	18.1
	95% CI	(13.8 , NE)
	Progression-free survival rates [a]	
	At 6 months (%)	78.7
	95% CI [b]	(70.2 , 85.0)
	At 12 months (%)	63.9
	95% CI [b]	(54.2 , 72.1)
	At 24 months (%)	43.6
	95% CI [b]	(32.8 , 53.9)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Progressive disease (PD) was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 9 Progression-free survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Age:		
>=65 years (N=44)		
	Progression-free survival, months	
	Subjects with events (%)	18 (40.9)
	Progressive disease (PD)	14 (31.8)
	Death	4 (9.1)
	Subjects censored (%)	26 (59.1)
	25th percentile [a]	8.5
	95% CI	(4.3 , 16.4)
	Median [a]	19.4
	95% CI	(12.4 , NE)
	Progression-free survival rates [a]	
	At 6 months (%)	85.5
	95% CI [b]	(70.5 , 93.2)
	At 12 months (%)	71.4
	95% CI [b]	(54.1 , 83.2)
	At 24 months (%)	36.9
	95% CI [b]	(17.6 , 56.4)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Progressive disease (PD) was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 9 Progression-free survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Region:		
Asia (N=63)		
	Progression-free survival, months	
	Subjects with events (%)	26 (41.3)
	Progressive disease (PD)	26 (41.3)
	Subjects censored (%)	37 (58.7)
	25th percentile [a]	6.7
	95% CI	(4.4 , 12.7)
	Median [a]	22.2
	95% CI	(12.7 , NE)
	Progression-free survival rates [a]	
	At 6 months (%)	80.7
	95% CI [b]	(67.9 , 88.8)
	At 12 months (%)	65.4
	95% CI [b]	(50.4 , 76.8)
	At 24 months (%)	45.4
	95% CI [b]	(29.7 , 59.9)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Progressive disease (PD) was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 9 Progression-free survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Region:		
North America (N=53)		
	Progression-free survival, months	
	Subjects with events (%)	16 (30.2)
	Progressive disease (PD)	12 (22.6)
	Death	4 (7.5)
	Subjects censored (%)	37 (69.8)
	25th percentile [a]	12.4
	95% CI	(4.3 , 19.5)
	Median [a]	22.9
	95% CI	(13.8 , NE)
	Progression-free survival rates [a]	
	At 6 months (%)	84.3
	95% CI [b]	(69.8 , 92.2)
	At 12 months (%)	76.7
	95% CI [b]	(60.9 , 86.8)
	At 24 months (%)	48.5
	95% CI [b]	(26.9 , 67.2)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Progressive disease (PD) was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 9 Progression-free survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Region:		
EU (N=68)		
	Progression-free survival, months	
	Subjects with events (%)	34 (50)
	Progressive disease (PD)	26 (38.2)
	Death	8 (11.8)
	Subjects censored (%)	34 (50)
	25th percentile [a]	6.6
	95% CI	(4.2 , 8.3)
	Median [a]	15.0
	95% CI	(8.3 , 22.1)
	Progression-free survival rates [a]	
	At 6 months (%)	77.0
	95% CI [b]	(64.3 , 85.7)
	At 12 months (%)	58.0
	95% CI [b]	(43.9 , 69.7)
	At 24 months (%)	33.8
	95% CI [b]	(19.9 , 48.1)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Progressive disease (PD) was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 9 Progression-free survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
ECOG performance status:		
0 (N=102)		
	Progression-free survival, months	
	Subjects with events (%)	41 (40.2)
	Progressive disease (PD)	37 (36.3)
	Death	4 (3.9)
	Subjects censored (%)	61 (59.8)
	25th percentile [a]	9.6
	95% CI	(6.3 , 12.9)
	Median [a]	22.9
	95% CI	(14.0 , NE)
	Progression-free survival rates [a]	
	At 6 months (%)	85.4
	95% CI [b]	(76.6 , 91.1)
	At 12 months (%)	69.2
	95% CI [b]	(58.1 , 77.8)
	At 24 months (%)	46.0
	95% CI [b]	(33.2 , 57.9)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Progressive disease (PD) was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 9 Progression-free survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
ECOG performance status:		
1 (N=81)		
	Progression-free survival, months	
	Subjects with events (%)	34 (42)
	Progressive disease (PD)	27 (33.3)
	Death	7 (8.6)
	Subjects censored (%)	47 (58)
	25th percentile [a]	6.0
	95% CI	(4.1 , 8.5)
	Median [a]	16.4
	95% CI	(10.6 , 25.0)
	Progression-free survival rates [a]	
	At 6 months (%)	74.1
	95% CI [b]	(61.6 , 83.1)
	At 12 months (%)	61.6
	95% CI [b]	(48.2 , 72.5)
	At 24 months (%)	37.4
	95% CI [b]	(23.2 , 51.5)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Progressive disease (PD) was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 9 Progression-free survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Baseline sum of diameters of target lesions:		
<5 cm (N=74)		
	Progression-free survival, months	
	Subjects with events (%)	24 (32.4)
	Progressive disease (PD)	18 (24.3)
	Death	6 (8.1)
	Subjects censored (%)	50 (67.6)
	25th percentile [a]	10.5
	95% CI	(5.5 , 22.1)
	Median [a]	25.0
	95% CI	(17.8 , NE)
	Progression-free survival rates [a]	
	At 6 months (%)	82.6
	95% CI [b]	(70.8 , 90.0)
	At 12 months (%)	72.9
	95% CI [b]	(59.3 , 82.6)
	At 24 months (%)	50.7
	95% CI [b]	(33.7 , 65.4)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Progressive disease (PD) was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 9 Progression-free survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Baseline sum of diameters of target lesions:		
>=5 cm (N=96)		
	Progression-free survival, months	
	Subjects with events (%)	49 (51)
	Progressive disease (PD)	43 (44.8)
	Death	6 (6.3)
	Subjects censored (%)	47 (49)
	25th percentile [a]	6.7
	95% CI	(4.3 , 8.3)
	Median [a]	12.9
	95% CI	(9.6 , 17.6)
	Progression-free survival rates [a]	
	At 6 months (%)	75.6
	95% CI [b]	(65.1 , 83.4)
	At 12 months (%)	57.4
	95% CI [b]	(45.5 , 67.6)
	At 24 months (%)	30.3
	95% CI [b]	(18.9 , 42.6)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Progressive disease (PD) was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 9 Progression-free survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
DS-8201a immediately following initial T-DM1:		
Yes (N=56)		
	Progression-free survival, months	
	Subjects with events (%)	17 (30.4)
	Progressive disease (PD)	16 (28.6)
	Death	1 (1.8)
	Subjects censored (%)	39 (69.6)
	25th percentile [a]	12.7
	95% CI	(5.4 , 25.0)
	Median [a]	NE
	95% CI	(17.6 , NE)
	Progression-free survival rates [a]	
	At 6 months (%)	82.3
	95% CI [b]	(68.7 , 90.4)
	At 12 months (%)	77.3
	95% CI [b]	(62.5 , 86.8)
	At 24 months (%)	61.7
	95% CI [b]	(44.1 , 75.2)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Progressive disease (PD) was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 9 Progression-free survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
DS-8201a immediately following initial T-DM1:		
No (N=128)		
	Progression-free survival, months	
	Subjects with events (%)	59 (46.1)
	Progressive disease (PD)	48 (37.5)
	Death	11 (8.6)
	Subjects censored (%)	69 (53.9)
	25th percentile [a]	6.7
	95% CI	(4.8 , 8.5)
	Median [a]	15.2
	95% CI	(12.3 , 19.5)
	Progression-free survival rates [a]	
	At 6 months (%)	79.7
	95% CI [b]	(71.0 , 86.0)
	At 12 months (%)	60.8
	95% CI [b]	(50.6 , 69.6)
	At 24 months (%)	32.0
	95% CI [b]	(21.0 , 43.6)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Progressive disease (PD) was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.

[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.

NE - Not Evaluable

Table 9 Progression-free survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
HER2 status:		
IHC3+ (N=154)		
	Progression-free survival, months	
	Subjects with events (%)	61 (39.6)
	Progressive disease (PD)	51 (33.1)
	Death	10 (6.5)
	Subjects censored (%)	93 (60.4)
	25th percentile [a]	7.2
	95% CI	(5.7 , 12.4)
	Median [a]	22.2
	95% CI	(16.4 , NE)
	Progression-free survival rates [a]	
	At 6 months (%)	81.9
	95% CI [b]	(74.4 , 87.4)
	At 12 months (%)	68.2
	95% CI [b]	(59.3 , 75.6)
	At 24 months (%)	45.7
	95% CI [b]	(35.1 , 55.6)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Progressive disease (PD) was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 9 Progression-free survival by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
HER2 status:		
ISH+ except IHC3+ (N=28)		
	Progression-free survival, months	
	Subjects with events (%)	13 (46.4)
	Progressive disease (PD)	12 (42.9)
	Death	1 (3.6)
	Subjects censored (%)	15 (53.6)
	25th percentile [a]	5.1
	95% CI	(2.7 , 9.7)
	Median [a]	12.3
	95% CI	(6.6 , 15.2)
	Progression-free survival rates [a]	
	At 6 months (%)	74.2
	95% CI [b]	(51.3 , 87.5)
	At 12 months (%)	52.3
	95% CI [b]	(28.9 , 71.3)
	At 24 months (%)	23.2
	95% CI [b]	(4.8 , 49.6)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Enrolled Analysis Set in each subgroup category. Progressive disease (PD) was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.
NE - Not Evaluable

Table 3 Summary of best percent change in sum of diameters based on ICR by subgroup - Enrolled Analysis Set

Subgroup	Best percent change in sum of diameters	Overall 5.4 mg/kg (N=184)
Estrogen receptors		
Positive (N=93)	N	85
	Mean	-51.4
	Std. Dev.	33.00
	Median	-53.0
	95% CI [a]	(-65.0, -39.0)
	Minimum	-100.0
	Maximum	22.0
Negative (N=88)	N	81
	Mean	-59.9
	Std. Dev.	28.00
	Median	-63.0
	95% CI [a]	(-68.0, -54.0)
	Minimum	-100.0
	Maximum	0.0

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Best percent change in the sum of the longest diameters (SLD) of measurable tumors is defined as a percent change in the smallest sum of diameters from all post-baseline tumor assessments, taking as reference the baseline sum of diameters based on RECIST 1.1 criteria. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided confidence intervals are based on the distribution-free confidence interval.

Table 3 Summary of best percent change in sum of diameters based on ICR by subgroup - Enrolled Analysis Set

Subgroup	Best percent change in sum of diameters	Overall 5.4 mg/kg (N=184)
Progesterone receptors		
Positive (N=51)	N	47
	Mean	-54.2
	Std. Dev.	28.90
	Median	-57.0
	95% CI [a]	(-71.0, -43.0)
	Minimum	-100.0
	Maximum	2.0
Negative (N=125)	N	114
	Mean	-56.9
	Std. Dev.	31.90
	Median	-61.5
	95% CI [a]	(-68.0, -51.0)
	Minimum	-100.0
	Maximum	22.0

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Best percent change in the sum of the longest diameters (SLD) of measurable tumors is defined as a percent change in the smallest sum of diameters from all post-baseline tumor assessments, taking as reference the baseline sum of diameters based on RECIST 1.1 criteria. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided confidence intervals are based on the distribution-free confidence interval.

Table 3 Summary of best percent change in sum of diameters based on ICR by subgroup - Enrolled Analysis Set

Subgroup	Best percent change in sum of diameters	Overall 5.4 mg/kg (N=184)
Hormone receptors		
Positive (N=97)	N	88
	Mean	-51.4
	Std. Dev.	32.73
	Median	-54.5
	95% CI [a]	(-65.0, -42.0)
	Minimum	-100.0
	Maximum	22.0
Negative (N=83)	N	77
	Mean	-60.1
	Std. Dev.	28.30
	Median	-62.0
	95% CI [a]	(-69.0, -53.0)
	Minimum	-100.0
	Maximum	0.0

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Best percent change in the sum of the longest diameters (SLD) of measurable tumors is defined as a percent change in the smallest sum of diameters from all post-baseline tumor assessments, taking as reference the baseline sum of diameters based on RECIST 1.1 criteria. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided confidence intervals are based on the distribution-free confidence interval.

Table 3 Summary of best percent change in sum of diameters based on ICR by subgroup - Enrolled Analysis Set

Subgroup	Best percent change in sum of diameters	Overall 5.4 mg/kg (N=184)
Lines of prior systemic therapy not including hormone therapy		
< 3 lines (N=17)	N	16
	Mean	-62.7
	Std. Dev.	28.22
	Median	-66.0
	95% CI [a]	(-82.0, -42.0)
	Minimum	-100.0
	Maximum	0.0
>= 3 lines (N=167)	N	153
	Mean	-54.1
	Std. Dev.	31.39
	Median	-58.0
	95% CI [a]	(-64.0, -47.0)
	Minimum	-100.0
	Maximum	22.0

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Best percent change in the sum of the longest diameters (SLD) of measurable tumors is defined as a percent change in the smallest sum of diameters from all post-baseline tumor assessments, taking as reference the baseline sum of diameters based on RECIST 1.1 criteria. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided confidence intervals are based on the distribution-free confidence interval.

Table 3 Summary of best percent change in sum of diameters based on ICR by subgroup - Enrolled Analysis Set

Subgroup	Best percent change in sum of diameters	Overall 5.4 mg/kg (N=184)
Prior pertuzumab		
Yes (N=121)	N	112
	Mean	-56.5
	Std. Dev.	30.22
	Median	-60.5
	95% CI [a]	(-67.0, -51.0)
	Minimum	-100.0
	Maximum	9.0
No (N=63)	N	57
	Mean	-51.6
	Std. Dev.	32.86
	Median	-53.0
	95% CI [a]	(-65.0, -38.0)
	Minimum	-100.0
	Maximum	22.0

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Best percent change in the sum of the longest diameters (SLD) of measurable tumors is defined as a percent change in the smallest sum of diameters from all post-baseline tumor assessments, taking as reference the baseline sum of diameters based on RECIST 1.1 criteria. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided confidence intervals are based on the distribution-free confidence interval.

Table 3 Summary of best percent change in sum of diameters based on ICR by subgroup - Enrolled Analysis Set

Subgroup	Best percent change in sum of diameters	Overall 5.4 mg/kg (N=184)
Prior pertuzumab in 1st or 2nd line in advanced/metastatic breast cancer		
Yes (N=51)	N	48
	Mean	-59.8
	Std. Dev.	28.07
	Median	-65.0
	95% CI [a]	(-72.0, -56.0)
	Minimum	-100.0
	Maximum	2.0
No (N=133)	N	121
	Mean	-53.0
	Std. Dev.	32.17
	Median	-52.0
	95% CI [a]	(-61.0, -43.0)
	Minimum	-100.0
	Maximum	22.0

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Best percent change in the sum of the longest diameters (SLD) of measurable tumors is defined as a percent change in the smallest sum of diameters from all post-baseline tumor assessments, taking as reference the baseline sum of diameters based on RECIST 1.1 criteria. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided confidence intervals are based on the distribution-free confidence interval.

Table 3 Summary of best percent change in sum of diameters based on ICR by subgroup - Enrolled Analysis Set

Subgroup	Best percent change in sum of diameters	Overall 5.4 mg/kg (N=184)
Renal impairment at baseline		
Within Normal Range (N=90)	N	84
	Mean	-57.4
	Std. Dev.	30.45
	Median	-61.5
	95% CI [a]	(-69.0, -52.0)
	Minimum	-100.0
	Maximum	22.0
Mild Impairment (N=69)	N	62
	Mean	-56.7
	Std. Dev.	31.58
	Median	-60.0
	95% CI [a]	(-72.0, -47.0)
	Minimum	-100.0
	Maximum	6.0

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Best percent change in the sum of the longest diameters (SLD) of measurable tumors is defined as a percent change in the smallest sum of diameters from all post-baseline tumor assessments, taking as reference the baseline sum of diameters based on RECIST 1.1 criteria. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided confidence intervals are based on the distribution-free confidence interval.

Table 3 Summary of best percent change in sum of diameters based on ICR by subgroup - Enrolled Analysis Set

Subgroup	Best percent change in sum of diameters	Overall 5.4 mg/kg (N=184)
Renal impairment at baseline		
Moderate Impairment (N=25)	N	23
	Mean	-40.9
	Std. Dev.	29.95
	Median	-35.0
	95% CI [a]	(-61.0, -21.0)
	Minimum	-100.0
	Maximum	9.0

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Best percent change in the sum of the longest diameters (SLD) of measurable tumors is defined as a percent change in the smallest sum of diameters from all post-baseline tumor assessments, taking as reference the baseline sum of diameters based on RECIST 1.1 criteria. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided confidence intervals are based on the distribution-free confidence interval.

Table 3 Summary of best percent change in sum of diameters based on ICR by subgroup - Enrolled Analysis Set

Subgroup	Best percent change in sum of diameters	Overall 5.4 mg/kg (N=184)
Hepatic impairment at baseline		
Within Normal Range (N=105)	N	95
	Mean	-58.6
	Std. Dev.	30.41
	Median	-59.0
	95% CI [a]	(-71.0, -49.0)
	Minimum	-100.0
	Maximum	9.0
Mild Impairment (N=76)	N	71
	Mean	-50.3
	Std. Dev.	31.30
	Median	-57.0
	95% CI [a]	(-65.0, -42.0)
	Minimum	-100.0
	Maximum	22.0

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Best percent change in the sum of the longest diameters (SLD) of measurable tumors is defined as a percent change in the smallest sum of diameters from all post-baseline tumor assessments, taking as reference the baseline sum of diameters based on RECIST 1.1 criteria. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided confidence intervals are based on the distribution-free confidence interval.

Table 3 Summary of best percent change in sum of diameters based on ICR by subgroup - Enrolled Analysis Set

Subgroup	Best percent change in sum of diameters	Overall 5.4 mg/kg (N=184)
Best response to T-DM1 therapy		
CR/PR/SD (N=79)	N	71
	Mean	-55.0
	Std. Dev.	32.57
	Median	-60.0
	95% CI [a]	(-67.0, -44.0)
	Minimum	-100.0
	Maximum	22.0
PD (N=66)	N	64
	Mean	-56.5
	Std. Dev.	29.48
	Median	-58.0
	95% CI [a]	(-68.0, -46.0)
	Minimum	-100.0
	Maximum	-3.0

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Best percent change in the sum of the longest diameters (SLD) of measurable tumors is defined as a percent change in the smallest sum of diameters from all post-baseline tumor assessments, taking as reference the baseline sum of diameters based on RECIST 1.1 criteria. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided confidence intervals are based on the distribution-free confidence interval.

Table 3 Summary of best percent change in sum of diameters based on ICR by subgroup - Enrolled Analysis Set

Subgroup	Best percent change in sum of diameters	Overall 5.4 mg/kg (N=184)
Brain metastases		
Yes (N=24)	N	21
	Mean	-49.9
	Std. Dev.	27.62
	Median	-45.0
	95% CI [a]	(-66.0, -36.0)
	Minimum	-100.0
	Maximum	-5.0
No (N=160)	N	148
	Mean	-55.6
	Std. Dev.	31.61
	Median	-60.0
	95% CI [a]	(-66.0, -51.0)
	Minimum	-100.0
	Maximum	22.0

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Best percent change in the sum of the longest diameters (SLD) of measurable tumors is defined as a percent change in the smallest sum of diameters from all post-baseline tumor assessments, taking as reference the baseline sum of diameters based on RECIST 1.1 criteria. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided confidence intervals are based on the distribution-free confidence interval.

Table 3 Summary of best percent change in sum of diameters based on ICR by subgroup - Enrolled Analysis Set

Subgroup	Best percent change in sum of diameters	Overall 5.4 mg/kg (N=184)
Bone metastases		
Yes (N=53)	N	47
	Mean	-48.2
	Std. Dev.	32.60
	Median	-53.0
	95% CI [a]	(-66.0, -32.0)
	Minimum	-100.0
	Maximum	9.0
No (N=131)	N	122
	Mean	-57.5
	Std. Dev.	30.28
	Median	-59.5
	95% CI [a]	(-67.0, -51.0)
	Minimum	-100.0
	Maximum	22.0

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Best percent change in the sum of the longest diameters (SLD) of measurable tumors is defined as a percent change in the smallest sum of diameters from all post-baseline tumor assessments, taking as reference the baseline sum of diameters based on RECIST 1.1 criteria. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided confidence intervals are based on the distribution-free confidence interval.

Table 3 Summary of best percent change in sum of diameters based on ICR by subgroup - Enrolled Analysis Set

Subgroup	Best percent change in sum of diameters	Overall 5.4 mg/kg (N=184)
History of visceral disease		
Yes (N=169)	N	154
	Mean	-54.5
	Std. Dev.	31.05
	Median	-57.5
	95% CI [a]	(-65.0, -48.0)
	Minimum	-100.0
	Maximum	22.0
No (N=15)	N	15
	Mean	-59.3
	Std. Dev.	32.69
	Median	-61.0
	95% CI [a]	(-100, -29.0)
	Minimum	-100.0
	Maximum	0.0

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Best percent change in the sum of the longest diameters (SLD) of measurable tumors is defined as a percent change in the smallest sum of diameters from all post-baseline tumor assessments, taking as reference the baseline sum of diameters based on RECIST 1.1 criteria. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided confidence intervals are based on the distribution-free confidence interval.

Table 3 Summary of best percent change in sum of diameters based on ICR by subgroup - Enrolled Analysis Set

Subgroup	Best percent change in sum of diameters	Overall 5.4 mg/kg (N=184)
Age		
<65 years (N=140)	N	130
	Mean	-55.1
	Std. Dev.	31.48
	Median	-60.5
	95% CI [a]	(-66.0, -51.0)
	Minimum	-100.0
	Maximum	22.0
>=65 years (N=44)	N	39
	Mean	-54.1
	Std. Dev.	30.31
	Median	-51.0
	95% CI [a]	(-72.0, -39.0)
	Minimum	-100.0
	Maximum	0.0

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Best percent change in the sum of the longest diameters (SLD) of measurable tumors is defined as a percent change in the smallest sum of diameters from all post-baseline tumor assessments, taking as reference the baseline sum of diameters based on RECIST 1.1 criteria. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided confidence intervals are based on the distribution-free confidence interval.

Table 3 Summary of best percent change in sum of diameters based on ICR by subgroup - Enrolled Analysis Set

Subgroup	Best percent change in sum of diameters	Overall 5.4 mg/kg (N=184)
Region		
Asia (N=63)	N	58
	Mean	-53.1
	Std. Dev.	33.12
	Median	-56.0
	95% CI [a]	(-67.0, -43.0)
	Minimum	-100.0
	Maximum	22.0
North America (N=53)	N	49
	Mean	-54.5
	Std. Dev.	28.78
	Median	-59.0
	95% CI [a]	(-68.0, -42.0)
	Minimum	-100.0
	Maximum	-3.0

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Best percent change in the sum of the longest diameters (SLD) of measurable tumors is defined as a percent change in the smallest sum of diameters from all post-baseline tumor assessments, taking as reference the baseline sum of diameters based on RECIST 1.1 criteria. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided confidence intervals are based on the distribution-free confidence interval.

Table 3 Summary of best percent change in sum of diameters based on ICR by subgroup - Enrolled Analysis Set

Subgroup	Best percent change in sum of diameters	Overall 5.4 mg/kg (N=184)
Region		
EU (N=68)	N	62
	Mean	-56.9
	Std. Dev.	31.38
	Median	-59.5
	95% CI [a]	(-70.0, -44.0)
	Minimum	-100.0
	Maximum	0.0

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Best percent change in the sum of the longest diameters (SLD) of measurable tumors is defined as a percent change in the smallest sum of diameters from all post-baseline tumor assessments, taking as reference the baseline sum of diameters based on RECIST 1.1 criteria. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided confidence intervals are based on the distribution-free confidence interval.

Table 3 Summary of best percent change in sum of diameters based on ICR by subgroup - Enrolled Analysis Set

Subgroup	Best percent change in sum of diameters	Overall 5.4 mg/kg (N=184)
ECOG performance status		
0 (N=102)	N	91
	Mean	-58.1
	Std. Dev.	30.52
	Median	-61.0
	95% CI [a]	(-70.0, -52.0)
	Minimum	-100.0
	Maximum	2.0
1 (N=81)	N	77
	Mean	-51.2
	Std. Dev.	31.82
	Median	-53.0
	95% CI [a]	(-65.0, -39.0)
	Minimum	-100.0
	Maximum	22.0

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Best percent change in the sum of the longest diameters (SLD) of measurable tumors is defined as a percent change in the smallest sum of diameters from all post-baseline tumor assessments, taking as reference the baseline sum of diameters based on RECIST 1.1 criteria. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided confidence intervals are based on the distribution-free confidence interval.

Table 3 Summary of best percent change in sum of diameters based on ICR by subgroup - Enrolled Analysis Set

Subgroup	Best percent change in sum of diameters	Overall 5.4 mg/kg (N=184)
Baseline sum of diameters of target lesions		
<5 cm (N=74)	N	73
	Mean	-58.7
	Std. Dev.	33.41
	Median	-59.0
	95% CI [a]	(-73.0, -47.0)
	Minimum	-100.0
	Maximum	2.0
>=5 cm (N=96)	N	96
	Mean	-52.0
	Std. Dev.	29.11
	Median	-57.5
	95% CI [a]	(-64.0, -44.0)
	Minimum	-100.0
	Maximum	22.0

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Best percent change in the sum of the longest diameters (SLD) of measurable tumors is defined as a percent change in the smallest sum of diameters from all post-baseline tumor assessments, taking as reference the baseline sum of diameters based on RECIST 1.1 criteria. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided confidence intervals are based on the distribution-free confidence interval.

Table 3 Summary of best percent change in sum of diameters based on ICR by subgroup - Enrolled Analysis Set

Subgroup	Best percent change in sum of diameters	Overall 5.4 mg/kg (N=184)
DS-8201a immediately following initial T-DM1		
Yes (N=56)	N	51
	Mean	-59.9
	Std. Dev.	30.79
	Median	-62.0
	95% CI [a]	(-72.0, -47.0)
	Minimum	-100.0
	Maximum	6.0
No (N=128)	N	118
	Mean	-52.7
	Std. Dev.	31.15
	Median	-56.5
	95% CI [a]	(-64.0, -44.0)
	Minimum	-100.0
	Maximum	22.0

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Best percent change in the sum of the longest diameters (SLD) of measurable tumors is defined as a percent change in the smallest sum of diameters from all post-baseline tumor assessments, taking as reference the baseline sum of diameters based on RECIST 1.1 criteria. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided confidence intervals are based on the distribution-free confidence interval.

Table 3 Summary of best percent change in sum of diameters based on ICR by subgroup - Enrolled Analysis Set

Subgroup	Best percent change in sum of diameters	Overall 5.4 mg/kg (N=184)
HER2 status		
IHC3+ (N=154)	N	143
	Mean	-56.7
	Std. Dev.	31.52
	Median	-60.0
	95% CI [a]	(-67.0, -53.0)
	Minimum	-100.0
	Maximum	22.0
ISH+ except IHC3+ (N=28)	N	24
	Mean	-45.0
	Std. Dev.	28.45
	Median	-43.0
	95% CI [a]	(-65.0, -20.0)
	Minimum	-100.0
	Maximum	2.0

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Best percent change in the sum of the longest diameters (SLD) of measurable tumors is defined as a percent change in the smallest sum of diameters from all post-baseline tumor assessments, taking as reference the baseline sum of diameters based on RECIST 1.1 criteria. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided confidence intervals are based on the distribution-free confidence interval.

Table 13 Time to response based on ICR by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Estrogen receptors:		
Positive (N=93)		
	Time to response, months	
	Subjects with CR/PR	55
	25th percentile [a]	1.4
	95% CI	(1.3 , 1.4)
	Median [a]	1.5
	95% CI	(1.4 , 2.7)
Negative (N=88)		
	Time to response, months	
	Subjects with CR/PR	59
	25th percentile [a]	1.4
	95% CI	(1.2 , 1.4)
	Median [a]	2.6
	95% CI	(1.4 , 2.7)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Best overall response with confirmation was assessed by independent central review (ICR) using RECIST criteria, Version 1.1. Time to response is summarized for subjects who achieved PR or CR only. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] Median and 25th percentile are based on Kaplan-Meier Estimate.
[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.

Table 13 Time to response based on ICR by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Progesterone receptors:		
Positive (N=51)		
	Time to response, months	
	Subjects with CR/PR	32
	25th percentile [a]	1.3
	95% CI	(1.3 , 1.4)
	Median [a]	1.4
	95% CI	(1.4 , 2.6)
Negative (N=125)		
	Time to response, months	
	Subjects with CR/PR	80
	25th percentile [a]	1.4
	95% CI	(1.3 , 1.4)
	Median [a]	2.6
	95% CI	(1.4 , 2.7)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Best overall response with confirmation was assessed by independent central review (ICR) using RECIST criteria, Version 1.1. Time to response is summarized for subjects who achieved PR or CR only. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] Median and 25th percentile are based on Kaplan-Meier Estimate.

[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.

Table 13 Time to response based on ICR by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Hormone receptors:		
Positive (N=97)		
	Time to response, months	
	Subjects with CR/PR	57
	25th percentile [a]	1.4
	95% CI	(1.3 , 1.4)
	Median [a]	1.5
	95% CI	(1.4 , 2.7)
Negative (N=83)		
	Time to response, months	
	Subjects with CR/PR	56
	25th percentile [a]	1.4
	95% CI	(1.2 , 1.4)
	Median [a]	2.6
	95% CI	(1.4 , 2.7)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Best overall response with confirmation was assessed by independent central review (ICR) using RECIST criteria, Version 1.1. Time to response is summarized for subjects who achieved PR or CR only. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] Median and 25th percentile are based on Kaplan-Meier Estimate.

[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.

Table 13 Time to response based on ICR by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Lines of prior systemic therapy not including hormone therapy:		
< 3 lines (N=17)		
	Time to response, months	
	Subjects with CR/PR	15
	25th percentile [a]	1.2
	95% CI	(1.2 , 1.3)
	Median [a]	1.4
	95% CI	(1.2 , 2.7)
>= 3 lines (N=167)		
	Time to response, months	
	Subjects with CR/PR	99
	25th percentile [a]	1.4
	95% CI	(1.3 , 1.4)
	Median [a]	2.6
	95% CI	(1.4 , 2.7)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Best overall response with confirmation was assessed by independent central review (ICR) using RECIST criteria, Version 1.1. Time to response is summarized for subjects who achieved PR or CR only. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] Median and 25th percentile are based on Kaplan-Meier Estimate.

[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.

Table 13 Time to response based on ICR by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Prior pertuzumab:		
Yes (N=121)		
	Time to response, months	
	Subjects with CR/PR	79
	25th percentile [a]	1.4
	95% CI	(1.3 , 1.4)
	Median [a]	1.6
	95% CI	(1.4 , 2.7)
No (N=63)		
	Time to response, months	
	Subjects with CR/PR	35
	25th percentile [a]	1.4
	95% CI	(1.3 , 1.4)
	Median [a]	1.5
	95% CI	(1.4 , 2.7)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Best overall response with confirmation was assessed by independent central review (ICR) using RECIST criteria, Version 1.1. Time to response is summarized for subjects who achieved PR or CR only. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] Median and 25th percentile are based on Kaplan-Meier Estimate.

[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.

Table 13 Time to response based on ICR by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Prior pertuzumab in 1st or 2nd line in advanced/metastatic breast cancer:		
Yes (N=51)		
	Time to response, months	
	Subjects with CR/PR	39
	25th percentile [a]	1.3
	95% CI	(1.2 , 1.4)
	Median [a]	1.4
	95% CI	(1.3 , 2.6)
No (N=133)		
	Time to response, months	
	Subjects with CR/PR	75
	25th percentile [a]	1.4
	95% CI	(1.3 , 1.4)
	Median [a]	2.6
	95% CI	(1.5 , 2.7)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Best overall response with confirmation was assessed by independent central review (ICR) using RECIST criteria, Version 1.1. Time to response is summarized for subjects who achieved PR or CR only. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] Median and 25th percentile are based on Kaplan-Meier Estimate.

[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.

Table 13 Time to response based on ICR by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Renal impairment at baseline:		
Within Normal Range (N=90)		
	Time to response, months	
	Subjects with CR/PR	60
	25th percentile [a]	1.4
	95% CI	(1.3 , 1.4)
	Median [a]	2.1
	95% CI	(1.4 , 2.7)
Mild Impairment (N=69)		
	Time to response, months	
	Subjects with CR/PR	45
	25th percentile [a]	1.3
	95% CI	(1.3 , 1.4)
	Median [a]	1.5
	95% CI	(1.4 , 2.7)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Best overall response with confirmation was assessed by independent central review (ICR) using RECIST criteria, Version 1.1. Time to response is summarized for subjects who achieved PR or CR only. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] Median and 25th percentile are based on Kaplan-Meier Estimate.

[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.

Table 13 Time to response based on ICR by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Renal impairment at baseline:		
Moderate Impairment (N=25)		
	Time to response, months	
	Subjects with CR/PR	9
	25th percentile [a]	1.4
	95% CI	(1.2 , 1.5)
	Median [a]	1.5
	95% CI	(1.2 , 2.8)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Best overall response with confirmation was assessed by independent central review (ICR) using RECIST criteria, Version 1.1. Time to response is summarized for subjects who achieved PR or CR only. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] Median and 25th percentile are based on Kaplan-Meier Estimate.

[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.

Table 13 Time to response based on ICR by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Hepatic impairment at baseline:		
Within Normal Range (N=105)		
	Time to response, months	
	Subjects with CR/PR	68
	25th percentile [a]	1.4
	95% CI	(1.3 , 1.4)
	Median [a]	1.5
	95% CI	(1.4 , 2.7)
Mild Impairment (N=76)		
	Time to response, months	
	Subjects with CR/PR	45
	25th percentile [a]	1.4
	95% CI	(1.2 , 1.4)
	Median [a]	2.6
	95% CI	(1.4 , 2.8)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Best overall response with confirmation was assessed by independent central review (ICR) using RECIST criteria, Version 1.1. Time to response is summarized for subjects who achieved PR or CR only. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] Median and 25th percentile are based on Kaplan-Meier Estimate.

[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.

Table 13 Time to response based on ICR by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Best response to T-DM1 therapy:		
CR/PR/SD (N=79)		
	Time to response, months	
	Subjects with CR/PR	50
	25th percentile [a]	1.4
	95% CI	(1.3 , 1.4)
	Median [a]	1.6
	95% CI	(1.4 , 2.7)
PD (N=66)		
	Time to response, months	
	Subjects with CR/PR	43
	25th percentile [a]	1.3
	95% CI	(1.2 , 1.4)
	Median [a]	1.4
	95% CI	(1.4 , 2.7)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Best overall response with confirmation was assessed by independent central review (ICR) using RECIST criteria, Version 1.1. Time to response is summarized for subjects who achieved PR or CR only. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] Median and 25th percentile are based on Kaplan-Meier Estimate.

[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.

Table 13 Time to response based on ICR by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Brain metastases:		
Yes (N=24)		
	Time to response, months	
	Subjects with CR/PR	14
	25th percentile [a]	1.3
	95% CI	(1.1 , 2.6)
	Median [a]	2.7
	95% CI	(1.3 , 4.1)
No (N=160)		
	Time to response, months	
	Subjects with CR/PR	100
	25th percentile [a]	1.4
	95% CI	(1.3 , 1.4)
	Median [a]	1.5
	95% CI	(1.4 , 2.7)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Best overall response with confirmation was assessed by independent central review (ICR) using RECIST criteria, Version 1.1. Time to response is summarized for subjects who achieved PR or CR only. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] Median and 25th percentile are based on Kaplan-Meier Estimate.

[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.

Table 13 Time to response based on ICR by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Bone metastases:		
Yes (N=53)		
	Time to response, months	
	Subjects with CR/PR	28
	25th percentile [a]	1.4
	95% CI	(1.3 , 1.4)
	Median [a]	2.6
	95% CI	(1.4 , 2.8)
No (N=131)		
	Time to response, months	
	Subjects with CR/PR	86
	25th percentile [a]	1.3
	95% CI	(1.3 , 1.4)
	Median [a]	1.5
	95% CI	(1.4 , 2.7)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Best overall response with confirmation was assessed by independent central review (ICR) using RECIST criteria, Version 1.1. Time to response is summarized for subjects who achieved PR or CR only. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] Median and 25th percentile are based on Kaplan-Meier Estimate.

[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.

Table 13 Time to response based on ICR by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
History of visceral disease:		
Yes (N=169)		
	Time to response, months	
	Subjects with CR/PR	104
	25th percentile [a]	1.4
	95% CI	(1.3 , 1.4)
	Median [a]	1.6
	95% CI	(1.4 , 2.7)
No (N=15)		
	Time to response, months	
	Subjects with CR/PR	10
	25th percentile [a]	1.4
	95% CI	(1.2 , 2.6)
	Median [a]	2.1
	95% CI	(1.2 , 2.7)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Best overall response with confirmation was assessed by independent central review (ICR) using RECIST criteria, Version 1.1. Time to response is summarized for subjects who achieved PR or CR only. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] Median and 25th percentile are based on Kaplan-Meier Estimate.

[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.

Table 13 Time to response based on ICR by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Age:		
<65 years (N=140)		
	Time to response, months	
	Subjects with CR/PR	87
	25th percentile [a]	1.4
	95% CI	(1.3 , 1.4)
	Median [a]	1.5
	95% CI	(1.4 , 2.6)
>=65 years (N=44)		
	Time to response, months	
	Subjects with CR/PR	27
	25th percentile [a]	1.3
	95% CI	(1.2 , 1.4)
	Median [a]	2.7
	95% CI	(1.3 , 2.9)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Best overall response with confirmation was assessed by independent central review (ICR) using RECIST criteria, Version 1.1. Time to response is summarized for subjects who achieved PR or CR only. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] Median and 25th percentile are based on Kaplan-Meier Estimate.

[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.

Table 13 Time to response based on ICR by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Region:		
Asia (N=63)		
	Time to response, months	
	Subjects with CR/PR	39
	25th percentile [a]	1.3
	95% CI	(1.2 , 1.4)
	Median [a]	1.5
	95% CI	(1.4 , 2.8)
North America (N=53)		
	Time to response, months	
	Subjects with CR/PR	33
	25th percentile [a]	1.4
	95% CI	(1.2 , 1.4)
	Median [a]	1.6
	95% CI	(1.4 , 2.7)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Best overall response with confirmation was assessed by independent central review (ICR) using RECIST criteria, Version 1.1. Time to response is summarized for subjects who achieved PR or CR only. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] Median and 25th percentile are based on Kaplan-Meier Estimate.

[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.

Table 13 Time to response based on ICR by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Region:		
EU (N=68)		
	Time to response, months	
	Subjects with CR/PR	42
	25th percentile [a]	1.4
	95% CI	(1.3 , 1.4)
	Median [a]	2.6
	95% CI	(1.4 , 2.7)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Best overall response with confirmation was assessed by independent central review (ICR) using RECIST criteria, Version 1.1. Time to response is summarized for subjects who achieved PR or CR only. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] Median and 25th percentile are based on Kaplan-Meier Estimate.

[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.

Table 13 Time to response based on ICR by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
ECOG performance status:		
0 (N=102)		
	Time to response, months	
	Subjects with CR/PR	68
	25th percentile [a]	1.4
	95% CI	(1.3 , 1.5)
	Median [a]	2.6
	95% CI	(1.5 , 2.8)
ECOG performance status:		
1 (N=81)		
	Time to response, months	
	Subjects with CR/PR	46
	25th percentile [a]	1.3
	95% CI	(1.2 , 1.4)
	Median [a]	1.4
	95% CI	(1.4 , 2.6)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Best overall response with confirmation was assessed by independent central review (ICR) using RECIST criteria, Version 1.1. Time to response is summarized for subjects who achieved PR or CR only. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] Median and 25th percentile are based on Kaplan-Meier Estimate.

[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.

Table 13 Time to response based on ICR by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Baseline sum of diameters of target lesions:		
<5 cm (N=74)		
	Time to response, months	
	Subjects with CR/PR	49
	25th percentile [a]	1.4
	95% CI	(1.3 , 1.4)
	Median [a]	1.4
	95% CI	(1.4 , 2.6)
>=5 cm (N=96)		
	Time to response, months	
	Subjects with CR/PR	63
	25th percentile [a]	1.4
	95% CI	(1.3 , 1.4)
	Median [a]	2.6
	95% CI	(1.4 , 2.7)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Best overall response with confirmation was assessed by independent central review (ICR) using RECIST criteria, Version 1.1. Time to response is summarized for subjects who achieved PR or CR only. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] Median and 25th percentile are based on Kaplan-Meier Estimate.

[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.

Table 13 Time to response based on ICR by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
DS-8201a immediately following initial T-DM1:		
Yes (N=56)		
	Time to response, months	
	Subjects with CR/PR	39
	25th percentile [a]	1.4
	95% CI	(1.2 , 1.4)
	Median [a]	2.6
	95% CI	(1.4 , 2.8)
No (N=128)		
	Time to response, months	
	Subjects with CR/PR	75
	25th percentile [a]	1.4
	95% CI	(1.3 , 1.4)
	Median [a]	1.5
	95% CI	(1.4 , 2.6)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Best overall response with confirmation was assessed by independent central review (ICR) using RECIST criteria, Version 1.1. Time to response is summarized for subjects who achieved PR or CR only. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] Median and 25th percentile are based on Kaplan-Meier Estimate.

[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.

Table 13 Time to response based on ICR by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
HER2 status:		
IHC3+ (N=154)		
	Time to response, months	
	Subjects with CR/PR	99
	25th percentile [a]	1.4
	95% CI	(1.3 , 1.4)
	Median [a]	2.6
	95% CI	(1.4 , 2.7)
ISH+ except IHC3+ (N=28)		
	Time to response, months	
	Subjects with CR/PR	13
	25th percentile [a]	1.4
	95% CI	(1.2 , 1.4)
	Median [a]	1.4
	95% CI	(1.3 , 2.7)

Notes: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Best overall response with confirmation was assessed by independent central review (ICR) using RECIST criteria, Version 1.1. Time to response is summarized for subjects who achieved PR or CR only. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] Median and 25th percentile are based on Kaplan-Meier Estimate.

[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.

Table 54 Duration of response based on ICR by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Estrogen receptors:		
Positive (N=93)	Duration of response (CR or PR), months	
	Subjects with CR/PR	55
	Subjects with events (%)	22 (40)
	Subjects censored (%)	33 (60)
	Ongoing without PD (%)	32 (58.2)
	Other (%)	1 (1.8)
	25th percentile [a]	9.0
	95% CI	(5.5 , 10.6)
	Median [a]	15.0
	95% CI	(10.0 , NE)
	Response probability (CR or PR) [a]	
	At 6 months (%)	82.6
	95% CI [b]	(68.1 , 90.9)
	At 12 months (%)	55.8
	95% CI [b]	(38.9 , 69.7)
	At 24 months (%)	40.1
	95% CI [b]	(22.9 , 56.8)

Notes: CR: Complete response; PR: Partial response, PD: progressive disease. Percentage is calculated using number of subjects with CR/PR as the denominator. Best overall response (CR/PR) with confirmation was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate. For point estimates asymptotic normality to the log-log transformation of rates was applied.

[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.

NE - Not Evaluable

Table 54 Duration of response based on ICR by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Estrogen receptors:		
Negative (N=88)	Duration of response (CR or PR), months	
	Subjects with CR/PR	59
	Subjects with events (%)	23 (39)
	Subjects censored (%)	36 (61)
	Ongoing without PD (%)	35 (59.3)
	Other (%)	1 (1.7)
	25th percentile [a]	9.7
	95% CI	(5.6 , 18.2)
	Median [a]	22.4
	95% CI	(16.9 , NE)
	Response probability (CR or PR) [a]	
	At 6 months (%)	81.0
	95% CI [b]	(67.5 , 89.4)
	At 12 months (%)	74.5
	95% CI [b]	(59.9 , 84.4)
	At 24 months (%)	38.4
	95% CI [b]	(19.5 , 57.0)

Notes: CR: Complete response; PR: Partial response, PD: progressive disease. Percentage is calculated using number of subjects with CR/PR as the denominator. Best overall response (CR/PR) with confirmation was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate. For point estimates asymptotic normality to the log-log transformation of rates was applied.

[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.

NE - Not Evaluable

Table 54 Duration of response based on ICR by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Progesterone receptors:		
Positive (N=51)	Duration of response (CR or PR), months	
	Subjects with CR/PR	32
	Subjects with events (%)	15 (46.9)
	Subjects censored (%)	17 (53.1)
	Ongoing without PD (%)	17 (53.1)
	25th percentile [a]	5.7
	95% CI	(4.6 , 10.6)
	Median [a]	15.0
	95% CI	(7.4 , NE)
	Response probability (CR or PR) [a]	
	At 6 months (%)	74.8
	95% CI [b]	(54.1 , 87.2)
	At 12 months (%)	58.8
	95% CI [b]	(37.8 , 74.8)
	At 24 months (%)	31.4
	95% CI [b]	(10.8 , 54.8)

Notes: CR: Complete response; PR: Partial response, PD: progressive disease. Percentage is calculated using number of subjects with CR/PR as the denominator. Best overall response (CR/PR) with confirmation was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate. For point estimates asymptotic normality to the log-log transformation of rates was applied.

[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.

NE - Not Evaluable

Table 54 Duration of response based on ICR by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Progesterone receptors:		
Negative (N=125)	Duration of response (CR or PR), months	
	Subjects with CR/PR	80
	Subjects with events (%)	29 (36.3)
	Subjects censored (%)	51 (63.8)
	Ongoing without PD (%)	49 (61.3)
	Other (%)	2 (2.5)
	25th percentile [a]	9.7
	95% CI	(5.7 , 15.5)
	Median [a]	21.5
	95% CI	(15.5 , NE)
	Response probability (CR or PR) [a]	
	At 6 months (%)	84.1
	95% CI [b]	(73.1 , 90.9)
	At 12 months (%)	69.6
	95% CI [b]	(56.3 , 79.6)
	At 24 months (%)	43.6
	95% CI [b]	(28.3 , 58.0)

Notes: CR: Complete response; PR: Partial response, PD: progressive disease. Percentage is calculated using number of subjects with CR/PR as the denominator. Best overall response (CR/PR) with confirmation was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate. For point estimates asymptotic normality to the log-log transformation of rates was applied.

[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.

NE - Not Evaluable

Table 54 Duration of response based on ICR by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Hormone receptors:		
Positive (N=97)	Duration of response (CR or PR), months	
	Subjects with CR/PR	57
	Subjects with events (%)	23 (40.4)
	Subjects censored (%)	34 (59.6)
	Ongoing without PD (%)	33 (57.9)
	Other (%)	1 (1.8)
	25th percentile [a]	9.0
	95% CI	(5.5 , 11.4)
	Median [a]	16.5
	95% CI	(10.6 , NE)
	Response probability (CR or PR) [a]	
	At 6 months (%)	83.3
	95% CI [b]	(69.3 , 91.3)
	At 12 months (%)	57.9
	95% CI [b]	(41.4 , 71.3)
	At 24 months (%)	35.7
	95% CI [b]	(17.6 , 54.3)

Notes: CR: Complete response; PR: Partial response, PD: progressive disease. Percentage is calculated using number of subjects with CR/PR as the denominator. Best overall response (CR/PR) with confirmation was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate. For point estimates asymptotic normality to the log-log transformation of rates was applied.

[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.

NE - Not Evaluable

Table 54 Duration of response based on ICR by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Hormone receptors:		
Negative (N=83)	Duration of response (CR or PR), months	
	Subjects with CR/PR	56
	Subjects with events (%)	22 (39.3)
	Subjects censored (%)	34 (60.7)
	Ongoing without PD (%)	33 (58.9)
	Other (%)	1 (1.8)
	25th percentile [a]	9.7
	95% CI	(4.5 , 16.9)
	Median [a]	21.5
	95% CI	(15.5 , NE)
	Response probability (CR or PR) [a]	
	At 6 months (%)	79.9
	95% CI [b]	(65.7 , 88.7)
	At 12 months (%)	72.8
	95% CI [b]	(57.6 , 83.3)
	At 24 months (%)	43.6
	95% CI [b]	(26.4 , 59.6)

Notes: CR: Complete response; PR: Partial response, PD: progressive disease. Percentage is calculated using number of subjects with CR/PR as the denominator. Best overall response (CR/PR) with confirmation was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate. For point estimates asymptotic normality to the log-log transformation of rates was applied.

[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.

NE - Not Evaluable

Table 54 Duration of response based on ICR by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Lines of prior systemic therapy not including hormone therapy:		
< 3 lines (N=17)	Duration of response (CR or PR), months	
	Subjects with CR/PR	15
	Subjects with events (%)	6 (40)
	Subjects censored (%)	9 (60)
	Ongoing without PD (%)	9 (60)
	25th percentile [a]	12.5
	95% CI	(2.8 , 20.8)
	Median [a]	20.8
	95% CI	(11.5 , NE)
	Response probability (CR or PR) [a]	
	At 6 months (%)	86.7
	95% CI [b]	(56.4 , 96.5)
	At 12 months (%)	79.4
	95% CI [b]	(48.8 , 92.9)
	At 24 months (%)	40.9
	95% CI [b]	(8.2 , 72.5)

Notes: CR: Complete response; PR: Partial response, PD: progressive disease. Percentage is calculated using number of subjects with CR/PR as the denominator. Best overall response (CR/PR) with confirmation was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate. For point estimates asymptotic normality to the log-log transformation of rates was applied.

[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.

NE - Not Evaluable

Table 54 Duration of response based on ICR by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Lines of prior systemic therapy not including hormone therapy:		
>= 3 lines (N=167)	Duration of response (CR or PR), months	
	Subjects with CR/PR	99
	Subjects with events (%)	39 (39.4)
	Subjects censored (%)	60 (60.6)
	Ongoing without PD (%)	58 (58.6)
	Other (%)	2 (2)
	25th percentile [a]	8.3
	95% CI	(5.6 , 10.6)
	Median [a]	18.2
	95% CI	(13.8 , NE)
	Response probability (CR or PR) [a]	
	At 6 months (%)	80.8
	95% CI [b]	(70.6 , 87.8)
	At 12 months (%)	63.3
	95% CI [b]	(51.2 , 73.2)
	At 24 months (%)	37.6
	95% CI [b]	(23.3 , 51.8)

Notes: CR: Complete response; PR: Partial response, PD: progressive disease. Percentage is calculated using number of subjects with CR/PR as the denominator. Best overall response (CR/PR) with confirmation was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate. For point estimates asymptotic normality to the log-log transformation of rates was applied.

[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.

NE - Not Evaluable

Table 54 Duration of response based on ICR by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Prior pertuzumab:		
Yes (N=121)	Duration of response (CR or PR), months	
	Subjects with CR/PR	79
	Subjects with events (%)	31 (39.2)
	Subjects censored (%)	48 (60.8)
	Ongoing without PD (%)	46 (58.2)
	Other (%)	2 (2.5)
	25th percentile [a]	9.7
	95% CI	(5.7 , 14.8)
	Median [a]	18.2
	95% CI	(14.8 , NE)
	Response probability (CR or PR) [a]	
	At 6 months (%)	85.4
	95% CI [b]	(74.5 , 91.9)
	At 12 months (%)	67.7
	95% CI [b]	(54.3 , 78.0)
	At 24 months (%)	37.2
	95% CI [b]	(22.1 , 52.4)

Notes: CR: Complete response; PR: Partial response, PD: progressive disease. Percentage is calculated using number of subjects with CR/PR as the denominator. Best overall response (CR/PR) with confirmation was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate. For point estimates asymptotic normality to the log-log transformation of rates was applied.

[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.

NE - Not Evaluable

Table 54 Duration of response based on ICR by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Prior pertuzumab:		
No (N=63)	Duration of response (CR or PR), months	
	Subjects with CR/PR	35
	Subjects with events (%)	14 (40)
	Subjects censored (%)	21 (60)
	Ongoing without PD (%)	21 (60)
	25th percentile [a]	5.7
	95% CI	(4.2 , 13.8)
	Median [a]	23.7
	95% CI	(9.0 , NE)
	Response probability (CR or PR) [a]	
	At 6 months (%)	73.7
	95% CI [b]	(54.1 , 85.9)
	At 12 months (%)	62.1
	95% CI [b]	(41.8 , 77.2)
	At 24 months (%)	42.1
	95% CI [b]	(18.6 , 64.0)

Notes: CR: Complete response; PR: Partial response, PD: progressive disease. Percentage is calculated using number of subjects with CR/PR as the denominator. Best overall response (CR/PR) with confirmation was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate. For point estimates asymptotic normality to the log-log transformation of rates was applied.

[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.

NE - Not Evaluable

Table 54 Duration of response based on ICR by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Prior pertuzumab in 1st or 2nd line in advanced/metastatic breast cancer:		
Yes (N=51)	Duration of response (CR or PR), months	
	Subjects with CR/PR	39
	Subjects with events (%)	16 (41)
	Subjects censored (%)	23 (59)
	Ongoing without PD (%)	22 (56.4)
	Other (%)	1 (2.6)
	25th percentile [a]	9.7
	95% CI	(2.9 , 14.8)
	Median [a]	17.8
	95% CI	(11.5 , NE)
	Response probability (CR or PR) [a]	
	At 6 months (%)	81.2
	95% CI [b]	(64.6 , 90.6)
	At 12 months (%)	67.8
	95% CI [b]	(49.0 , 80.9)
	At 24 months (%)	39.5
	95% CI [b]	(17.3 , 61.2)

Notes: CR: Complete response; PR: Partial response, PD: progressive disease. Percentage is calculated using number of subjects with CR/PR as the denominator. Best overall response (CR/PR) with confirmation was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate. For point estimates asymptotic normality to the log-log transformation of rates was applied.

[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.

NE - Not Evaluable

Table 54 Duration of response based on ICR by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Prior pertuzumab in 1st or 2nd line in advanced/metastatic breast cancer:		
No (N=133)	Duration of response (CR or PR), months	
	Subjects with CR/PR	75
	Subjects with events (%)	29 (38.7)
	Subjects censored (%)	46 (61.3)
	Ongoing without PD (%)	45 (60)
	Other (%)	1 (1.3)
	25th percentile [a]	8.3
	95% CI	(5.6 , 13.8)
	Median [a]	18.2
	95% CI	(13.8 , NE)
	Response probability (CR or PR) [a]	
	At 6 months (%)	82.0
	95% CI [b]	(69.8 , 89.6)
	At 12 months (%)	64.6
	95% CI [b]	(50.4 , 75.6)
	At 24 months (%)	38.4
	95% CI [b]	(22.7 , 53.8)

Notes: CR: Complete response; PR: Partial response, PD: progressive disease. Percentage is calculated using number of subjects with CR/PR as the denominator. Best overall response (CR/PR) with confirmation was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate. For point estimates asymptotic normality to the log-log transformation of rates was applied.

[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.

NE - Not Evaluable

Table 54 Duration of response based on ICR by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Renal impairment at baseline:		
Within Normal Range (N=90)	Duration of response (CR or PR), months	
	Subjects with CR/PR	60
	Subjects with events (%)	27 (45)
	Subjects censored (%)	33 (55)
	Ongoing without PD (%)	32 (53.3)
	Other (%)	1 (1.7)
	25th percentile [a]	6.9
	95% CI	(4.6 , 12.5)
	Median [a]	18.2
	95% CI	(9.7 , NE)
	Response probability (CR or PR) [a]	
	At 6 months (%)	76.7
	95% CI [b]	(63.2 , 85.7)
	At 12 months (%)	64.1
	95% CI [b]	(49.4 , 75.5)
	At 24 months (%)	39.9
	95% CI [b]	(23.9 , 55.5)

Notes: CR: Complete response; PR: Partial response, PD: progressive disease. Percentage is calculated using number of subjects with CR/PR as the denominator. Best overall response (CR/PR) with confirmation was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate. For point estimates asymptotic normality to the log-log transformation of rates was applied.

[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.

NE - Not Evaluable

Table 54 Duration of response based on ICR by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Renal impairment at baseline:		
Mild Impairment (N=69)	Duration of response (CR or PR), months	
	Subjects with CR/PR	45
	Subjects with events (%)	13 (28.9)
	Subjects censored (%)	32 (71.1)
	Ongoing without PD (%)	31 (68.9)
	Other (%)	1 (2.2)
	25th percentile [a]	10.6
	95% CI	(5.6 , 18.2)
	Median [a]	23.7
	95% CI	(15.0 , NE)
	Response probability (CR or PR) [a]	
	At 6 months (%)	89.4
	95% CI [b]	(74.0 , 95.9)
	At 12 months (%)	70.8
	95% CI [b]	(50.5 , 84.0)
	At 24 months (%)	47.8
	95% CI [b]	(24.8 , 67.7)

Notes: CR: Complete response; PR: Partial response, PD: progressive disease. Percentage is calculated using number of subjects with CR/PR as the denominator. Best overall response (CR/PR) with confirmation was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate. For point estimates asymptotic normality to the log-log transformation of rates was applied.

[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.

NE - Not Evaluable

Table 54 Duration of response based on ICR by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Renal impairment at baseline:		
Moderate Impairment (N=25)	Duration of response (CR or PR), months	
	Subjects with CR/PR	9
	Subjects with events (%)	5 (55.6)
	Subjects censored (%)	4 (44.4)
	Ongoing without PD (%)	4 (44.4)
	25th percentile [a]	7.9
	95% CI	(5.6 , 16.9)
	Median [a]	14.2
	95% CI	(5.6 , 21.5)
	Response probability (CR or PR) [a]	
	At 6 months (%)	83.3
	95% CI [b]	(27.3 , 97.5)
	At 12 months (%)	50.0
	95% CI [b]	(11.1 , 80.4)
	At 24 months (%)	NE
	95% CI [b]	(NE, NE)

Notes: CR: Complete response; PR: Partial response, PD: progressive disease. Percentage is calculated using number of subjects with CR/PR as the denominator. Best overall response (CR/PR) with confirmation was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate. For point estimates asymptotic normality to the log-log transformation of rates was applied.

[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.

NE - Not Evaluable

Table 54 Duration of response based on ICR by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Hepatic impairment at baseline:		
Within Normal Range (N=105)	Duration of response (CR or PR), months	
	Subjects with CR/PR	68
	Subjects with events (%)	26 (38.2)
	Subjects censored (%)	42 (61.8)
	Ongoing without PD (%)	41 (60.3)
	Other (%)	1 (1.5)
	25th percentile [a]	9.7
	95% CI	(5.7 , 14.8)
	Median [a]	21.5
	95% CI	(14.8 , NE)
	Response probability (CR or PR) [a]	
	At 6 months (%)	85.2
	95% CI [b]	(73.5 , 92.1)
	At 12 months (%)	69.5
	95% CI [b]	(55.3 , 79.9)
	At 24 months (%)	44.6
	95% CI [b]	(28.8 , 59.3)

Notes: CR: Complete response; PR: Partial response, PD: progressive disease. Percentage is calculated using number of subjects with CR/PR as the denominator. Best overall response (CR/PR) with confirmation was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate. For point estimates asymptotic normality to the log-log transformation of rates was applied.

[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.

NE - Not Evaluable

Table 54 Duration of response based on ICR by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Hepatic impairment at baseline:		
Mild Impairment (N=76)	Duration of response (CR or PR), months	
	Subjects with CR/PR	45
	Subjects with events (%)	19 (42.2)
	Subjects censored (%)	26 (57.8)
	Ongoing without PD (%)	25 (55.6)
	Other (%)	1 (2.2)
	25th percentile [a]	7.4
	95% CI	(4.2 , 11.5)
	Median [a]	17.8
	95% CI	(10.0 , NE)
	Response probability (CR or PR) [a]	
	At 6 months (%)	75.7
	95% CI [b]	(58.4 , 86.6)
	At 12 months (%)	60.0
	95% CI [b]	(41.7 , 74.2)
	At 24 months (%)	26.5
	95% CI [b]	(6.7 , 52.0)

Notes: CR: Complete response; PR: Partial response, PD: progressive disease. Percentage is calculated using number of subjects with CR/PR as the denominator. Best overall response (CR/PR) with confirmation was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate. For point estimates asymptotic normality to the log-log transformation of rates was applied.

[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.

NE - Not Evaluable

Table 54 Duration of response based on ICR by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Best response to T-DM1 therapy:		
CR/PR/SD (N=79)	Duration of response (CR or PR), months	
	Subjects with CR/PR	50
	Subjects with events (%)	24 (48)
	Subjects censored (%)	26 (52)
	Ongoing without PD (%)	24 (48)
	Other (%)	2 (4)
	25th percentile [a]	9.0
	95% CI	(5.5 , 12.5)
	Median [a]	15.5
	95% CI	(11.4 , 22.4)
	Response probability (CR or PR) [a]	
	At 6 months (%)	83.3
	95% CI [b]	(68.0 , 91.7)
	At 12 months (%)	62.2
	95% CI [b]	(45.1 , 75.3)
	At 24 months (%)	22.8
	95% CI [b]	(7.6 , 42.7)

Notes: CR: Complete response; PR: Partial response, PD: progressive disease. Percentage is calculated using number of subjects with CR/PR as the denominator. Best overall response (CR/PR) with confirmation was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate. For point estimates asymptotic normality to the log-log transformation of rates was applied.

[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.

NE - Not Evaluable

Table 54 Duration of response based on ICR by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Best response to T-DM1 therapy:		
PD (N=66)	Duration of response (CR or PR), months	
	Subjects with CR/PR	43
	Subjects with events (%)	16 (37.2)
	Subjects censored (%)	27 (62.8)
	Ongoing without PD (%)	27 (62.8)
	25th percentile [a]	5.7
	95% CI	(3.7 , 14.8)
	Median [a]	NE
	95% CI	(9.7 , NE)
	Response probability (CR or PR) [a]	
	At 6 months (%)	74.6
	95% CI [b]	(57.8 , 85.5)
	At 12 months (%)	64.9
	95% CI [b]	(46.9 , 78.1)
	At 24 months (%)	50.2
	95% CI [b]	(30.3 , 67.2)

Notes: CR: Complete response; PR: Partial response, PD: progressive disease. Percentage is calculated using number of subjects with CR/PR as the denominator. Best overall response (CR/PR) with confirmation was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate. For point estimates asymptotic normality to the log-log transformation of rates was applied.

[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.

NE - Not Evaluable

Table 54 Duration of response based on ICR by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Brain metastases:		
Yes (N=24)	Duration of response (CR or PR), months	
	Subjects with CR/PR	14
	Subjects with events (%)	6 (42.9)
	Subjects censored (%)	8 (57.1)
	Ongoing without PD (%)	8 (57.1)
	25th percentile [a]	16.9
	95% CI	(2.0 , 22.4)
	Median [a]	22.4
	95% CI	(5.7 , NE)
	Response probability (CR or PR) [a]	
	At 6 months (%)	76.0
	95% CI [b]	(42.2 , 91.6)
	At 12 months (%)	76.0
	95% CI [b]	(42.2 , 91.6)
	At 24 months (%)	33.8
	95% CI [b]	(6.1 , 65.7)

Notes: CR: Complete response; PR: Partial response, PD: progressive disease. Percentage is calculated using number of subjects with CR/PR as the denominator. Best overall response (CR/PR) with confirmation was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate. For point estimates asymptotic normality to the log-log transformation of rates was applied.

[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.

NE - Not Evaluable

Table 54 Duration of response based on ICR by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Brain metastases:		
No (N=160)	Duration of response (CR or PR), months	
	Subjects with CR/PR	100
	Subjects with events (%)	39 (39)
	Subjects censored (%)	61 (61)
	Ongoing without PD (%)	59 (59)
	Other (%)	2 (2)
	25th percentile [a]	9.0
	95% CI	(5.6 , 11.5)
	Median [a]	18.2
	95% CI	(13.8 , NE)
	Response probability (CR or PR) [a]	
	At 6 months (%)	82.6
	95% CI [b]	(72.7 , 89.2)
	At 12 months (%)	64.5
	95% CI [b]	(52.7 , 74.1)
	At 24 months (%)	40.2
	95% CI [b]	(26.0 , 54.0)

Notes: CR: Complete response; PR: Partial response, PD: progressive disease. Percentage is calculated using number of subjects with CR/PR as the denominator. Best overall response (CR/PR) with confirmation was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate. For point estimates asymptotic normality to the log-log transformation of rates was applied.

[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.

NE - Not Evaluable

Table 54 Duration of response based on ICR by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Bone metastases:		
Yes (N=53)	Duration of response (CR or PR), months	
	Subjects with CR/PR	28
	Subjects with events (%)	14 (50)
	Subjects censored (%)	14 (50)
	Ongoing without PD (%)	14 (50)
	25th percentile [a]	7.9
	95% CI	(4.5 , 11.4)
	Median [a]	15.0
	95% CI	(7.9 , 20.8)
	Response probability (CR or PR) [a]	
	At 6 months (%)	83.7
	95% CI [b]	(62.2 , 93.6)
	At 12 months (%)	56.1
	95% CI [b]	(33.4 , 73.7)
	At 24 months (%)	23.3
	95% CI [b]	(5.1 , 49.1)

Notes: CR: Complete response; PR: Partial response, PD: progressive disease. Percentage is calculated using number of subjects with CR/PR as the denominator. Best overall response (CR/PR) with confirmation was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate. For point estimates asymptotic normality to the log-log transformation of rates was applied.

[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.

NE - Not Evaluable

Table 54 Duration of response based on ICR by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Bone metastases:		
No (N=131)	Duration of response (CR or PR), months	
	Subjects with CR/PR	86
	Subjects with events (%)	31 (36)
	Subjects censored (%)	55 (64)
	Ongoing without PD (%)	53 (61.6)
	Other (%)	2 (2.3)
	25th percentile [a]	9.7
	95% CI	(5.6 , 14.8)
	Median [a]	22.4
	95% CI	(15.5 , NE)
	Response probability (CR or PR) [a]	
	At 6 months (%)	81.0
	95% CI [b]	(70.0 , 88.3)
	At 12 months (%)	69.4
	95% CI [b]	(56.8 , 79.0)
	At 24 months (%)	43.0
	95% CI [b]	(26.9 , 58.1)

Notes: CR: Complete response; PR: Partial response, PD: progressive disease. Percentage is calculated using number of subjects with CR/PR as the denominator. Best overall response (CR/PR) with confirmation was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate. For point estimates asymptotic normality to the log-log transformation of rates was applied.

[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.

NE - Not Evaluable

Table 54 Duration of response based on ICR by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
History of visceral disease:		
Yes (N=169)	Duration of response (CR or PR), months	
	Subjects with CR/PR	104
	Subjects with events (%)	40 (38.5)
	Subjects censored (%)	64 (61.5)
	Ongoing without PD (%)	62 (59.6)
	Other (%)	2 (1.9)
	25th percentile [a]	9.7
	95% CI	(5.6 , 12.5)
	Median [a]	18.2
	95% CI	(15.0 , NE)
	Response probability (CR or PR) [a]	
	At 6 months (%)	81.3
	95% CI [b]	(71.6 , 87.9)
	At 12 months (%)	66.8
	95% CI [b]	(55.5 , 75.9)
	At 24 months (%)	41.4
	95% CI [b]	(27.1 , 55.1)

Notes: CR: Complete response; PR: Partial response, PD: progressive disease. Percentage is calculated using number of subjects with CR/PR as the denominator. Best overall response (CR/PR) with confirmation was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate. For point estimates asymptotic normality to the log-log transformation of rates was applied.

[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.

NE - Not Evaluable

Table 54 Duration of response based on ICR by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
History of visceral disease:		
No (N=15)	Duration of response (CR or PR), months	
	Subjects with CR/PR	10
	Subjects with events (%)	5 (50)
	Subjects censored (%)	5 (50)
	Ongoing without PD (%)	5 (50)
	25th percentile [a]	8.3
	95% CI	(2.8 , 20.8)
	Median [a]	20.8
	95% CI	(2.8 , NE)
	Response probability (CR or PR) [a]	
	At 6 months (%)	90.0
	95% CI [b]	(47.3 , 98.5)
	At 12 months (%)	54.0
	95% CI [b]	(12.7 , 83.2)
	At 24 months (%)	18.0
	95% CI [b]	(0.8 , 54.2)

Notes: CR: Complete response; PR: Partial response, PD: progressive disease. Percentage is calculated using number of subjects with CR/PR as the denominator. Best overall response (CR/PR) with confirmation was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate. For point estimates asymptotic normality to the log-log transformation of rates was applied.

[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.

NE - Not Evaluable

Table 54 Duration of response based on ICR by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Age:		
<65 years (N=140)	Duration of response (CR or PR), months	
	Subjects with CR/PR	87
	Subjects with events (%)	32 (36.8)
	Subjects censored (%)	55 (63.2)
	Ongoing without PD (%)	53 (60.9)
	Other (%)	2 (2.3)
	25th percentile [a]	9.0
	95% CI	(5.6 , 13.8)
	Median [a]	20.8
	95% CI	(14.8 , NE)
	Response probability (CR or PR) [a]	
	At 6 months (%)	83.7
	95% CI [b]	(73.0 , 90.4)
	At 12 months (%)	65.9
	95% CI [b]	(53.1 , 76.0)
	At 24 months (%)	40.8
	95% CI [b]	(24.6 , 56.4)

Notes: CR: Complete response; PR: Partial response, PD: progressive disease. Percentage is calculated using number of subjects with CR/PR as the denominator. Best overall response (CR/PR) with confirmation was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate. For point estimates asymptotic normality to the log-log transformation of rates was applied.

[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.

NE - Not Evaluable

Table 54 Duration of response based on ICR by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Age:		
>=65 years (N=44)	Duration of response (CR or PR), months	
	Subjects with CR/PR	27
	Subjects with events (%)	13 (48.1)
	Subjects censored (%)	14 (51.9)
	Ongoing without PD (%)	14 (51.9)
	25th percentile [a]	9.7
	95% CI	(2.8 , 15.0)
	Median [a]	15.5
	95% CI	(9.7 , NE)
	Response probability (CR or PR) [a]	
	At 6 months (%)	76.0
	95% CI [b]	(54.0 , 88.4)
	At 12 months (%)	65.3
	95% CI [b]	(41.6 , 81.3)
	At 24 months (%)	28.8
	95% CI [b]	(8.8 , 53.0)

Notes: CR: Complete response; PR: Partial response, PD: progressive disease. Percentage is calculated using number of subjects with CR/PR as the denominator. Best overall response (CR/PR) with confirmation was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate. For point estimates asymptotic normality to the log-log transformation of rates was applied.

[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.

NE - Not Evaluable

Table 54 Duration of response based on ICR by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Region:		
Asia (N=63)	Duration of response (CR or PR), months	
	Subjects with CR/PR	39
	Subjects with events (%)	15 (38.5)
	Subjects censored (%)	24 (61.5)
	Ongoing without PD (%)	24 (61.5)
	25th percentile [a]	11.4
	95% CI	(5.4 , 16.9)
	Median [a]	22.4
	95% CI	(11.5 , NE)
	Response probability (CR or PR) [a]	
	At 6 months (%)	83.9
	95% CI [b]	(65.3 , 93.0)
	At 12 months (%)	69.6
	95% CI [b]	(49.4 , 82.9)
	At 24 months (%)	40.8
	95% CI [b]	(20.8 , 60.0)

Notes: CR: Complete response; PR: Partial response, PD: progressive disease. Percentage is calculated using number of subjects with CR/PR as the denominator. Best overall response (CR/PR) with confirmation was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate. For point estimates asymptotic normality to the log-log transformation of rates was applied.

[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.

NE - Not Evaluable

Table 54 Duration of response based on ICR by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Region:		
North America (N=53)	Duration of response (CR or PR), months	
	Subjects with CR/PR	33
	Subjects with events (%)	11 (33.3)
	Subjects censored (%)	22 (66.7)
	Ongoing without PD (%)	20 (60.6)
	Other (%)	2 (6.1)
	25th percentile [a]	9.7
	95% CI	(2.9 , 18.2)
	Median [a]	21.5
	95% CI	(9.7 , NE)
	Response probability (CR or PR) [a]	
	At 6 months (%)	86.5
	95% CI [b]	(67.9 , 94.7)
	At 12 months (%)	69.7
	95% CI [b]	(48.0 , 83.7)
	At 24 months (%)	34.1
	95% CI [b]	(7.2 , 64.4)

Notes: CR: Complete response; PR: Partial response, PD: progressive disease. Percentage is calculated using number of subjects with CR/PR as the denominator. Best overall response (CR/PR) with confirmation was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate. For point estimates asymptotic normality to the log-log transformation of rates was applied.

[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.

NE - Not Evaluable

Table 54 Duration of response based on ICR by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Region:		
EU (N=68)	Duration of response (CR or PR), months	
	Subjects with CR/PR	42
	Subjects with events (%)	19 (45.2)
	Subjects censored (%)	23 (54.8)
	Ongoing without PD (%)	23 (54.8)
	25th percentile [a]	6.9
	95% CI	(3.7 , 10.6)
	Median [a]	16.5
	95% CI	(9.7 , NE)
	Response probability (CR or PR) [a]	
	At 6 months (%)	75.8
	95% CI [b]	(58.5 , 86.6)
	At 12 months (%)	60.0
	95% CI [b]	(41.7 , 74.2)
	At 24 months (%)	40.6
	95% CI [b]	(22.9 , 57.6)

Notes: CR: Complete response; PR: Partial response, PD: progressive disease. Percentage is calculated using number of subjects with CR/PR as the denominator. Best overall response (CR/PR) with confirmation was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate. For point estimates asymptotic normality to the log-log transformation of rates was applied.

[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.

NE - Not Evaluable

Table 54 Duration of response based on ICR by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
ECOG performance status:		
0 (N=102)	Duration of response (CR or PR), months	
	Subjects with CR/PR	68
	Subjects with events (%)	26 (38.2)
	Subjects censored (%)	42 (61.8)
	Ongoing without PD (%)	41 (60.3)
	Other (%)	1 (1.5)
	25th percentile [a]	9.7
	95% CI	(5.7 , 14.8)
	Median [a]	21.5
	95% CI	(13.8 , NE)
	Response probability (CR or PR) [a]	
	At 6 months (%)	83.1
	95% CI [b]	(70.6 , 90.6)
	At 12 months (%)	66.8
	95% CI [b]	(52.3 , 77.8)
	At 24 months (%)	40.6
	95% CI [b]	(23.6 , 56.9)

Notes: CR: Complete response; PR: Partial response, PD: progressive disease. Percentage is calculated using number of subjects with CR/PR as the denominator. Best overall response (CR/PR) with confirmation was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate. For point estimates asymptotic normality to the log-log transformation of rates was applied.

[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.

NE - Not Evaluable

Table 54 Duration of response based on ICR by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
ECOG performance status:		
1 (N=81)	Duration of response (CR or PR), months	
	Subjects with CR/PR	46
	Subjects with events (%)	19 (41.3)
	Subjects censored (%)	27 (58.7)
	Ongoing without PD (%)	26 (56.5)
	Other (%)	1 (2.2)
	25th percentile [a]	7.9
	95% CI	(4.6 , 15.0)
	Median [a]	18.2
	95% CI	(11.5 , NE)
	Response probability (CR or PR) [a]	
	At 6 months (%)	79.8
	95% CI [b]	(63.6 , 89.4)
	At 12 months (%)	64.5
	95% CI [b]	(46.4 , 77.9)
	At 24 months (%)	38.1
	95% CI [b]	(19.4 , 56.7)

Notes: CR: Complete response; PR: Partial response, PD: progressive disease. Percentage is calculated using number of subjects with CR/PR as the denominator. Best overall response (CR/PR) with confirmation was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate. For point estimates asymptotic normality to the log-log transformation of rates was applied.

[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.

NE - Not Evaluable

Table 54 Duration of response based on ICR by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Baseline sum of diameters of target lesions:		
<5 cm (N=74)	Duration of response (CR or PR), months	
	Subjects with CR/PR	49
	Subjects with events (%)	15 (30.6)
	Subjects censored (%)	34 (69.4)
	Ongoing without PD (%)	33 (67.3)
	Other (%)	1 (2)
	25th percentile [a]	15.5
	95% CI	(5.7 , 21.5)
	Median [a]	23.7
	95% CI	(16.5 , NE)
	Response probability (CR or PR) [a]	
	At 6 months (%)	88.3
	95% CI [b]	(74.0 , 95.0)
	At 12 months (%)	82.4
	95% CI [b]	(66.3 , 91.3)
	At 24 months (%)	43.4
	95% CI [b]	(20.8 , 64.2)

Notes: CR: Complete response; PR: Partial response, PD: progressive disease. Percentage is calculated using number of subjects with CR/PR as the denominator. Best overall response (CR/PR) with confirmation was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate. For point estimates asymptotic normality to the log-log transformation of rates was applied.

[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.

NE - Not Evaluable

Table 54 Duration of response based on ICR by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
Baseline sum of diameters of target lesions:		
>=5 cm (N=96)	Duration of response (CR or PR), months	
	Subjects with CR/PR	63
	Subjects with events (%)	30 (47.6)
	Subjects censored (%)	33 (52.4)
	Ongoing without PD (%)	32 (50.8)
	Other (%)	1 (1.6)
	25th percentile [a]	6.9
	95% CI	(5.4 , 9.7)
	Median [a]	15.0
	95% CI	(9.7 , 18.2)
	Response probability (CR or PR) [a]	
	At 6 months (%)	76.5
	95% CI [b]	(62.9 , 85.7)
	At 12 months (%)	52.8
	95% CI [b]	(37.9 , 65.7)
	At 24 months (%)	33.9
	95% CI [b]	(19.4 , 49.0)

Notes: CR: Complete response; PR: Partial response, PD: progressive disease. Percentage is calculated using number of subjects with CR/PR as the denominator. Best overall response (CR/PR) with confirmation was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate. For point estimates asymptotic normality to the log-log transformation of rates was applied.

[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.

NE - Not Evaluable

Table 54 Duration of response based on ICR by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
DS-8201a immediately following initial T-DM1:		
Yes (N=56)	Duration of response (CR or PR), months	
	Subjects with CR/PR	39
	Subjects with events (%)	12 (30.8)
	Subjects censored (%)	27 (69.2)
	Ongoing without PD (%)	27 (69.2)
	25th percentile [a]	14.8
	95% CI	(3.7 , 23.7)
	Median [a]	NE
	95% CI	(15.5 , NE)
	Response probability (CR or PR) [a]	
	At 6 months (%)	85.5
	95% CI [b]	(68.5 , 93.7)
	At 12 months (%)	75.3
	95% CI [b]	(56.3 , 86.9)
	At 24 months (%)	51.7
	95% CI [b]	(27.5 , 71.5)

Notes: CR: Complete response; PR: Partial response, PD: progressive disease. Percentage is calculated using number of subjects with CR/PR as the denominator. Best overall response (CR/PR) with confirmation was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate. For point estimates asymptotic normality to the log-log transformation of rates was applied.

[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.

NE - Not Evaluable

Table 54 Duration of response based on ICR by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
DS-8201a immediately following initial T-DM1:		
No (N=128)	Duration of response (CR or PR), months	
	Subjects with CR/PR	75
	Subjects with events (%)	33 (44)
	Subjects censored (%)	42 (56)
	Ongoing without PD (%)	40 (53.3)
	Other (%)	2 (2.7)
	25th percentile [a]	8.3
	95% CI	(5.6 , 10.6)
	Median [a]	16.9
	95% CI	(10.6 , 22.4)
	Response probability (CR or PR) [a]	
	At 6 months (%)	79.9
	95% CI [b]	(67.8 , 87.8)
	At 12 months (%)	60.7
	95% CI [b]	(46.7 , 72.2)
	At 24 months (%)	32.3
	95% CI [b]	(18.0 , 47.4)

Notes: CR: Complete response; PR: Partial response, PD: progressive disease. Percentage is calculated using number of subjects with CR/PR as the denominator. Best overall response (CR/PR) with confirmation was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate. For point estimates asymptotic normality to the log-log transformation of rates was applied.

[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.

NE - Not Evaluable

Table 54 Duration of response based on ICR by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
HER2 status:		
IHC3+ (N=154)	Duration of response (CR or PR), months	
	Subjects with CR/PR	99
	Subjects with events (%)	36 (36.4)
	Subjects censored (%)	63 (63.6)
	Ongoing without PD (%)	61 (61.6)
	Other (%)	2 (2)
	25th percentile [a]	10.6
	95% CI	(5.7 , 15.5)
	Median [a]	21.5
	95% CI	(16.5 , NE)
	Response probability (CR or PR) [a]	
	At 6 months (%)	83.6
	95% CI [b]	(73.8 , 90.0)
	At 12 months (%)	70.9
	95% CI [b]	(59.3 , 79.7)
	At 24 months (%)	41.4
	95% CI [b]	(26.6 , 55.6)

Notes: CR: Complete response; PR: Partial response, PD: progressive disease. Percentage is calculated using number of subjects with CR/PR as the denominator. Best overall response (CR/PR) with confirmation was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate. For point estimates asymptotic normality to the log-log transformation of rates was applied.

[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.

NE - Not Evaluable

Table 54 Duration of response based on ICR by subgroup - Enrolled Analysis Set

Subgroup		Overall 5.4 mg/kg (N=184)
HER2 status:		
ISH+ except IHC3+ (N=28)	Duration of response (CR or PR), months	
	Subjects with CR/PR	13
	Subjects with events (%)	7 (53.8)
	Subjects censored (%)	6 (46.2)
	Ongoing without PD (%)	6 (46.2)
	25th percentile [a]	3.7
	95% CI	(2.8 , 10.0)
	Median [a]	10.0
	95% CI	(2.9 , NE)
	Response probability (CR or PR) [a]	
	At 6 months (%)	74.1
	95% CI [b]	(39.1 , 90.9)
	At 12 months (%)	42.3
	95% CI [b]	(13.5 , 69.1)
	At 24 months (%)	21.2
	95% CI [b]	(1.4 , 56.7)

Notes: CR: Complete response; PR: Partial response, PD: progressive disease. Percentage is calculated using number of subjects with CR/PR as the denominator. Best overall response (CR/PR) with confirmation was assessed by independent central review using RECIST criteria, Version 1.1. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] Median, 25th percentile, and point estimates at 6, 12, and 24 months are based on Kaplan-Meier Estimate. For point estimates asymptotic normality to the log-log transformation of rates was applied.

[b] 95% confidence interval (CI) is computed using the Brookmeyer-Crowley method.

NE - Not Evaluable

Table 16 Summary of treatment-emergent adverse events overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
Any TEAE	183 (99.5)	(97.0, 100.0)
Estrogen receptors		
Positive (N=93)	92 (98.9)	(94.2, 100.0)
Negative (N=88)	88 (100.0)	(95.9, 100.0)
Progesterone receptors		
Positive (N=51)	50 (98.0)	(89.6, 100.0)
Negative (N=125)	125 (100.0)	(97.1, 100.0)
Hormone receptors		
Positive (N=97)	96 (99.0)	(94.4, 100.0)
Negative (N=83)	83 (100.0)	(95.7, 100.0)
Lines of prior systemic therapy not including hormone therapy		
< 3 lines (N=17)	17 (100.0)	(80.5, 100.0)
>= 3 lines (N=167)	166 (99.4)	(96.7, 100.0)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 16 Summary of treatment-emergent adverse events overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
Prior pertuzumab		
Yes (N=121)	121 (100.0)	(97.0, 100.0)
No (N=63)	62 (98.4)	(91.5, 100.0)
Prior pertuzumab in 1st or 2nd line in advanced/metastatic breast cancer		
Yes (N=51)	51 (100.0)	(93.0, 100.0)
No (N=133)	132 (99.2)	(95.9, 100.0)
Renal impairment at baseline		
Within Normal Range (N=90)	89 (98.9)	(94.0, 100.0)
Mild Impairment (N=69)	69 (100.0)	(94.8, 100.0)
Moderate Impairment (N=25)	25 (100.0)	(86.3, 100.0)
Hepatic impairment at baseline		
Within Normal Range (N=105)	104 (99.0)	(94.8, 100.0)
Mild Impairment (N=76)	76 (100.0)	(95.3, 100.0)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 16 Summary of treatment-emergent adverse events overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
Best response to T-DM1 therapy		
CR/PR/SD (N=79)	78 (98.7)	(93.1, 100.0)
PD (N=66)	66 (100.0)	(94.6, 100.0)
Brain metastases		
Yes (N=24)	24 (100.0)	(85.8, 100.0)
No (N=160)	159 (99.4)	(96.6, 100.0)
Bone metastases		
Yes (N=53)	53 (100.0)	(93.3, 100.0)
No (N=131)	130 (99.2)	(95.8, 100.0)
History of visceral disease		
Yes (N=169)	168 (99.4)	(96.7, 100.0)
No (N=15)	15 (100.0)	(78.2, 100.0)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 16 Summary of treatment-emergent adverse events overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
Age		
<65 years (N=140)	139 (99.3)	(96.1, 100.0)
>=65 years (N=44)	44 (100.0)	(92.0, 100.0)
Region		
Asia (N=63)	63 (100.0)	(94.3, 100.0)
North America (N=53)	53 (100.0)	(93.3, 100.0)
EU (N=68)	67 (98.5)	(92.1, 100.0)
ECOG performance status		
0 (N=102)	101 (99.0)	(94.7, 100.0)
1 (N=81)	81 (100.0)	(95.5, 100.0)
Baseline sum of diameters of target lesions		
<5 cm (N=74)	74 (100.0)	(95.1, 100.0)
>=5 cm (N=96)	95 (99.0)	(94.3, 100.0)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 16 Summary of treatment-emergent adverse events overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
DS-8201a immediately following initial T-DM1		
Yes (N=56)	56 (100.0)	(93.6, 100.0)
No (N=128)	127 (99.2)	(95.7, 100.0)
HER2 status		
IHC3+ (N=154)	153 (99.4)	(96.4, 100.0)
ISH+ except IHC3+ (N=28)	28 (100.0)	(87.7, 100.0)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 18 Summary of treatment-emergent adverse events by worst CTCAE grade overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	Worst CTCAE Grade	n (%)	95% CI [a]
Overall			
	Worst CTCAE Grade 1	10 (5.4)	(2.6, 9.8)
	Worst CTCAE Grade 2	57 (31.0)	(24.4, 38.2)
	Worst CTCAE Grade 3	99 (53.8)	(46.3, 61.2)
	Worst CTCAE Grade 4	7 (3.8)	(1.5, 7.7)
	Worst CTCAE Grade 5	10 (5.4)	(2.6, 9.8)

Notes: CTCAE: Common Terminology Criteria for Adverse Events; TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

NE - Not Evaluable

Table 18 Summary of treatment-emergent adverse events by worst CTCAE grade overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	Worst CTCAE Grade	n (%)	95% CI [a]
Estrogen receptors			
Positive (N = 93)			
	Worst CTCAE Grade 1	4 (4.3)	(1.2, 10.6)
	Worst CTCAE Grade 2	29 (31.2)	(22.0, 41.6)
	Worst CTCAE Grade 3	49 (52.7)	(42.1, 63.1)
	Worst CTCAE Grade 4	6 (6.5)	(2.4, 13.5)
	Worst CTCAE Grade 5	4 (4.3)	(1.2, 10.6)
Negative (N = 88)			
	Worst CTCAE Grade 1	5 (5.7)	(1.9, 12.8)
	Worst CTCAE Grade 2	27 (30.7)	(21.3, 41.4)
	Worst CTCAE Grade 3	50 (56.8)	(45.8, 67.3)
	Worst CTCAE Grade 4	1 (1.1)	(0.0, 6.2)
	Worst CTCAE Grade 5	5 (5.7)	(1.9, 12.8)

Notes: CTCAE: Common Terminology Criteria for Adverse Events; TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

NE - Not Evaluable

Table 18 Summary of treatment-emergent adverse events by worst CTCAE grade overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	Worst CTCAE Grade	n (%)	95% CI [a]
Progesterone receptors			
Positive (N = 51)			
	Worst CTCAE Grade 1	2 (3.9)	(0.5, 13.5)
	Worst CTCAE Grade 2	18 (35.3)	(22.4, 49.9)
	Worst CTCAE Grade 3	27 (52.9)	(38.5, 67.1)
	Worst CTCAE Grade 4	1 (2.0)	(0.0, 10.4)
	Worst CTCAE Grade 5	2 (3.9)	(0.5, 13.5)
Negative (N = 125)			
	Worst CTCAE Grade 1	6 (4.8)	(1.8, 10.2)
	Worst CTCAE Grade 2	36 (28.8)	(21.1, 37.6)
	Worst CTCAE Grade 3	70 (56.0)	(46.8, 64.9)
	Worst CTCAE Grade 4	6 (4.8)	(1.8, 10.2)
	Worst CTCAE Grade 5	7 (5.6)	(2.3, 11.2)

Notes: CTCAE: Common Terminology Criteria for Adverse Events; TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

NE - Not Evaluable

Table 18 Summary of treatment-emergent adverse events by worst CTCAE grade overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	Worst CTCAE Grade	n (%)	95% CI [a]
Hormone receptors			
Positive (N = 97)			
	Worst CTCAE Grade 1	4 (4.1)	(1.1, 10.2)
	Worst CTCAE Grade 2	30 (30.9)	(21.9, 41.1)
	Worst CTCAE Grade 3	52 (53.6)	(43.2, 63.8)
	Worst CTCAE Grade 4	6 (6.2)	(2.3, 13.0)
	Worst CTCAE Grade 5	4 (4.1)	(1.1, 10.2)
Negative (N = 83)			
	Worst CTCAE Grade 1	5 (6.0)	(2.0, 13.5)
	Worst CTCAE Grade 2	25 (30.1)	(20.5, 41.2)
	Worst CTCAE Grade 3	47 (56.6)	(45.3, 67.5)
	Worst CTCAE Grade 4	1 (1.2)	(0.0, 6.5)
	Worst CTCAE Grade 5	5 (6.0)	(2.0, 13.5)

Notes: CTCAE: Common Terminology Criteria for Adverse Events; TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

NE - Not Evaluable

Table 18 Summary of treatment-emergent adverse events by worst CTCAE grade overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	Worst CTCAE Grade	n (%)	95% CI [a]
Lines of prior systemic therapy not including hormone therapy			
< 3 lines (N = 17)			
	Worst CTCAE Grade 1	2 (11.8)	(1.5, 36.4)
	Worst CTCAE Grade 2	4 (23.5)	(6.8, 49.9)
	Worst CTCAE Grade 3	10 (58.8)	(32.9, 81.6)
	Worst CTCAE Grade 4	0 (0.0)	(NE, NE)
	Worst CTCAE Grade 5	1 (5.9)	(0.1, 28.7)
>= 3 lines (N = 167)			
	Worst CTCAE Grade 1	8 (4.8)	(2.1, 9.2)
	Worst CTCAE Grade 2	53 (31.7)	(24.8, 39.4)
	Worst CTCAE Grade 3	89 (53.3)	(45.4, 61.0)
	Worst CTCAE Grade 4	7 (4.2)	(1.7, 8.4)
	Worst CTCAE Grade 5	9 (5.4)	(2.5, 10.0)

Notes: CTCAE: Common Terminology Criteria for Adverse Events; TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

NE - Not Evaluable

Table 18 Summary of treatment-emergent adverse events by worst CTCAE grade overall and by subgroup - Safety Analysis Set

Subgroup	Worst CTCAE Grade	Overall 5.4 mg/kg (N = 184) n (%)	95% CI [a]
Prior pertuzumab			
Yes (N = 121)			
	Worst CTCAE Grade 1	5 (4.1)	(1.4, 9.4)
	Worst CTCAE Grade 2	44 (36.4)	(27.8, 45.6)
	Worst CTCAE Grade 3	64 (52.9)	(43.6, 62.0)
	Worst CTCAE Grade 4	4 (3.3)	(0.9, 8.2)
	Worst CTCAE Grade 5	4 (3.3)	(0.9, 8.2)
No (N = 63)			
	Worst CTCAE Grade 1	5 (7.9)	(2.6, 17.6)
	Worst CTCAE Grade 2	13 (20.6)	(11.5, 32.7)
	Worst CTCAE Grade 3	35 (55.6)	(42.5, 68.1)
	Worst CTCAE Grade 4	3 (4.8)	(1.0, 13.3)
	Worst CTCAE Grade 5	6 (9.5)	(3.6, 19.6)

Notes: CTCAE: Common Terminology Criteria for Adverse Events; TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

NE - Not Evaluable

Table 18 Summary of treatment-emergent adverse events by worst CTCAE grade overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	Worst CTCAE Grade	n (%)	95% CI [a]
Prior pertuzumab in 1st or 2nd line in advanced/metastatic breast cancer			
Yes (N = 51)			
	Worst CTCAE Grade 1	2 (3.9)	(0.5, 13.5)
	Worst CTCAE Grade 2	18 (35.3)	(22.4, 49.9)
	Worst CTCAE Grade 3	28 (54.9)	(40.3, 68.9)
	Worst CTCAE Grade 4	1 (2.0)	(0.0, 10.4)
	Worst CTCAE Grade 5	2 (3.9)	(0.5, 13.5)
No (N = 133)			
	Worst CTCAE Grade 1	8 (6.0)	(2.6, 11.5)
	Worst CTCAE Grade 2	39 (29.3)	(21.8, 37.8)
	Worst CTCAE Grade 3	71 (53.4)	(44.5, 62.1)
	Worst CTCAE Grade 4	6 (4.5)	(1.7, 9.6)
	Worst CTCAE Grade 5	8 (6.0)	(2.6, 11.5)

Notes: CTCAE: Common Terminology Criteria for Adverse Events; TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

NE - Not Evaluable

Table 18 Summary of treatment-emergent adverse events by worst CTCAE grade overall and by subgroup - Safety Analysis Set

Subgroup	Worst CTCAE Grade	Overall 5.4 mg/kg (N = 184) n (%)	95% CI [a]
Renal impairment at baseline			
Within Normal Range (N = 90)			
	Worst CTCAE Grade 1	5 (5.6)	(1.8, 12.5)
	Worst CTCAE Grade 2	29 (32.2)	(22.8, 42.9)
	Worst CTCAE Grade 3	44 (48.9)	(38.2, 59.7)
	Worst CTCAE Grade 4	5 (5.6)	(1.8, 12.5)
	Worst CTCAE Grade 5	6 (6.7)	(2.5, 13.9)
Mild Impairment (N = 69)			
	Worst CTCAE Grade 1	3 (4.3)	(0.9, 12.2)
	Worst CTCAE Grade 2	19 (27.5)	(17.5, 39.6)
	Worst CTCAE Grade 3	44 (63.8)	(51.3, 75.0)
	Worst CTCAE Grade 4	1 (1.4)	(0.0, 7.8)
	Worst CTCAE Grade 5	2 (2.9)	(0.4, 10.1)

Notes: CTCAE: Common Terminology Criteria for Adverse Events; TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

NE - Not Evaluable

Table 18 Summary of treatment-emergent adverse events by worst CTCAE grade overall and by subgroup - Safety Analysis Set

Subgroup	Worst CTCAE Grade	Overall 5.4 mg/kg (N = 184) n (%)	95% CI [a]
Renal impairment at baseline			
Moderate Impairment (N = 25)			
	Worst CTCAE Grade 1	2 (8.0)	(1.0, 26.0)
	Worst CTCAE Grade 2	9 (36.0)	(18.0, 57.5)
	Worst CTCAE Grade 3	11 (44.0)	(24.4, 65.1)
	Worst CTCAE Grade 4	1 (4.0)	(0.1, 20.4)
	Worst CTCAE Grade 5	2 (8.0)	(1.0, 26.0)

Notes: CTCAE: Common Terminology Criteria for Adverse Events; TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

NE - Not Evaluable

Table 18 Summary of treatment-emergent adverse events by worst CTCAE grade overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	Worst CTCAE Grade	n (%)	95% CI [a]
Hepatic impairment at baseline			
Within Normal Range (N = 105)			
	Worst CTCAE Grade 1	4 (3.8)	(1.0, 9.5)
	Worst CTCAE Grade 2	27 (25.7)	(17.7, 35.2)
	Worst CTCAE Grade 3	63 (60.0)	(50.0, 69.4)
	Worst CTCAE Grade 4	3 (2.9)	(0.6, 8.1)
	Worst CTCAE Grade 5	7 (6.7)	(2.7, 13.3)
Mild Impairment (N = 76)			
	Worst CTCAE Grade 1	6 (7.9)	(3.0, 16.4)
	Worst CTCAE Grade 2	30 (39.5)	(28.4, 51.4)
	Worst CTCAE Grade 3	33 (43.4)	(32.1, 55.3)
	Worst CTCAE Grade 4	4 (5.3)	(1.5, 12.9)
	Worst CTCAE Grade 5	3 (3.9)	(0.8, 11.1)

Notes: CTCAE: Common Terminology Criteria for Adverse Events; TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

NE - Not Evaluable

Table 18 Summary of treatment-emergent adverse events by worst CTCAE grade overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	Worst CTCAE Grade	n (%)	95% CI [a]
Best response to T-DM1 therapy			
CR/PR/SD (N = 79)			
	Worst CTCAE Grade 1	5 (6.3)	(2.1, 14.2)
	Worst CTCAE Grade 2	22 (27.8)	(18.3, 39.1)
	Worst CTCAE Grade 3	46 (58.2)	(46.6, 69.2)
	Worst CTCAE Grade 4	3 (3.8)	(0.8, 10.7)
	Worst CTCAE Grade 5	2 (2.5)	(0.3, 8.8)
PD (N = 66)			
	Worst CTCAE Grade 1	5 (7.6)	(2.5, 16.8)
	Worst CTCAE Grade 2	18 (27.3)	(17.0, 39.6)
	Worst CTCAE Grade 3	36 (54.5)	(41.8, 66.9)
	Worst CTCAE Grade 4	2 (3.0)	(0.4, 10.5)
	Worst CTCAE Grade 5	5 (7.6)	(2.5, 16.8)

Notes: CTCAE: Common Terminology Criteria for Adverse Events; TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

NE - Not Evaluable

Table 18 Summary of treatment-emergent adverse events by worst CTCAE grade overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	Worst CTCAE Grade	n (%)	95% CI [a]
Brain metastases			
Yes (N = 24)			
	Worst CTCAE Grade 1	3 (12.5)	(2.7, 32.4)
	Worst CTCAE Grade 2	6 (25.0)	(9.8, 46.7)
	Worst CTCAE Grade 3	13 (54.2)	(32.8, 74.4)
	Worst CTCAE Grade 4	0 (0.0)	(NE, NE)
	Worst CTCAE Grade 5	2 (8.3)	(1.0, 27.0)
No (N = 160)			
	Worst CTCAE Grade 1	7 (4.4)	(1.8, 8.8)
	Worst CTCAE Grade 2	51 (31.9)	(24.7, 39.7)
	Worst CTCAE Grade 3	86 (53.8)	(45.7, 61.7)
	Worst CTCAE Grade 4	7 (4.4)	(1.8, 8.8)
	Worst CTCAE Grade 5	8 (5.0)	(2.2, 9.6)

Notes: CTCAE: Common Terminology Criteria for Adverse Events; TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

NE - Not Evaluable

Table 18 Summary of treatment-emergent adverse events by worst CTCAE grade overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	Worst CTCAE Grade	n (%)	95% CI [a]
Bone metastases			
Yes (N = 53)			
	Worst CTCAE Grade 1	1 (1.9)	(0.0, 10.1)
	Worst CTCAE Grade 2	14 (26.4)	(15.3, 40.3)
	Worst CTCAE Grade 3	30 (56.6)	(42.3, 70.2)
	Worst CTCAE Grade 4	4 (7.5)	(2.1, 18.2)
	Worst CTCAE Grade 5	4 (7.5)	(2.1, 18.2)
No (N = 131)			
	Worst CTCAE Grade 1	9 (6.9)	(3.2, 12.6)
	Worst CTCAE Grade 2	43 (32.8)	(24.9, 41.6)
	Worst CTCAE Grade 3	69 (52.7)	(43.8, 61.5)
	Worst CTCAE Grade 4	3 (2.3)	(0.5, 6.5)
	Worst CTCAE Grade 5	6 (4.6)	(1.7, 9.7)

Notes: CTCAE: Common Terminology Criteria for Adverse Events; TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

NE - Not Evaluable

Table 18 Summary of treatment-emergent adverse events by worst CTCAE grade overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	Worst CTCAE Grade	n (%)	95% CI [a]
History of visceral disease			
Yes (N = 169)			
	Worst CTCAE Grade 1	9 (5.3)	(2.5, 9.9)
	Worst CTCAE Grade 2	51 (30.2)	(23.4, 37.7)
	Worst CTCAE Grade 3	94 (55.6)	(47.8, 63.2)
	Worst CTCAE Grade 4	5 (3.0)	(1.0, 6.8)
	Worst CTCAE Grade 5	9 (5.3)	(2.5, 9.9)
No (N = 15)			
	Worst CTCAE Grade 1	1 (6.7)	(0.2, 31.9)
	Worst CTCAE Grade 2	6 (40.0)	(16.3, 67.7)
	Worst CTCAE Grade 3	5 (33.3)	(11.8, 61.6)
	Worst CTCAE Grade 4	2 (13.3)	(1.7, 40.5)
	Worst CTCAE Grade 5	1 (6.7)	(0.2, 31.9)

Notes: CTCAE: Common Terminology Criteria for Adverse Events; TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

NE - Not Evaluable

Table 18 Summary of treatment-emergent adverse events by worst CTCAE grade overall and by subgroup - Safety Analysis Set

Subgroup	Worst CTCAE Grade	Overall 5.4 mg/kg (N = 184) n (%)	95% CI [a]
Age			
<65 years (N = 140)			
	Worst CTCAE Grade 1	8 (5.7)	(2.5, 10.9)
	Worst CTCAE Grade 2	46 (32.9)	(25.2, 41.3)
	Worst CTCAE Grade 3	73 (52.1)	(43.5, 60.7)
	Worst CTCAE Grade 4	5 (3.6)	(1.2, 8.1)
	Worst CTCAE Grade 5	7 (5.0)	(2.0, 10.0)
>=65 years (N = 44)			
	Worst CTCAE Grade 1	2 (4.5)	(0.6, 15.5)
	Worst CTCAE Grade 2	11 (25.0)	(13.2, 40.3)
	Worst CTCAE Grade 3	26 (59.1)	(43.2, 73.7)
	Worst CTCAE Grade 4	2 (4.5)	(0.6, 15.5)
	Worst CTCAE Grade 5	3 (6.8)	(1.4, 18.7)

Notes: CTCAE: Common Terminology Criteria for Adverse Events; TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

NE - Not Evaluable

Table 18 Summary of treatment-emergent adverse events by worst CTCAE grade overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	Worst CTCAE Grade	n (%)	95% CI [a]
Region			
Asia (N = 63)			
	Worst CTCAE Grade 1	3 (4.8)	(1.0, 13.3)
	Worst CTCAE Grade 2	23 (36.5)	(24.7, 49.6)
	Worst CTCAE Grade 3	35 (55.6)	(42.5, 68.1)
	Worst CTCAE Grade 4	2 (3.2)	(0.4, 11.0)
	Worst CTCAE Grade 5	0 (0.0)	(NE, NE)
North America (N = 53)			
	Worst CTCAE Grade 1	3 (5.7)	(1.2, 15.7)
	Worst CTCAE Grade 2	16 (30.2)	(18.3, 44.3)
	Worst CTCAE Grade 3	27 (50.9)	(36.8, 64.9)
	Worst CTCAE Grade 4	4 (7.5)	(2.1, 18.2)
	Worst CTCAE Grade 5	3 (5.7)	(1.2, 15.7)

Notes: CTCAE: Common Terminology Criteria for Adverse Events; TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

NE - Not Evaluable

Table 18 Summary of treatment-emergent adverse events by worst CTCAE grade overall and by subgroup - Safety Analysis Set

Subgroup	Worst CTCAE Grade	Overall 5.4 mg/kg (N = 184) n (%)	95% CI [a]
Region			
EU (N = 68)			
	Worst CTCAE Grade 1	4 (5.9)	(1.6, 14.4)
	Worst CTCAE Grade 2	18 (26.5)	(16.5, 38.6)
	Worst CTCAE Grade 3	37 (54.4)	(41.9, 66.5)
	Worst CTCAE Grade 4	1 (1.5)	(0.0, 7.9)
	Worst CTCAE Grade 5	7 (10.3)	(4.2, 20.1)

Notes: CTCAE: Common Terminology Criteria for Adverse Events; TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

NE - Not Evaluable

Table 18 Summary of treatment-emergent adverse events by worst CTCAE grade overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	Worst CTCAE Grade	n (%)	95% CI [a]
ECOG performance status			
0 (N = 102)			
	Worst CTCAE Grade 1	6 (5.9)	(2.2, 12.4)
	Worst CTCAE Grade 2	31 (30.4)	(21.7, 40.3)
	Worst CTCAE Grade 3	54 (52.9)	(42.8, 62.9)
	Worst CTCAE Grade 4	5 (4.9)	(1.6, 11.1)
	Worst CTCAE Grade 5	5 (4.9)	(1.6, 11.1)
1 (N = 81)			
	Worst CTCAE Grade 1	4 (4.9)	(1.4, 12.2)
	Worst CTCAE Grade 2	26 (32.1)	(22.2, 43.4)
	Worst CTCAE Grade 3	45 (55.6)	(44.1, 66.6)
	Worst CTCAE Grade 4	2 (2.5)	(0.3, 8.6)
	Worst CTCAE Grade 5	4 (4.9)	(1.4, 12.2)

Notes: CTCAE: Common Terminology Criteria for Adverse Events; TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

NE - Not Evaluable

Table 18 Summary of treatment-emergent adverse events by worst CTCAE grade overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	Worst CTCAE Grade	n (%)	95% CI [a]
Baseline sum of diameters of target lesions			
<5 cm (N = 74)			
	Worst CTCAE Grade 1	5 (6.8)	(2.2, 15.1)
	Worst CTCAE Grade 2	25 (33.8)	(23.2, 45.7)
	Worst CTCAE Grade 3	36 (48.6)	(36.9, 60.6)
	Worst CTCAE Grade 4	2 (2.7)	(0.3, 9.4)
	Worst CTCAE Grade 5	6 (8.1)	(3.0, 16.8)
>=5 cm (N = 96)			
	Worst CTCAE Grade 1	5 (5.2)	(1.7, 11.7)
	Worst CTCAE Grade 2	29 (30.2)	(21.3, 40.4)
	Worst CTCAE Grade 3	53 (55.2)	(44.7, 65.4)
	Worst CTCAE Grade 4	4 (4.2)	(1.1, 10.3)
	Worst CTCAE Grade 5	4 (4.2)	(1.1, 10.3)

Notes: CTCAE: Common Terminology Criteria for Adverse Events; TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

NE - Not Evaluable

Table 18 Summary of treatment-emergent adverse events by worst CTCAE grade overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	Worst CTCAE Grade	n (%)	95% CI [a]
DS-8201a immediately following initial T-DM1			
Yes (N = 56)			
	Worst CTCAE Grade 1	5 (8.9)	(3.0, 19.6)
	Worst CTCAE Grade 2	23 (41.1)	(28.1, 55.0)
	Worst CTCAE Grade 3	26 (46.4)	(33.0, 60.3)
	Worst CTCAE Grade 4	1 (1.8)	(0.0, 9.6)
	Worst CTCAE Grade 5	1 (1.8)	(0.0, 9.6)
No (N = 128)			
	Worst CTCAE Grade 1	5 (3.9)	(1.3, 8.9)
	Worst CTCAE Grade 2	34 (26.6)	(19.1, 35.1)
	Worst CTCAE Grade 3	73 (57.0)	(48.0, 65.7)
	Worst CTCAE Grade 4	6 (4.7)	(1.7, 9.9)
	Worst CTCAE Grade 5	9 (7.0)	(3.3, 12.9)

Notes: CTCAE: Common Terminology Criteria for Adverse Events; TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

NE - Not Evaluable

Table 18 Summary of treatment-emergent adverse events by worst CTCAE grade overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	Worst CTCAE Grade	n (%)	95% CI [a]
HER2 status			
IHC3+ (N = 154)			
	Worst CTCAE Grade 1	6 (3.9)	(1.4, 8.3)
	Worst CTCAE Grade 2	47 (30.5)	(23.4, 38.4)
	Worst CTCAE Grade 3	86 (55.8)	(47.6, 63.8)
	Worst CTCAE Grade 4	6 (3.9)	(1.4, 8.3)
	Worst CTCAE Grade 5	8 (5.2)	(2.3, 10.0)
ISH+ except IHC3+ (N = 28)			
	Worst CTCAE Grade 1	4 (14.3)	(4.0, 32.7)
	Worst CTCAE Grade 2	10 (35.7)	(18.6, 55.9)
	Worst CTCAE Grade 3	12 (42.9)	(24.5, 62.8)
	Worst CTCAE Grade 4	1 (3.6)	(0.1, 18.3)
	Worst CTCAE Grade 5	1 (3.6)	(0.1, 18.3)

Notes: CTCAE: Common Terminology Criteria for Adverse Events; TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

NE - Not Evaluable

Table 17 Summary of serious treatment-emergent adverse events overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
Any TEAE	51 (27.7)	(21.4, 34.8)
Estrogen receptors		
Positive (N=93)	27 (29.0)	(20.1, 39.4)
Negative (N=88)	23 (26.1)	(17.3, 36.6)
Progesterone receptors		
Positive (N=51)	12 (23.5)	(12.8, 37.5)
Negative (N=125)	37 (29.6)	(21.8, 38.4)
Hormone receptors		
Positive (N=97)	28 (28.9)	(20.1, 39.0)
Negative (N=83)	22 (26.5)	(17.4, 37.3)
Lines of prior systemic therapy not including hormone therapy		
< 3 lines (N=17)	1 (5.9)	(0.1, 28.7)
>= 3 lines (N=167)	50 (29.9)	(23.1, 37.5)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 17 Summary of serious treatment-emergent adverse events overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
Prior pertuzumab		
Yes (N=121)	21 (17.4)	(11.1, 25.3)
No (N=63)	30 (47.6)	(34.9, 60.6)
Prior pertuzumab in 1st or 2nd line in advanced/metastatic breast cancer		
Yes (N=51)	7 (13.7)	(5.7, 26.3)
No (N=133)	44 (33.1)	(25.2, 41.8)
Renal impairment at baseline		
Within Normal Range (N=90)	28 (31.1)	(21.8, 41.7)
Mild Impairment (N=69)	17 (24.6)	(15.1, 36.5)
Moderate Impairment (N=25)	6 (24.0)	(9.4, 45.1)
Hepatic impairment at baseline		
Within Normal Range (N=105)	32 (30.5)	(21.9, 40.2)
Mild Impairment (N=76)	18 (23.7)	(14.7, 34.8)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 17 Summary of serious treatment-emergent adverse events overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
Best response to T-DM1 therapy		
CR/PR/SD (N=79)	17 (21.5)	(13.1, 32.2)
PD (N=66)	22 (33.3)	(22.2, 46.0)
Brain metastases		
Yes (N=24)	5 (20.8)	(7.1, 42.2)
No (N=160)	46 (28.8)	(21.9, 36.4)
Bone metastases		
Yes (N=53)	20 (37.7)	(24.8, 52.1)
No (N=131)	31 (23.7)	(16.7, 31.9)
History of visceral disease		
Yes (N=169)	47 (27.8)	(21.2, 35.2)
No (N=15)	4 (26.7)	(7.8, 55.1)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 17 Summary of serious treatment-emergent adverse events overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
Age		
<65 years (N=140)	38 (27.1)	(20.0, 35.3)
>=65 years (N=44)	13 (29.5)	(16.8, 45.2)
Region		
Asia (N=63)	11 (17.5)	(9.1, 29.1)
North America (N=53)	13 (24.5)	(13.8, 38.3)
EU (N=68)	27 (39.7)	(28.0, 52.3)
ECOG performance status		
0 (N=102)	24 (23.5)	(15.7, 33.0)
1 (N=81)	26 (32.1)	(22.2, 43.4)
Baseline sum of diameters of target lesions		
<5 cm (N=74)	20 (27.0)	(17.4, 38.6)
>=5 cm (N=96)	26 (27.1)	(18.5, 37.1)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 17 Summary of serious treatment-emergent adverse events overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
DS-8201a immediately following initial T-DM1		
Yes (N=56)	9 (16.1)	(7.6, 28.3)
No (N=128)	42 (32.8)	(24.8, 41.7)
HER2 status		
IHC3+ (N=154)	43 (27.9)	(21.0, 35.7)
ISH+ except IHC3+ (N=28)	7 (25.0)	(10.7, 44.9)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 19 Summary of severe (CTCAE Grade >= 3) treatment-emergent adverse events overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
Any TEAE	116 (63.0)	(55.6, 70.0)
Estrogen receptors		
Positive (N=93)	59 (63.4)	(52.8, 73.2)
Negative (N=88)	56 (63.6)	(52.7, 73.6)
Progesterone receptors		
Positive (N=51)	30 (58.8)	(44.2, 72.4)
Negative (N=125)	83 (66.4)	(57.4, 74.6)
Hormone receptors		
Positive (N=97)	62 (63.9)	(53.5, 73.4)
Negative (N=83)	53 (63.9)	(52.6, 74.1)
Lines of prior systemic therapy not including hormone therapy		
< 3 lines (N=17)	11 (64.7)	(38.3, 85.8)
>= 3 lines (N=167)	105 (62.9)	(55.1, 70.2)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 19 Summary of severe (CTCAE Grade >= 3) treatment-emergent adverse events overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
Prior pertuzumab		
Yes (N=121)	72 (59.5)	(50.2, 68.3)
No (N=63)	44 (69.8)	(57.0, 80.8)
Prior pertuzumab in 1st or 2nd line in advanced/metastatic breast cancer		
Yes (N=51)	31 (60.8)	(46.1, 74.2)
No (N=133)	85 (63.9)	(55.1, 72.1)
Renal impairment at baseline		
Within Normal Range (N=90)	55 (61.1)	(50.3, 71.2)
Mild Impairment (N=69)	47 (68.1)	(55.8, 78.8)
Moderate Impairment (N=25)	14 (56.0)	(34.9, 75.6)
Hepatic impairment at baseline		
Within Normal Range (N=105)	73 (69.5)	(59.8, 78.1)
Mild Impairment (N=76)	40 (52.6)	(40.8, 64.2)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 19 Summary of severe (CTCAE Grade >= 3) treatment-emergent adverse events overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
Best response to T-DM1 therapy		
CR/PR/SD (N=79)	51 (64.6)	(53.0, 75.0)
PD (N=66)	43 (65.2)	(52.4, 76.5)
Brain metastases		
Yes (N=24)	15 (62.5)	(40.6, 81.2)
No (N=160)	101 (63.1)	(55.1, 70.6)
Bone metastases		
Yes (N=53)	38 (71.7)	(57.7, 83.2)
No (N=131)	78 (59.5)	(50.6, 68.0)
History of visceral disease		
Yes (N=169)	108 (63.9)	(56.2, 71.1)
No (N=15)	8 (53.3)	(26.6, 78.7)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 19 Summary of severe (CTCAE Grade >= 3) treatment-emergent adverse events overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
Age		
<65 years (N=140)	85 (60.7)	(52.1, 68.9)
>=65 years (N=44)	31 (70.5)	(54.8, 83.2)
Region		
Asia (N=63)	37 (58.7)	(45.6, 71.0)
North America (N=53)	34 (64.2)	(49.8, 76.9)
EU (N=68)	45 (66.2)	(53.7, 77.2)
ECOG performance status		
0 (N=102)	64 (62.7)	(52.6, 72.1)
1 (N=81)	51 (63.0)	(51.5, 73.4)
Baseline sum of diameters of target lesions		
<5 cm (N=74)	44 (59.5)	(47.4, 70.7)
>=5 cm (N=96)	61 (63.5)	(53.1, 73.1)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 19 Summary of severe (CTCAE Grade >= 3) treatment-emergent adverse events overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
DS-8201a immediately following initial T-DM1		
Yes (N=56)	28 (50.0)	(36.3, 63.7)
No (N=128)	88 (68.8)	(60.0, 76.6)
HER2 status		
IHC3+ (N=154)	100 (64.9)	(56.8, 72.4)
ISH+ except IHC3+ (N=28)	14 (50.0)	(30.6, 69.4)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 20 Summary of non-severe (CTCAE Grade < 3) treatment-emergent adverse events overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
Any TEAE	183 (99.5)	(97.0, 100.0)
Estrogen receptors		
Positive (N=93)	92 (98.9)	(94.2, 100.0)
Negative (N=88)	88 (100.0)	(95.9, 100.0)
Progesterone receptors		
Positive (N=51)	50 (98.0)	(89.6, 100.0)
Negative (N=125)	125 (100.0)	(97.1, 100.0)
Hormone receptors		
Positive (N=97)	96 (99.0)	(94.4, 100.0)
Negative (N=83)	83 (100.0)	(95.7, 100.0)
Lines of prior systemic therapy not including hormone therapy		
< 3 lines (N=17)	17 (100.0)	(80.5, 100.0)
>= 3 lines (N=167)	166 (99.4)	(96.7, 100.0)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 20 Summary of non-severe (CTCAE Grade < 3) treatment-emergent adverse events overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
Prior pertuzumab		
Yes (N=121)	121 (100.0)	(97.0, 100.0)
No (N=63)	62 (98.4)	(91.5, 100.0)
Prior pertuzumab in 1st or 2nd line in advanced/metastatic breast cancer		
Yes (N=51)	51 (100.0)	(93.0, 100.0)
No (N=133)	132 (99.2)	(95.9, 100.0)
Renal impairment at baseline		
Within Normal Range (N=90)	89 (98.9)	(94.0, 100.0)
Mild Impairment (N=69)	69 (100.0)	(94.8, 100.0)
Moderate Impairment (N=25)	25 (100.0)	(86.3, 100.0)
Hepatic impairment at baseline		
Within Normal Range (N=105)	104 (99.0)	(94.8, 100.0)
Mild Impairment (N=76)	76 (100.0)	(95.3, 100.0)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 20 Summary of non-severe (CTCAE Grade < 3) treatment-emergent adverse events overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
Best response to T-DM1 therapy		
CR/PR/SD (N=79)	78 (98.7)	(93.1, 100.0)
PD (N=66)	66 (100.0)	(94.6, 100.0)
Brain metastases		
Yes (N=24)	24 (100.0)	(85.8, 100.0)
No (N=160)	159 (99.4)	(96.6, 100.0)
Bone metastases		
Yes (N=53)	53 (100.0)	(93.3, 100.0)
No (N=131)	130 (99.2)	(95.8, 100.0)
History of visceral disease		
Yes (N=169)	168 (99.4)	(96.7, 100.0)
No (N=15)	15 (100.0)	(78.2, 100.0)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 20 Summary of non-severe (CTCAE Grade < 3) treatment-emergent adverse events overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
Age		
<65 years (N=140)	139 (99.3)	(96.1, 100.0)
>=65 years (N=44)	44 (100.0)	(92.0, 100.0)
Region		
Asia (N=63)	63 (100.0)	(94.3, 100.0)
North America (N=53)	53 (100.0)	(93.3, 100.0)
EU (N=68)	67 (98.5)	(92.1, 100.0)
ECOG performance status		
0 (N=102)	101 (99.0)	(94.7, 100.0)
1 (N=81)	81 (100.0)	(95.5, 100.0)
Baseline sum of diameters of target lesions		
<5 cm (N=74)	74 (100.0)	(95.1, 100.0)
>=5 cm (N=96)	95 (99.0)	(94.3, 100.0)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 20 Summary of non-severe (CTCAE Grade < 3) treatment-emergent adverse events overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
DS-8201a immediately following initial T-DM1		
Yes (N=56)	56 (100.0)	(93.6, 100.0)
No (N=128)	127 (99.2)	(95.7, 100.0)
HER2 status		
IHC3+ (N=154)	153 (99.4)	(96.4, 100.0)
ISH+ except IHC3+ (N=28)	28 (100.0)	(87.7, 100.0)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 21 Summary of treatment-emergent adverse events leading to death overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
Any TEAE	10 (5.4)	(2.6, 9.8)
Estrogen receptors		
Positive (N=93)	4 (4.3)	(1.2, 10.6)
Negative (N=88)	5 (5.7)	(1.9, 12.8)
Progesterone receptors		
Positive (N=51)	2 (3.9)	(0.5, 13.5)
Negative (N=125)	7 (5.6)	(2.3, 11.2)
Hormone receptors		
Positive (N=97)	4 (4.1)	(1.1, 10.2)
Negative (N=83)	5 (6.0)	(2.0, 13.5)
Lines of prior systemic therapy not including hormone therapy		
< 3 lines (N=17)	1 (5.9)	(0.1, 28.7)
>= 3 lines (N=167)	9 (5.4)	(2.5, 10.0)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

NE - Not Evaluable

Table 21 Summary of treatment-emergent adverse events leading to death overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
Prior pertuzumab		
Yes (N=121)	4 (3.3)	(0.9, 8.2)
No (N=63)	6 (9.5)	(3.6, 19.6)
Prior pertuzumab in 1st or 2nd line in advanced/metastatic breast cancer		
Yes (N=51)	2 (3.9)	(0.5, 13.5)
No (N=133)	8 (6.0)	(2.6, 11.5)
Renal impairment at baseline		
Within Normal Range (N=90)	6 (6.7)	(2.5, 13.9)
Mild Impairment (N=69)	2 (2.9)	(0.4, 10.1)
Moderate Impairment (N=25)	2 (8.0)	(1.0, 26.0)
Hepatic impairment at baseline		
Within Normal Range (N=105)	7 (6.7)	(2.7, 13.3)
Mild Impairment (N=76)	3 (3.9)	(0.8, 11.1)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

NE - Not Evaluable

Table 21 Summary of treatment-emergent adverse events leading to death overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
Best response to T-DM1 therapy		
CR/PR/SD (N=79)	2 (2.5)	(0.3, 8.8)
PD (N=66)	5 (7.6)	(2.5, 16.8)
Brain metastases		
Yes (N=24)	2 (8.3)	(1.0, 27.0)
No (N=160)	8 (5.0)	(2.2, 9.6)
Bone metastases		
Yes (N=53)	4 (7.5)	(2.1, 18.2)
No (N=131)	6 (4.6)	(1.7, 9.7)
History of visceral disease		
Yes (N=169)	9 (5.3)	(2.5, 9.9)
No (N=15)	1 (6.7)	(0.2, 31.9)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

NE - Not Evaluable

Table 21 Summary of treatment-emergent adverse events leading to death overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
Age		
<65 years (N=140)	7 (5.0)	(2.0, 10.0)
>=65 years (N=44)	3 (6.8)	(1.4, 18.7)
Region		
Asia (N=63)	0	(NE, NE)
North America (N=53)	3 (5.7)	(1.2, 15.7)
EU (N=68)	7 (10.3)	(4.2, 20.1)
ECOG performance status		
0 (N=102)	5 (4.9)	(1.6, 11.1)
1 (N=81)	4 (4.9)	(1.4, 12.2)
Baseline sum of diameters of target lesions		
<5 cm (N=74)	6 (8.1)	(3.0, 16.8)
>=5 cm (N=96)	4 (4.2)	(1.1, 10.3)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

NE - Not Evaluable

Table 21 Summary of treatment-emergent adverse events leading to death overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
DS-8201a immediately following initial T-DM1		
Yes (N=56)	1 (1.8)	(0.0, 9.6)
No (N=128)	9 (7.0)	(3.3, 12.9)
HER2 status		
IHC3+ (N=154)	8 (5.2)	(2.3, 10.0)
ISH+ except IHC3+ (N=28)	1 (3.6)	(0.1, 18.3)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

NE - Not Evaluable

Table 29 Summary of interstitial lung disease overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
Any TEAE	28 (15.2)	(10.4, 21.2)
Estrogen receptors		
Positive (N=93)	15 (16.1)	(9.3, 25.2)
Negative (N=88)	13 (14.8)	(8.1, 23.9)
Progesterone receptors		
Positive (N=51)	10 (19.6)	(9.8, 33.1)
Negative (N=125)	18 (14.4)	(8.8, 21.8)
Hormone receptors		
Positive (N=97)	16 (16.5)	(9.7, 25.4)
Negative (N=83)	12 (14.5)	(7.7, 23.9)
Lines of prior systemic therapy not including hormone therapy		
< 3 lines (N=17)	2 (11.8)	(1.5, 36.4)
>= 3 lines (N=167)	26 (15.6)	(10.4, 22.0)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 29 Summary of interstitial lung disease overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
Prior pertuzumab		
Yes (N=121)	20 (16.5)	(10.4, 24.4)
No (N=63)	8 (12.7)	(5.6, 23.5)
Prior pertuzumab in 1st or 2nd line in advanced/metastatic breast cancer		
Yes (N=51)	7 (13.7)	(5.7, 26.3)
No (N=133)	21 (15.8)	(10.0, 23.1)
Renal impairment at baseline		
Within Normal Range (N=90)	10 (11.1)	(5.5, 19.5)
Mild Impairment (N=69)	9 (13.0)	(6.1, 23.3)
Moderate Impairment (N=25)	9 (36.0)	(18.0, 57.5)
Hepatic impairment at baseline		
Within Normal Range (N=105)	21 (20.0)	(12.8, 28.9)
Mild Impairment (N=76)	7 (9.2)	(3.8, 18.1)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 29 Summary of interstitial lung disease overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
Best response to T-DM1 therapy		
CR/PR/SD (N=79)	12 (15.2)	(8.1, 25.0)
PD (N=66)	12 (18.2)	(9.8, 29.6)
Brain metastases		
Yes (N=24)	6 (25.0)	(9.8, 46.7)
No (N=160)	22 (13.8)	(8.8, 20.1)
Bone metastases		
Yes (N=53)	11 (20.8)	(10.8, 34.1)
No (N=131)	17 (13.0)	(7.7, 20.0)
History of visceral disease		
Yes (N=169)	25 (14.8)	(9.8, 21.1)
No (N=15)	3 (20.0)	(4.3, 48.1)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 29 Summary of interstitial lung disease overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
Age		
<65 years (N=140)	18 (12.9)	(7.8, 19.6)
>=65 years (N=44)	10 (22.7)	(11.5, 37.8)
Region		
Asia (N=63)	15 (23.8)	(14.0, 36.2)
North America (N=53)	4 (7.5)	(2.1, 18.2)
EU (N=68)	9 (13.2)	(6.2, 23.6)
ECOG performance status		
0 (N=102)	21 (20.6)	(13.2, 29.7)
1 (N=81)	7 (8.6)	(3.5, 17.0)
Baseline sum of diameters of target lesions		
<5 cm (N=74)	15 (20.3)	(11.8, 31.2)
>=5 cm (N=96)	8 (8.3)	(3.7, 15.8)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 29 Summary of interstitial lung disease overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
DS-8201a immediately following initial T-DM1		
Yes (N=56)	6 (10.7)	(4.0, 21.9)
No (N=128)	22 (17.2)	(11.1, 24.9)
HER2 status		
IHC3+ (N=154)	25 (16.2)	(10.8, 23.0)
ISH+ except IHC3+ (N=28)	3 (10.7)	(2.3, 28.2)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 30 Summary of serious interstitial lung disease overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
Any TEAE	6 (3.3)	(1.2, 7.0)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 31 Summary of severe (CTCAE Grade >= 3) interstitial lung disease overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
Any TEAE	5 (2.7)	(0.9, 6.2)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 32 Summary of non-severe (CTCAE Grade < 3) interstitial lung disease overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
Any TEAE	23 (12.5)	(8.1, 18.2)
Estrogen receptors		
Positive (N=93)	12 (12.9)	(6.8, 21.5)
Negative (N=88)	11 (12.5)	(6.4, 21.3)
Progesterone receptors		
Positive (N=51)	9 (17.6)	(8.4, 30.9)
Negative (N=125)	14 (11.2)	(6.3, 18.1)
Hormone receptors		
Positive (N=97)	13 (13.4)	(7.3, 21.8)
Negative (N=83)	10 (12.0)	(5.9, 21.0)
Lines of prior systemic therapy not including hormone therapy		
< 3 lines (N=17)	2 (11.8)	(1.5, 36.4)
>= 3 lines (N=167)	21 (12.6)	(8.0, 18.6)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 32 Summary of non-severe (CTCAE Grade < 3) interstitial lung disease overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
Prior pertuzumab		
Yes (N=121)	18 (14.9)	(9.1, 22.5)
No (N=63)	5 (7.9)	(2.6, 17.6)
Prior pertuzumab in 1st or 2nd line in advanced/metastatic breast cancer		
Yes (N=51)	7 (13.7)	(5.7, 26.3)
No (N=133)	16 (12.0)	(7.0, 18.8)
Renal impairment at baseline		
Within Normal Range (N=90)	6 (6.7)	(2.5, 13.9)
Mild Impairment (N=69)	9 (13.0)	(6.1, 23.3)
Moderate Impairment (N=25)	8 (32.0)	(14.9, 53.5)
Hepatic impairment at baseline		
Within Normal Range (N=105)	16 (15.2)	(9.0, 23.6)
Mild Impairment (N=76)	7 (9.2)	(3.8, 18.1)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 32 Summary of non-severe (CTCAE Grade < 3) interstitial lung disease overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
Best response to T-DM1 therapy		
CR/PR/SD (N=79)	9 (11.4)	(5.3, 20.5)
PD (N=66)	11 (16.7)	(8.6, 27.9)
Brain metastases		
Yes (N=24)	6 (25.0)	(9.8, 46.7)
No (N=160)	17 (10.6)	(6.3, 16.5)
Bone metastases		
Yes (N=53)	9 (17.0)	(8.1, 29.8)
No (N=131)	14 (10.7)	(6.0, 17.3)
History of visceral disease		
Yes (N=169)	21 (12.4)	(7.9, 18.4)
No (N=15)	2 (13.3)	(1.7, 40.5)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 32 Summary of non-severe (CTCAE Grade < 3) interstitial lung disease overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
Age		
<65 years (N=140)	15 (10.7)	(6.1, 17.1)
>=65 years (N=44)	8 (18.2)	(8.2, 32.7)
Region		
Asia (N=63)	15 (23.8)	(14.0, 36.2)
North America (N=53)	3 (5.7)	(1.2, 15.7)
EU (N=68)	5 (7.4)	(2.4, 16.3)
ECOG performance status		
0 (N=102)	17 (16.7)	(10.0, 25.3)
1 (N=81)	6 (7.4)	(2.8, 15.4)
Baseline sum of diameters of target lesions		
<5 cm (N=74)	11 (14.9)	(7.7, 25.0)
>=5 cm (N=96)	8 (8.3)	(3.7, 15.8)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 32 Summary of non-severe (CTCAE Grade < 3) interstitial lung disease overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
DS-8201a immediately following initial T-DM1		
Yes (N=56)	6 (10.7)	(4.0, 21.9)
No (N=128)	17 (13.3)	(7.9, 20.4)
HER2 status		
IHC3+ (N=154)	21 (13.6)	(8.6, 20.1)
ISH+ except IHC3+ (N=28)	2 (7.1)	(0.9, 23.5)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 37 Summary of adjudicated drug-related interstitial lung disease overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
Any TEAE	29 (15.8)	(10.8, 21.8)
Estrogen receptors		
Positive (N=93)	15 (16.1)	(9.3, 25.2)
Negative (N=88)	13 (14.8)	(8.1, 23.9)
Progesterone receptors		
Positive (N=51)	10 (19.6)	(9.8, 33.1)
Negative (N=125)	18 (14.4)	(8.8, 21.8)
Hormone receptors		
Positive (N=97)	16 (16.5)	(9.7, 25.4)
Negative (N=83)	12 (14.5)	(7.7, 23.9)
Lines of prior systemic therapy not including hormone therapy		
< 3 lines (N=17)	2 (11.8)	(1.5, 36.4)
>= 3 lines (N=167)	27 (16.2)	(10.9, 22.6)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 37 Summary of adjudicated drug-related interstitial lung disease overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
Prior pertuzumab		
Yes (N=121)	19 (15.7)	(9.7, 23.4)
No (N=63)	10 (15.9)	(7.9, 27.3)
Prior pertuzumab in 1st or 2nd line in advanced/metastatic breast cancer		
Yes (N=51)	7 (13.7)	(5.7, 26.3)
No (N=133)	22 (16.5)	(10.7, 24.0)
Renal impairment at baseline		
Within Normal Range (N=90)	12 (13.3)	(7.1, 22.1)
Mild Impairment (N=69)	8 (11.6)	(5.1, 21.6)
Moderate Impairment (N=25)	9 (36.0)	(18.0, 57.5)
Hepatic impairment at baseline		
Within Normal Range (N=105)	23 (21.9)	(14.4, 31.0)
Mild Impairment (N=76)	6 (7.9)	(3.0, 16.4)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 37 Summary of adjudicated drug-related interstitial lung disease overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
Best response to T-DM1 therapy		
CR/PR/SD (N=79)	12 (15.2)	(8.1, 25.0)
PD (N=66)	13 (19.7)	(10.9, 31.3)
Brain metastases		
Yes (N=24)	5 (20.8)	(7.1, 42.2)
No (N=160)	24 (15.0)	(9.9, 21.5)
Bone metastases		
Yes (N=53)	11 (20.8)	(10.8, 34.1)
No (N=131)	18 (13.7)	(8.4, 20.8)
History of visceral disease		
Yes (N=169)	26 (15.4)	(10.3, 21.7)
No (N=15)	3 (20.0)	(4.3, 48.1)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 37 Summary of adjudicated drug-related interstitial lung disease overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
Age		
<65 years (N=140)	20 (14.3)	(8.9, 21.2)
>=65 years (N=44)	9 (20.5)	(9.8, 35.3)
Region		
Asia (N=63)	13 (20.6)	(11.5, 32.7)
North America (N=53)	4 (7.5)	(2.1, 18.2)
EU (N=68)	12 (17.6)	(9.5, 28.8)
ECOG performance status		
0 (N=102)	20 (19.6)	(12.4, 28.6)
1 (N=81)	8 (9.9)	(4.4, 18.5)
Baseline sum of diameters of target lesions		
<5 cm (N=74)	15 (20.3)	(11.8, 31.2)
>=5 cm (N=96)	9 (9.4)	(4.4, 17.1)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 37 Summary of adjudicated drug-related interstitial lung disease overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
DS-8201a immediately following initial T-DM1		
Yes (N=56)	5 (8.9)	(3.0, 19.6)
No (N=128)	24 (18.8)	(12.4, 26.6)
HER2 status		
IHC3+ (N=154)	26 (16.9)	(11.3, 23.8)
ISH+ except IHC3+ (N=28)	3 (10.7)	(2.3, 28.2)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 38 Summary of serious adjudicated drug-related interstitial lung disease overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
Any TEAE	9 (4.9)	(2.3, 9.1)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 39 Summary of severe (CTCAE Grade >= 3) adjudicated drug-related interstitial lung disease overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
Any TEAE	7 (3.8)	(1.5, 7.7)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 40 Summary of non-severe (CTCAE Grade < 3) adjudicated drug-related interstitial lung disease overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
Any TEAE	23 (12.5)	(8.1, 18.2)
Estrogen receptors		
Positive (N=93)	13 (14.0)	(7.7, 22.7)
Negative (N=88)	10 (11.4)	(5.6, 19.9)
Progesterone receptors		
Positive (N=51)	9 (17.6)	(8.4, 30.9)
Negative (N=125)	14 (11.2)	(6.3, 18.1)
Hormone receptors		
Positive (N=97)	14 (14.4)	(8.1, 23.0)
Negative (N=83)	9 (10.8)	(5.1, 19.6)
Lines of prior systemic therapy not including hormone therapy		
< 3 lines (N=17)	2 (11.8)	(1.5, 36.4)
>= 3 lines (N=167)	21 (12.6)	(8.0, 18.6)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 40 Summary of non-severe (CTCAE Grade < 3) adjudicated drug-related interstitial lung disease overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
Prior pertuzumab		
Yes (N=121)	17 (14.0)	(8.4, 21.5)
No (N=63)	6 (9.5)	(3.6, 19.6)
Prior pertuzumab in 1st or 2nd line in advanced/metastatic breast cancer		
Yes (N=51)	7 (13.7)	(5.7, 26.3)
No (N=133)	16 (12.0)	(7.0, 18.8)
Renal impairment at baseline		
Within Normal Range (N=90)	8 (8.9)	(3.9, 16.8)
Mild Impairment (N=69)	8 (11.6)	(5.1, 21.6)
Moderate Impairment (N=25)	7 (28.0)	(12.1, 49.4)
Hepatic impairment at baseline		
Within Normal Range (N=105)	17 (16.2)	(9.7, 24.7)
Mild Impairment (N=76)	6 (7.9)	(3.0, 16.4)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 40 Summary of non-severe (CTCAE Grade < 3) adjudicated drug-related interstitial lung disease overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
Best response to T-DM1 therapy		
CR/PR/SD (N=79)	10 (12.7)	(6.2, 22.0)
PD (N=66)	11 (16.7)	(8.6, 27.9)
Brain metastases		
Yes (N=24)	5 (20.8)	(7.1, 42.2)
No (N=160)	18 (11.3)	(6.8, 17.2)
Bone metastases		
Yes (N=53)	9 (17.0)	(8.1, 29.8)
No (N=131)	14 (10.7)	(6.0, 17.3)
History of visceral disease		
Yes (N=169)	21 (12.4)	(7.9, 18.4)
No (N=15)	2 (13.3)	(1.7, 40.5)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 40 Summary of non-severe (CTCAE Grade < 3) adjudicated drug-related interstitial lung disease overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
Age		
<65 years (N=140)	16 (11.4)	(6.7, 17.9)
>=65 years (N=44)	7 (15.9)	(6.6, 30.1)
Region		
Asia (N=63)	13 (20.6)	(11.5, 32.7)
North America (N=53)	3 (5.7)	(1.2, 15.7)
EU (N=68)	7 (10.3)	(4.2, 20.1)
ECOG performance status		
0 (N=102)	17 (16.7)	(10.0, 25.3)
1 (N=81)	6 (7.4)	(2.8, 15.4)
Baseline sum of diameters of target lesions		
<5 cm (N=74)	10 (13.5)	(6.7, 23.5)
>=5 cm (N=96)	8 (8.3)	(3.7, 15.8)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 40 Summary of non-severe (CTCAE Grade < 3) adjudicated drug-related interstitial lung disease overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
DS-8201a immediately following initial T-DM1		
Yes (N=56)	5 (8.9)	(3.0, 19.6)
No (N=128)	18 (14.1)	(8.6, 21.3)
HER2 status		
IHC3+ (N=154)	21 (13.6)	(8.6, 20.1)
ISH+ except IHC3+ (N=28)	2 (7.1)	(0.9, 23.5)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 41 Summary of LVEF decrease overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
Any TEAE	6 (3.3)	(1.2, 7.0)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 42 Summary of serious LVEF decrease overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
Any TEAE	1 (0.5)	(0.0, 3.0)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 43 Summary of severe (CTCAE Grade >= 3) LVEF decrease overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
Any TEAE	1 (0.5)	(0.0, 3.0)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 44 Summary of non-severe (CTCAE Grade < 3) LVEF decrease overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
Any TEAE	5 (2.7)	(0.9, 6.2)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 45 Summary of QT prolongation overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
Any TEAE	11 (6.0)	(3.0, 10.4)
Estrogen receptors		
Positive (N=93)	6 (6.5)	(2.4, 13.5)
Negative (N=88)	5 (5.7)	(1.9, 12.8)
Progesterone receptors		
Positive (N=51)	2 (3.9)	(0.5, 13.5)
Negative (N=125)	9 (7.2)	(3.3, 13.2)
Hormone receptors		
Positive (N=97)	6 (6.2)	(2.3, 13.0)
Negative (N=83)	5 (6.0)	(2.0, 13.5)
Lines of prior systemic therapy not including hormone therapy		
< 3 lines (N=17)	1 (5.9)	(0.1, 28.7)
>= 3 lines (N=167)	10 (6.0)	(2.9, 10.7)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 45 Summary of QT prolongation overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
Prior pertuzumab		
Yes (N=121)	8 (6.6)	(2.9, 12.6)
No (N=63)	3 (4.8)	(1.0, 13.3)
Prior pertuzumab in 1st or 2nd line in advanced/metastatic breast cancer		
Yes (N=51)	2 (3.9)	(0.5, 13.5)
No (N=133)	9 (6.8)	(3.1, 12.5)
Renal impairment at baseline		
Within Normal Range (N=90)	5 (5.6)	(1.8, 12.5)
Mild Impairment (N=69)	3 (4.3)	(0.9, 12.2)
Moderate Impairment (N=25)	3 (12.0)	(2.5, 31.2)
Hepatic impairment at baseline		
Within Normal Range (N=105)	8 (7.6)	(3.3, 14.5)
Mild Impairment (N=76)	3 (3.9)	(0.8, 11.1)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 45 Summary of QT prolongation overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
Best response to T-DM1 therapy		
CR/PR/SD (N=79)	3 (3.8)	(0.8, 10.7)
PD (N=66)	5 (7.6)	(2.5, 16.8)
Brain metastases		
Yes (N=24)	4 (16.7)	(4.7, 37.4)
No (N=160)	7 (4.4)	(1.8, 8.8)
Bone metastases		
Yes (N=53)	7 (13.2)	(5.5, 25.3)
No (N=131)	4 (3.1)	(0.8, 7.6)
History of visceral disease		
Yes (N=169)	10 (5.9)	(2.9, 10.6)
No (N=15)	1 (6.7)	(0.2, 31.9)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 45 Summary of QT prolongation overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
Age		
<65 years (N=140)	7 (5.0)	(2.0, 10.0)
>=65 years (N=44)	4 (9.1)	(2.5, 21.7)
Region		
Asia (N=63)	5 (7.9)	(2.6, 17.6)
North America (N=53)	2 (3.8)	(0.5, 13.0)
EU (N=68)	4 (5.9)	(1.6, 14.4)
ECOG performance status		
0 (N=102)	7 (6.9)	(2.8, 13.6)
1 (N=81)	4 (4.9)	(1.4, 12.2)
Baseline sum of diameters of target lesions		
<5 cm (N=74)	5 (6.8)	(2.2, 15.1)
>=5 cm (N=96)	5 (5.2)	(1.7, 11.7)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 45 Summary of QT prolongation overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
DS-8201a immediately following initial T-DM1		
Yes (N=56)	2 (3.6)	(0.4, 12.3)
No (N=128)	9 (7.0)	(3.3, 12.9)
HER2 status		
IHC3+ (N=154)	10 (6.5)	(3.2, 11.6)
ISH+ except IHC3+ (N=28)	1 (3.6)	(0.1, 18.3)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 46 Summary of serious QT prolongation overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
Any TEAE	1 (0.5)	(0.0, 3.0)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 47 Summary of severe (CTCAE Grade >= 3) QT prolongation overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
Any TEAE	3 (1.6)	(0.3, 4.7)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 48 Summary of non-severe (CTCAE Grade < 3) QT prolongation overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
Any TEAE	9 (4.9)	(2.3, 9.1)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 49 Summary of infusion related reactions overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
Any TEAE	18 (9.8)	(5.9, 15.0)
Estrogen receptors		
Positive (N=93)	8 (8.6)	(3.8, 16.2)
Negative (N=88)	9 (10.2)	(4.8, 18.5)
Progesterone receptors		
Positive (N=51)	4 (7.8)	(2.2, 18.9)
Negative (N=125)	13 (10.4)	(5.7, 17.1)
Hormone receptors		
Positive (N=97)	9 (9.3)	(4.3, 16.9)
Negative (N=83)	8 (9.6)	(4.3, 18.1)
Lines of prior systemic therapy not including hormone therapy		
< 3 lines (N=17)	1 (5.9)	(0.1, 28.7)
>= 3 lines (N=167)	17 (10.2)	(6.0, 15.8)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 49 Summary of infusion related reactions overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
Prior pertuzumab		
Yes (N=121)	12 (9.9)	(5.2, 16.7)
No (N=63)	6 (9.5)	(3.6, 19.6)
Prior pertuzumab in 1st or 2nd line in advanced/metastatic breast cancer		
Yes (N=51)	3 (5.9)	(1.2, 16.2)
No (N=133)	15 (11.3)	(6.5, 17.9)
Renal impairment at baseline		
Within Normal Range (N=90)	8 (8.9)	(3.9, 16.8)
Mild Impairment (N=69)	6 (8.7)	(3.3, 18.0)
Moderate Impairment (N=25)	4 (16.0)	(4.5, 36.1)
Hepatic impairment at baseline		
Within Normal Range (N=105)	14 (13.3)	(7.5, 21.4)
Mild Impairment (N=76)	4 (5.3)	(1.5, 12.9)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 49 Summary of infusion related reactions overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
Best response to T-DM1 therapy		
CR/PR/SD (N=79)	8 (10.1)	(4.5, 19.0)
PD (N=66)	7 (10.6)	(4.4, 20.6)
Brain metastases		
Yes (N=24)	5 (20.8)	(7.1, 42.2)
No (N=160)	13 (8.1)	(4.4, 13.5)
Bone metastases		
Yes (N=53)	3 (5.7)	(1.2, 15.7)
No (N=131)	15 (11.5)	(6.6, 18.2)
History of visceral disease		
Yes (N=169)	16 (9.5)	(5.5, 14.9)
No (N=15)	2 (13.3)	(1.7, 40.5)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 49 Summary of infusion related reactions overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
Age		
<65 years (N=140)	11 (7.9)	(4.0, 13.6)
>=65 years (N=44)	7 (15.9)	(6.6, 30.1)
Region		
Asia (N=63)	5 (7.9)	(2.6, 17.6)
North America (N=53)	7 (13.2)	(5.5, 25.3)
EU (N=68)	6 (8.8)	(3.3, 18.2)
ECOG performance status		
0 (N=102)	9 (8.8)	(4.1, 16.1)
1 (N=81)	8 (9.9)	(4.4, 18.5)
Baseline sum of diameters of target lesions		
<5 cm (N=74)	8 (10.8)	(4.8, 20.2)
>=5 cm (N=96)	8 (8.3)	(3.7, 15.8)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 49 Summary of infusion related reactions overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
DS-8201a immediately following initial T-DM1		
Yes (N=56)	3 (5.4)	(1.1, 14.9)
No (N=128)	15 (11.7)	(6.7, 18.6)
HER2 status		
IHC3+ (N=154)	14 (9.1)	(5.1, 14.8)
ISH+ except IHC3+ (N=28)	4 (14.3)	(4.0, 32.7)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 50 Summary of serious infusion related reactions overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
Any TEAE	1 (0.5)	(0.0, 3.0)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 51 Summary of severe (CTCAE Grade >= 3) infusion related reactions overall and by subgroup - Safety Analysis Set

No severe (CTCAE Grade >= 3) infusion related reactions have been observed

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 52 Summary of non-severe (CTCAE Grade < 3) infusion related reactions overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
Any TEAE	18 (9.8)	(5.9, 15.0)
Estrogen receptors		
Positive (N=93)	8 (8.6)	(3.8, 16.2)
Negative (N=88)	9 (10.2)	(4.8, 18.5)
Progesterone receptors		
Positive (N=51)	4 (7.8)	(2.2, 18.9)
Negative (N=125)	13 (10.4)	(5.7, 17.1)
Hormone receptors		
Positive (N=97)	9 (9.3)	(4.3, 16.9)
Negative (N=83)	8 (9.6)	(4.3, 18.1)
Lines of prior systemic therapy not including hormone therapy		
< 3 lines (N=17)	1 (5.9)	(0.1, 28.7)
>= 3 lines (N=167)	17 (10.2)	(6.0, 15.8)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 52 Summary of non-severe (CTCAE Grade < 3) infusion related reactions overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
Prior pertuzumab		
Yes (N=121)	12 (9.9)	(5.2, 16.7)
No (N=63)	6 (9.5)	(3.6, 19.6)
Prior pertuzumab in 1st or 2nd line in advanced/metastatic breast cancer		
Yes (N=51)	3 (5.9)	(1.2, 16.2)
No (N=133)	15 (11.3)	(6.5, 17.9)
Renal impairment at baseline		
Within Normal Range (N=90)	8 (8.9)	(3.9, 16.8)
Mild Impairment (N=69)	6 (8.7)	(3.3, 18.0)
Moderate Impairment (N=25)	4 (16.0)	(4.5, 36.1)
Hepatic impairment at baseline		
Within Normal Range (N=105)	14 (13.3)	(7.5, 21.4)
Mild Impairment (N=76)	4 (5.3)	(1.5, 12.9)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 52 Summary of non-severe (CTCAE Grade < 3) infusion related reactions overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
Best response to T-DM1 therapy		
CR/PR/SD (N=79)	8 (10.1)	(4.5, 19.0)
PD (N=66)	7 (10.6)	(4.4, 20.6)
Brain metastases		
Yes (N=24)	5 (20.8)	(7.1, 42.2)
No (N=160)	13 (8.1)	(4.4, 13.5)
Bone metastases		
Yes (N=53)	3 (5.7)	(1.2, 15.7)
No (N=131)	15 (11.5)	(6.6, 18.2)
History of visceral disease		
Yes (N=169)	16 (9.5)	(5.5, 14.9)
No (N=15)	2 (13.3)	(1.7, 40.5)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 52 Summary of non-severe (CTCAE Grade < 3) infusion related reactions overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
Age		
<65 years (N=140)	11 (7.9)	(4.0, 13.6)
>=65 years (N=44)	7 (15.9)	(6.6, 30.1)
Region		
Asia (N=63)	5 (7.9)	(2.6, 17.6)
North America (N=53)	7 (13.2)	(5.5, 25.3)
EU (N=68)	6 (8.8)	(3.3, 18.2)
ECOG performance status		
0 (N=102)	9 (8.8)	(4.1, 16.1)
1 (N=81)	8 (9.9)	(4.4, 18.5)
Baseline sum of diameters of target lesions		
<5 cm (N=74)	8 (10.8)	(4.8, 20.2)
>=5 cm (N=96)	8 (8.3)	(3.7, 15.8)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 52 Summary of non-severe (CTCAE Grade < 3) infusion related reactions overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
DS-8201a immediately following initial T-DM1		
Yes (N=56)	3 (5.4)	(1.1, 14.9)
No (N=128)	15 (11.7)	(6.7, 18.6)
HER2 status		
IHC3+ (N=154)	14 (9.1)	(5.1, 14.8)
ISH+ except IHC3+ (N=28)	4 (14.3)	(4.0, 32.7)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 22 Summary of treatment-emergent adverse events leading to discontinuation of treatment overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
Any TEAE	77 (41.8)	(34.6, 49.3)
Estrogen receptors		
Positive (N=93)	37 (39.8)	(29.8, 50.5)
Negative (N=88)	40 (45.5)	(34.8, 56.4)
Progesterone receptors		
Positive (N=51)	21 (41.2)	(27.6, 55.8)
Negative (N=125)	54 (43.2)	(34.4, 52.4)
Hormone receptors		
Positive (N=97)	38 (39.2)	(29.4, 49.6)
Negative (N=83)	38 (45.8)	(34.8, 57.1)
Lines of prior systemic therapy not including hormone therapy		
< 3 lines (N=17)	9 (52.9)	(27.8, 77.0)
>= 3 lines (N=167)	68 (40.7)	(33.2, 48.6)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 22 Summary of treatment-emergent adverse events leading to discontinuation of treatment overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
Prior pertuzumab		
Yes (N=121)	46 (38.0)	(29.3, 47.3)
No (N=63)	31 (49.2)	(36.4, 62.1)
Prior pertuzumab in 1st or 2nd line in advanced/metastatic breast cancer		
Yes (N=51)	22 (43.1)	(29.3, 57.8)
No (N=133)	55 (41.4)	(32.9, 50.2)
Renal impairment at baseline		
Within Normal Range (N=90)	40 (44.4)	(34.0, 55.3)
Mild Impairment (N=69)	29 (42.0)	(30.2, 54.5)
Moderate Impairment (N=25)	8 (32.0)	(14.9, 53.5)
Hepatic impairment at baseline		
Within Normal Range (N=105)	50 (47.6)	(37.8, 57.6)
Mild Impairment (N=76)	26 (34.2)	(23.7, 46.0)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 22 Summary of treatment-emergent adverse events leading to discontinuation of treatment overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
Best response to T-DM1 therapy		
CR/PR/SD (N=79)	37 (46.8)	(35.5, 58.4)
PD (N=66)	29 (43.9)	(31.7, 56.7)
Brain metastases		
Yes (N=24)	12 (50.0)	(29.1, 70.9)
No (N=160)	65 (40.6)	(32.9, 48.7)
Bone metastases		
Yes (N=53)	27 (50.9)	(36.8, 64.9)
No (N=131)	50 (38.2)	(29.8, 47.1)
History of visceral disease		
Yes (N=169)	70 (41.4)	(33.9, 49.2)
No (N=15)	7 (46.7)	(21.3, 73.4)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 22 Summary of treatment-emergent adverse events leading to discontinuation of treatment overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
Age		
<65 years (N=140)	60 (42.9)	(34.5, 51.5)
>=65 years (N=44)	17 (38.6)	(24.4, 54.5)
Region		
Asia (N=63)	26 (41.3)	(29.0, 54.4)
North America (N=53)	18 (34.0)	(21.5, 48.3)
EU (N=68)	33 (48.5)	(36.2, 61.0)
ECOG performance status		
0 (N=102)	40 (39.2)	(29.7, 49.4)
1 (N=81)	37 (45.7)	(34.6, 57.1)
Baseline sum of diameters of target lesions		
<5 cm (N=74)	34 (45.9)	(34.3, 57.9)
>=5 cm (N=96)	37 (38.5)	(28.8, 49.0)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 22 Summary of treatment-emergent adverse events leading to discontinuation of treatment overall and by subgroup - Safety Analysis Set

	Overall 5.4 mg/kg (N = 184)	
Subgroup	n (%)	95% CI [a]
DS-8201a immediately following initial T-DM1		
Yes (N=56)	21 (37.5)	(24.9, 51.5)
No (N=128)	56 (43.8)	(35.0, 52.8)
HER2 status		
IHC3+ (N=154)	68 (44.2)	(36.2, 52.4)
ISH+ except IHC3+ (N=28)	9 (32.1)	(15.9, 52.4)

Notes: TEAE: Treatment-emergent adverse event; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 28 Treatment-emergent adverse events leading to discontinuation of treatment by system organ class, preferred term when observed for >= 10 patients, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Overall	SOC: Respiratory, thoracic and mediastinal disorders	23 (12.5)	(8.1, 18.2)
	Pneumonitis	14 (7.6)	(4.2, 12.4)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 28 Treatment-emergent adverse events leading to discontinuation of treatment by system organ class, preferred term when observed for >= 10 patients, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Estrogen receptors	SOC: Respiratory, thoracic and mediastinal disorders	13 (14.0)	(7.7, 22.7)
Positive (N = 93)	Pneumonitis	7 (7.5)	(3.1, 14.9)
Negative (N = 88)	SOC: Respiratory, thoracic and mediastinal disorders	10 (11.4)	(5.6, 19.9)
	Pneumonitis	7 (8.0)	(3.3, 15.7)
Progesterone receptors	SOC: Respiratory, thoracic and mediastinal disorders	9 (17.6)	(8.4, 30.9)
Positive (N = 51)	Pneumonitis	4 (7.8)	(2.2, 18.9)
Negative (N = 125)	SOC: Respiratory, thoracic and mediastinal disorders	14 (11.2)	(6.3, 18.1)
	Pneumonitis	10 (8.0)	(3.9, 14.2)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 28 Treatment-emergent adverse events leading to discontinuation of treatment by system organ class, preferred term when observed for >= 10 patients, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Hormone receptors	SOC: Respiratory, thoracic and mediastinal disorders	14 (14.4)	(8.1, 23.0)
Positive (N = 97)	Pneumonitis	7 (7.2)	(3.0, 14.3)
Negative (N = 83)	SOC: Respiratory, thoracic and mediastinal disorders	9 (10.8)	(5.1, 19.6)
	Pneumonitis	7 (8.4)	(3.5, 16.6)
Lines of prior systemic therapy not including hormone therapy < 3 lines (N = 17)	SOC: Respiratory, thoracic and mediastinal disorders	2 (11.8)	(1.5, 36.4)
	Pneumonitis	1 (5.9)	(0.1, 28.7)
>= 3 lines (N = 167)	SOC: Respiratory, thoracic and mediastinal disorders	21 (12.6)	(8.0, 18.6)
	Pneumonitis	13 (7.8)	(4.2, 12.9)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 28 Treatment-emergent adverse events leading to discontinuation of treatment by system organ class, preferred term when observed for >= 10 patients, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Prior pertuzumab	SOC: Respiratory, thoracic and mediastinal disorders	15 (12.4)	(7.1, 19.6)
Yes (N = 121)	Pneumonitis	9 (7.4)	(3.5, 13.7)
No (N = 63)	SOC: Respiratory, thoracic and mediastinal disorders	8 (12.7)	(5.6, 23.5)
	Pneumonitis	5 (7.9)	(2.6, 17.6)
Prior pertuzumab in 1st or 2nd line in advanced/	SOC: Respiratory, thoracic and mediastinal disorders	6 (11.8)	(4.4, 23.9)
metastatic breast cancer Yes (N = 51)	Pneumonitis	2 (3.9)	(0.5, 13.5)
No (N = 133)	SOC: Respiratory, thoracic and mediastinal disorders	17 (12.8)	(7.6, 19.7)
	Pneumonitis	12 (9.0)	(4.7, 15.2)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 28 Treatment-emergent adverse events leading to discontinuation of treatment by system organ class, preferred term when observed for >= 10 patients, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Renal impairment at baseline	SOC: Respiratory, thoracic and mediastinal disorders	10 (11.1)	(5.5, 19.5)
Within Normal Range (N = 90)	Pneumonitis	5 (5.6)	(1.8, 12.5)
Mild Impairment (N = 69)	SOC: Respiratory, thoracic and mediastinal disorders	7 (10.1)	(4.2, 19.8)
	Pneumonitis	5 (7.2)	(2.4, 16.1)
Moderate Impairment (N = 25)	SOC: Respiratory, thoracic and mediastinal disorders	6 (24.0)	(9.4, 45.1)
	Pneumonitis	4 (16.0)	(4.5, 36.1)
Hepatic impairment at baseline	SOC: Respiratory, thoracic and mediastinal disorders	17 (16.2)	(9.7, 24.7)
Within Normal Range (N = 105)	Pneumonitis	10 (9.5)	(4.7, 16.8)
Mild Impairment (N = 76)	SOC: Respiratory, thoracic and mediastinal disorders	6 (7.9)	(3.0, 16.4)
	Pneumonitis	4 (5.3)	(1.5, 12.9)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 28 Treatment-emergent adverse events leading to discontinuation of treatment by system organ class, preferred term when observed for >= 10 patients, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Best response to T-DM1 therapy	SOC: Respiratory, thoracic and mediastinal disorders	10 (12.7)	(6.2, 22.0)
CR/PR/SD (N = 79)	Pneumonitis	7 (8.9)	(3.6, 17.4)
PD (N = 66)	SOC: Respiratory, thoracic and mediastinal disorders	9 (13.6)	(6.4, 24.3)
	Pneumonitis	3 (4.5)	(0.9, 12.7)
Brain metastases	SOC: Respiratory, thoracic and mediastinal disorders	3 (12.5)	(2.7, 32.4)
Yes (N = 24)	Pneumonitis	2 (8.3)	(1.0, 27.0)
No (N = 160)	SOC: Respiratory, thoracic and mediastinal disorders	20 (12.5)	(7.8, 18.6)
	Pneumonitis	12 (7.5)	(3.9, 12.7)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 28 Treatment-emergent adverse events leading to discontinuation of treatment by system organ class, preferred term when observed for >= 10 patients, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Bone metastases	SOC: Respiratory, thoracic and mediastinal disorders	10 (18.9)	(9.4, 32.0)
Yes (N = 53)	Pneumonitis	6 (11.3)	(4.3, 23.0)
No (N = 131)	SOC: Respiratory, thoracic and mediastinal disorders	13 (9.9)	(5.4, 16.4)
	Pneumonitis	8 (6.1)	(2.7, 11.7)
History of visceral disease	SOC: Respiratory, thoracic and mediastinal disorders	20 (11.8)	(7.4, 17.7)
Yes (N = 169)	Pneumonitis	13 (7.7)	(4.2, 12.8)
No (N = 15)	SOC: Respiratory, thoracic and mediastinal disorders	3 (20.0)	(4.3, 48.1)
	Pneumonitis	1 (6.7)	(0.2, 31.9)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 28 Treatment-emergent adverse events leading to discontinuation of treatment by system organ class, preferred term when observed for >= 10 patients, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Age	SOC: Respiratory, thoracic and mediastinal disorders	16 (11.4)	(6.7, 17.9)
<65 years (N = 140)	Pneumonitis	11 (7.9)	(4.0, 13.6)
>=65 years (N = 44)	SOC: Respiratory, thoracic and mediastinal disorders	7 (15.9)	(6.6, 30.1)
	Pneumonitis	3 (6.8)	(1.4, 18.7)
Region	SOC: Respiratory, thoracic and mediastinal disorders	11 (17.5)	(9.1, 29.1)
Asia (N = 63)	Pneumonitis	6 (9.5)	(3.6, 19.6)
North America (N = 53)	SOC: Respiratory, thoracic and mediastinal disorders	4 (7.5)	(2.1, 18.2)
	Pneumonitis	4 (7.5)	(2.1, 18.2)
EU (N = 68)	SOC: Respiratory, thoracic and mediastinal disorders	8 (11.8)	(5.2, 21.9)
	Pneumonitis	4 (5.9)	(1.6, 14.4)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 28 Treatment-emergent adverse events leading to discontinuation of treatment by system organ class, preferred term when observed for >= 10 patients, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
ECOG performance status	SOC: Respiratory, thoracic and mediastinal disorders	17 (16.7)	(10.0, 25.3)
0 (N = 102)	Pneumonitis	10 (9.8)	(4.8, 17.3)
1 (N = 81)	SOC: Respiratory, thoracic and mediastinal disorders	6 (7.4)	(2.8, 15.4)
	Pneumonitis	4 (4.9)	(1.4, 12.2)
Baseline sum of diameters of target lesions	SOC: Respiratory, thoracic and mediastinal disorders	14 (18.9)	(10.7, 29.7)
<5 cm (N = 74)	Pneumonitis	10 (13.5)	(6.7, 23.5)
>=5 cm (N = 96)	SOC: Respiratory, thoracic and mediastinal disorders	6 (6.3)	(2.3, 13.1)
	Pneumonitis	2 (2.1)	(0.3, 7.3)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 28 Treatment-emergent adverse events leading to discontinuation of treatment by system organ class, preferred term when observed for >= 10 patients, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
DS-8201a immediately following initial T-DM1	SOC: Respiratory, thoracic and mediastinal disorders	7 (12.5)	(5.2, 24.1)
Yes (N = 56)	Pneumonitis	3 (5.4)	(1.1, 14.9)
No (N = 128)	SOC: Respiratory, thoracic and mediastinal disorders	16 (12.5)	(7.3, 19.5)
	Pneumonitis	11 (8.6)	(4.4, 14.9)
HER2 status	SOC: Respiratory, thoracic and mediastinal disorders	19 (12.3)	(7.6, 18.6)
IHC3+ (N = 154)	Pneumonitis	11 (7.1)	(3.6, 12.4)
ISH+ except IHC3+ (N = 28)	SOC: Respiratory, thoracic and mediastinal disorders	4 (14.3)	(4.0, 32.7)
	Pneumonitis	3 (10.7)	(2.3, 28.2)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Overall	SOC: Gastrointestinal disorders	173 (94.0)	(89.6, 97.0)
	Nausea	144 (78.3)	(71.6, 84.0)
	Vomiting	88 (47.8)	(40.4, 55.3)
	Constipation	65 (35.3)	(28.4, 42.7)
	Diarrhoea	58 (31.5)	(24.9, 38.8)
	Dyspepsia	31 (16.8)	(11.7, 23.1)
	Stomatitis	29 (15.8)	(10.8, 21.8)
	Abdominal pain	25 (13.6)	(9.0, 19.4)
	SOC: General disorders and administration site conditions	137 (74.5)	(67.5, 80.6)
	Fatigue	92 (50.0)	(42.6, 57.4)
	Asthenia	26 (14.1)	(9.4, 20.0)
	SOC: Skin and subcutaneous tissue disorders	116 (63.0)	(55.6, 70.0)
	Alopecia	89 (48.4)	(41.0, 55.8)
	Rash	19 (10.3)	(6.3, 15.7)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Overall	SOC: Investigations	106 (57.6)	(50.1, 64.8)
	Neutrophil count decreased	41 (22.3)	(16.5, 29.0)
	White blood cell count decreased	36 (19.6)	(14.1, 26.0)
	Aspartate aminotransferase increased	33 (17.9)	(12.7, 24.3)
	Platelet count decreased	30 (16.3)	(11.3, 22.5)
	Alanine aminotransferase increased	21 (11.4)	(7.2, 16.9)
	Lymphocyte count decreased	19 (10.3)	(6.3, 15.7)
	SOC: Respiratory, thoracic and mediastinal disorders	105 (57.1)	(49.6, 64.3)
	Cough	45 (24.5)	(18.4, 31.3)
	Dyspnoea	31 (16.8)	(11.7, 23.1)
	Epistaxis	26 (14.1)	(9.4, 20.0)
	SOC: Infections and infestations	99 (53.8)	(46.3, 61.2)
	Upper respiratory tract infection	24 (13.0)	(8.5, 18.8)
	Urinary tract infection	22 (12.0)	(7.6, 17.5)
	Nasopharyngitis	20 (10.9)	(6.8, 16.3)
	SOC: Nervous system disorders	91 (49.5)	(42.0, 56.9)
	Headache	40 (21.7)	(16.0, 28.4)
	Dizziness	19 (10.3)	(6.3, 15.7)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Overall	SOC: Metabolism and nutrition disorders	84 (45.7)	(38.3, 53.1)
	Decreased appetite	59 (32.1)	(25.4, 39.3)
	Hypokalaemia	22 (12.0)	(7.6, 17.5)
	SOC: Blood and lymphatic system disorders	80 (43.5)	(36.2, 51.0)
	Anaemia	58 (31.5)	(24.9, 38.8)
	Neutropenia	27 (14.7)	(9.9, 20.6)
	SOC: Musculoskeletal and connective tissue disorders	70 (38.0)	(31.0, 45.5)
	Arthralgia	24 (13.0)	(8.5, 18.8)
	Back pain	20 (10.9)	(6.8, 16.3)
	SOC: Eye disorders	61 (33.2)	(26.4, 40.5)
	Dry eye	21 (11.4)	(7.2, 16.9)
	SOC: Psychiatric disorders	28 (15.2)	(10.4, 21.2)
	SOC: Vascular disorders	27 (14.7)	(9.9, 20.6)
	SOC: Injury, poisoning and procedural complications	26 (14.1)	(9.4, 20.0)
	SOC: Cardiac disorders	22 (12.0)	(7.6, 17.5)
	SOC: Ear and labyrinth disorders	19 (10.3)	(6.3, 15.7)
	SOC: Renal and urinary disorders	19 (10.3)	(6.3, 15.7)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Estrogen receptors	SOC: Gastrointestinal disorders	90 (96.8)	(90.9, 99.3)
Positive (N = 93)	Nausea	72 (77.4)	(67.6, 85.4)
	Vomiting	52 (55.9)	(45.2, 66.2)
	Constipation	39 (41.9)	(31.8, 52.6)
	Diarrhoea	30 (32.3)	(22.9, 42.7)
	Abdominal pain	20 (21.5)	(13.7, 31.2)
	Dyspepsia	18 (19.4)	(11.9, 28.9)
	Stomatitis	16 (17.2)	(10.2, 26.4)
	SOC: General disorders and administration site conditions	73 (78.5)	(68.8, 86.3)
	Fatigue	49 (52.7)	(42.1, 63.1)
	Asthenia	14 (15.1)	(8.5, 24.0)
	SOC: Skin and subcutaneous tissue disorders	56 (60.2)	(49.5, 70.2)
	Alopecia	46 (49.5)	(38.9, 60.0)
	Rash	10 (10.8)	(5.3, 18.9)
	SOC: Respiratory, thoracic and mediastinal disorders	54 (58.1)	(47.4, 68.2)
	Cough	24 (25.8)	(17.3, 35.9)
	Dyspnoea	15 (16.1)	(9.3, 25.2)
	Epistaxis	10 (10.8)	(5.3, 18.9)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Estrogen receptors	SOC: Investigations	53 (57.0)	(46.3, 67.2)
Positive (N = 93)	Neutrophil count decreased	22 (23.7)	(15.5, 33.6)
	White blood cell count decreased	20 (21.5)	(13.7, 31.2)
	Platelet count decreased	18 (19.4)	(11.9, 28.9)
	Aspartate aminotransferase increased	15 (16.1)	(9.3, 25.2)
	Lymphocyte count decreased	13 (14.0)	(7.7, 22.7)
	Alanine aminotransferase increased	8 (8.6)	(3.8, 16.2)
	SOC: Infections and infestations	51 (54.8)	(44.2, 65.2)
	Upper respiratory tract infection	12 (12.9)	(6.8, 21.5)
	Nasopharyngitis	11 (11.8)	(6.1, 20.2)
	Urinary tract infection	8 (8.6)	(3.8, 16.2)
	SOC: Nervous system disorders	47 (50.5)	(40.0, 61.1)
	Headache	20 (21.5)	(13.7, 31.2)
	Dizziness	9 (9.7)	(4.5, 17.6)
	SOC: Metabolism and nutrition disorders	46 (49.5)	(38.9, 60.0)
	Decreased appetite	33 (35.5)	(25.8, 46.1)
	Hypokalaemia	10 (10.8)	(5.3, 18.9)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Estrogen receptors	SOC: Blood and lymphatic system disorders	39 (41.9)	(31.8, 52.6)
Positive (N = 93)	Anaemia	29 (31.2)	(22.0, 41.6)
	Neutropenia	11 (11.8)	(6.1, 20.2)
	SOC: Eye disorders	38 (40.9)	(30.8, 51.5)
	Dry eye	14 (15.1)	(8.5, 24.0)
	SOC: Musculoskeletal and connective tissue disorders	37 (39.8)	(29.8, 50.5)
	Back pain	12 (12.9)	(6.8, 21.5)
	Arthralgia	9 (9.7)	(4.5, 17.6)
	SOC: Injury, poisoning and procedural complications	15 (16.1)	(9.3, 25.2)
	SOC: Cardiac disorders	14 (15.1)	(8.5, 24.0)
	SOC: Psychiatric disorders	14 (15.1)	(8.5, 24.0)
	SOC: Ear and labyrinth disorders	13 (14.0)	(7.7, 22.7)
	SOC: Vascular disorders	13 (14.0)	(7.7, 22.7)
	SOC: Renal and urinary disorders	8 (8.6)	(3.8, 16.2)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Estrogen receptors	SOC: Gastrointestinal disorders	81 (92.0)	(84.3, 96.7)
Negative (N = 88)	Nausea	70 (79.5)	(69.6, 87.4)
	Vomiting	35 (39.8)	(29.5, 50.8)
	Diarrhoea	28 (31.8)	(22.3, 42.6)
	Constipation	26 (29.5)	(20.3, 40.2)
	Dyspepsia	13 (14.8)	(8.1, 23.9)
	Stomatitis	13 (14.8)	(8.1, 23.9)
	Abdominal pain	5 (5.7)	(1.9, 12.8)
	SOC: General disorders and administration site conditions	63 (71.6)	(61.0, 80.7)
	Fatigue	43 (48.9)	(38.1, 59.8)
	Asthenia	12 (13.6)	(7.2, 22.6)
	SOC: Skin and subcutaneous tissue disorders	57 (64.8)	(53.9, 74.7)
	Alopecia	40 (45.5)	(34.8, 56.4)
	Rash	9 (10.2)	(4.8, 18.5)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Estrogen receptors	SOC: Investigations	53 (60.2)	(49.2, 70.5)
Negative (N = 88)	Neutrophil count decreased	19 (21.6)	(13.5, 31.6)
	Aspartate aminotransferase increased	18 (20.5)	(12.6, 30.4)
	White blood cell count decreased	16 (18.2)	(10.8, 27.8)
	Alanine aminotransferase increased	13 (14.8)	(8.1, 23.9)
	Platelet count decreased	12 (13.6)	(7.2, 22.6)
	Lymphocyte count decreased	6 (6.8)	(2.5, 14.3)
	SOC: Respiratory, thoracic and mediastinal disorders	49 (55.7)	(44.7, 66.3)
	Cough	20 (22.7)	(14.5, 32.9)
	Epistaxis	16 (18.2)	(10.8, 27.8)
	Dyspnoea	14 (15.9)	(9.0, 25.2)
	SOC: Infections and infestations	46 (52.3)	(41.4, 63.0)
	Upper respiratory tract infection	12 (13.6)	(7.2, 22.6)
	Urinary tract infection	12 (13.6)	(7.2, 22.6)
	Nasopharyngitis	9 (10.2)	(4.8, 18.5)
	SOC: Nervous system disorders	44 (50.0)	(39.1, 60.9)
	Headache	20 (22.7)	(14.5, 32.9)
	Dizziness	10 (11.4)	(5.6, 19.9)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Estrogen receptors	SOC: Blood and lymphatic system disorders	41 (46.6)	(35.9, 57.5)
Negative (N = 88)	Anaemia	29 (33.0)	(23.3, 43.8)
	Neutropenia	16 (18.2)	(10.8, 27.8)
	SOC: Metabolism and nutrition disorders	38 (43.2)	(32.7, 54.2)
	Decreased appetite	26 (29.5)	(20.3, 40.2)
	Hypokalaemia	12 (13.6)	(7.2, 22.6)
	SOC: Musculoskeletal and connective tissue disorders	32 (36.4)	(26.4, 47.3)
	Arthralgia	15 (17.0)	(9.9, 26.6)
	Back pain	8 (9.1)	(4.0, 17.1)
	SOC: Eye disorders	23 (26.1)	(17.3, 36.6)
	Dry eye	7 (8.0)	(3.3, 15.7)
	SOC: Psychiatric disorders	14 (15.9)	(9.0, 25.2)
	SOC: Vascular disorders	14 (15.9)	(9.0, 25.2)
	SOC: Injury, poisoning and procedural complications	11 (12.5)	(6.4, 21.3)
	SOC: Renal and urinary disorders	11 (12.5)	(6.4, 21.3)
	SOC: Cardiac disorders	8 (9.1)	(4.0, 17.1)
	SOC: Ear and labyrinth disorders	6 (6.8)	(2.5, 14.3)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Progesterone receptors Positive (N = 51)	SOC: Gastrointestinal disorders	48 (94.1)	(83.8, 98.8)
	Nausea	36 (70.6)	(56.2, 82.5)
	Vomiting	26 (51.0)	(36.6, 65.2)
	Constipation	16 (31.4)	(19.1, 45.9)
	Diarrhoea	13 (25.5)	(14.3, 39.6)
	Abdominal pain	10 (19.6)	(9.8, 33.1)
	Dyspepsia	8 (15.7)	(7.0, 28.6)
	Stomatitis	8 (15.7)	(7.0, 28.6)
	SOC: General disorders and administration site conditions	41 (80.4)	(66.9, 90.2)
	Fatigue	25 (49.0)	(34.8, 63.4)
	Asthenia	9 (17.6)	(8.4, 30.9)
	SOC: Infections and infestations	34 (66.7)	(52.1, 79.2)
	Nasopharyngitis	9 (17.6)	(8.4, 30.9)
	Upper respiratory tract infection	8 (15.7)	(7.0, 28.6)
	Urinary tract infection	6 (11.8)	(4.4, 23.9)
	SOC: Skin and subcutaneous tissue disorders	32 (62.7)	(48.1, 75.9)
	Alopecia	23 (45.1)	(31.1, 59.7)
	Rash	7 (13.7)	(5.7, 26.3)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Progesterone receptors Positive (N = 51)	SOC: Respiratory, thoracic and mediastinal disorders	30 (58.8)	(44.2, 72.4)
	Cough	15 (29.4)	(17.5, 43.8)
	Dyspnoea	9 (17.6)	(8.4, 30.9)
	Epistaxis	5 (9.8)	(3.3, 21.4)
	SOC: Investigations	25 (49.0)	(34.8, 63.4)
	Neutrophil count decreased	9 (17.6)	(8.4, 30.9)
	White blood cell count decreased	9 (17.6)	(8.4, 30.9)
	Aspartate aminotransferase increased	7 (13.7)	(5.7, 26.3)
	Platelet count decreased	7 (13.7)	(5.7, 26.3)
	Lymphocyte count decreased	6 (11.8)	(4.4, 23.9)
	Alanine aminotransferase increased	5 (9.8)	(3.3, 21.4)
	SOC: Musculoskeletal and connective tissue disorders	24 (47.1)	(32.9, 61.5)
	Back pain	12 (23.5)	(12.8, 37.5)
	Arthralgia	5 (9.8)	(3.3, 21.4)
	SOC: Metabolism and nutrition disorders	23 (45.1)	(31.1, 59.7)
	Decreased appetite	16 (31.4)	(19.1, 45.9)
	Hypokalaemia	6 (11.8)	(4.4, 23.9)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Progesterone receptors	SOC: Nervous system disorders	23 (45.1)	(31.1, 59.7)
Positive (N = 51)	Headache	11 (21.6)	(11.3, 35.3)
	Dizziness	3 (5.9)	(1.2, 16.2)
	SOC: Blood and lymphatic system disorders	21 (41.2)	(27.6, 55.8)
	Anaemia	12 (23.5)	(12.8, 37.5)
	Neutropenia	7 (13.7)	(5.7, 26.3)
	SOC: Eye disorders	20 (39.2)	(25.8, 53.9)
	Dry eye	8 (15.7)	(7.0, 28.6)
	SOC: Injury, poisoning and procedural complications	10 (19.6)	(9.8, 33.1)
	SOC: Cardiac disorders	8 (15.7)	(7.0, 28.6)
	SOC: Psychiatric disorders	7 (13.7)	(5.7, 26.3)
	SOC: Ear and labyrinth disorders	6 (11.8)	(4.4, 23.9)
	SOC: Vascular disorders	6 (11.8)	(4.4, 23.9)
	SOC: Renal and urinary disorders	5 (9.8)	(3.3, 21.4)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Progesterone receptors	SOC: Gastrointestinal disorders	118 (94.4)	(88.8, 97.7)
Negative (N = 125)	Nausea	104 (83.2)	(75.5, 89.3)
	Vomiting	58 (46.4)	(37.4, 55.5)
	Constipation	48 (38.4)	(29.8, 47.5)
	Diarrhoea	42 (33.6)	(25.4, 42.6)
	Dyspepsia	22 (17.6)	(11.4, 25.4)
	Stomatitis	21 (16.8)	(10.7, 24.5)
	Abdominal pain	14 (11.2)	(6.3, 18.1)
	SOC: General disorders and administration site conditions	91 (72.8)	(64.1, 80.4)
	Fatigue	65 (52.0)	(42.9, 61.0)
	Asthenia	15 (12.0)	(6.9, 19.0)
	SOC: Skin and subcutaneous tissue disorders	79 (63.2)	(54.1, 71.6)
	Alopecia	62 (49.6)	(40.5, 58.7)
	Rash	12 (9.6)	(5.1, 16.2)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Progesterone receptors	SOC: Investigations	78 (62.4)	(53.3, 70.9)
Negative (N = 125)	Neutrophil count decreased	31 (24.8)	(17.5, 33.3)
	Aspartate aminotransferase increased	26 (20.8)	(14.1, 29.0)
	White blood cell count decreased	26 (20.8)	(14.1, 29.0)
	Platelet count decreased	21 (16.8)	(10.7, 24.5)
	Alanine aminotransferase increased	16 (12.8)	(7.5, 20.0)
	Lymphocyte count decreased	12 (9.6)	(5.1, 16.2)
	SOC: Respiratory, thoracic and mediastinal disorders	71 (56.8)	(47.6, 65.6)
	Cough	28 (22.4)	(15.4, 30.7)
	Dyspnoea	20 (16.0)	(10.1, 23.6)
	Epistaxis	20 (16.0)	(10.1, 23.6)
	SOC: Nervous system disorders	65 (52.0)	(42.9, 61.0)
	Headache	29 (23.2)	(16.1, 31.6)
	Dizziness	16 (12.8)	(7.5, 20.0)
	SOC: Infections and infestations	60 (48.0)	(39.0, 57.1)
	Upper respiratory tract infection	16 (12.8)	(7.5, 20.0)
	Urinary tract infection	13 (10.4)	(5.7, 17.1)
	Nasopharyngitis	11 (8.8)	(4.5, 15.2)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Progesterone receptors Negative (N = 125)	SOC: Metabolism and nutrition disorders	59 (47.2)	(38.2, 56.3)
	Decreased appetite	41 (32.8)	(24.7, 41.8)
	Hypokalaemia	16 (12.8)	(7.5, 20.0)
	SOC: Blood and lymphatic system disorders	56 (44.8)	(35.9, 54.0)
	Anaemia	43 (34.4)	(26.1, 43.4)
	Neutropenia	19 (15.2)	(9.4, 22.7)
	SOC: Musculoskeletal and connective tissue disorders	45 (36.0)	(27.6, 45.1)
	Arthralgia	19 (15.2)	(9.4, 22.7)
	Back pain	8 (6.4)	(2.8, 12.2)
	SOC: Eye disorders	40 (32.0)	(23.9, 40.9)
	Dry eye	13 (10.4)	(5.7, 17.1)
	SOC: Psychiatric disorders	20 (16.0)	(10.1, 23.6)
	SOC: Vascular disorders	20 (16.0)	(10.1, 23.6)
	SOC: Injury, poisoning and procedural complications	16 (12.8)	(7.5, 20.0)
	SOC: Cardiac disorders	14 (11.2)	(6.3, 18.1)
	SOC: Renal and urinary disorders	14 (11.2)	(6.3, 18.1)
	SOC: Ear and labyrinth disorders	13 (10.4)	(5.7, 17.1)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Hormone receptors	SOC: Gastrointestinal disorders	93 (95.9)	(89.8, 98.9)
Positive (N = 97)	Nausea	74 (76.3)	(66.6, 84.3)
	Vomiting	52 (53.6)	(43.2, 63.8)
	Constipation	39 (40.2)	(30.4, 50.7)
	Diarrhoea	30 (30.9)	(21.9, 41.1)
	Abdominal pain	20 (20.6)	(13.1, 30.0)
	Dyspepsia	18 (18.6)	(11.4, 27.7)
	Stomatitis	17 (17.5)	(10.6, 26.6)
	SOC: General disorders and administration site conditions	77 (79.4)	(70.0, 86.9)
	Fatigue	51 (52.6)	(42.2, 62.8)
	Asthenia	15 (15.5)	(8.9, 24.2)
	SOC: Skin and subcutaneous tissue disorders	60 (61.9)	(51.4, 71.5)
	Alopecia	49 (50.5)	(40.2, 60.8)
	Rash	11 (11.3)	(5.8, 19.4)
	SOC: Respiratory, thoracic and mediastinal disorders	56 (57.7)	(47.3, 67.7)
	Cough	25 (25.8)	(17.4, 35.7)
	Dyspnoea	16 (16.5)	(9.7, 25.4)
	Epistaxis	10 (10.3)	(5.1, 18.1)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Hormone receptors	SOC: Investigations	55 (56.7)	(46.3, 66.7)
Positive (N = 97)	Neutrophil count decreased	23 (23.7)	(15.7, 33.4)
	White blood cell count decreased	21 (21.6)	(13.9, 31.2)
	Platelet count decreased	19 (19.6)	(12.2, 28.9)
	Aspartate aminotransferase increased	15 (15.5)	(8.9, 24.2)
	Lymphocyte count decreased	13 (13.4)	(7.3, 21.8)
	Alanine aminotransferase increased	8 (8.2)	(3.6, 15.6)
	SOC: Infections and infestations	53 (54.6)	(44.2, 64.8)
	Upper respiratory tract infection	13 (13.4)	(7.3, 21.8)
	Nasopharyngitis	12 (12.4)	(6.6, 20.6)
	Urinary tract infection	9 (9.3)	(4.3, 16.9)
	SOC: Metabolism and nutrition disorders	48 (49.5)	(39.2, 59.8)
	Decreased appetite	35 (36.1)	(26.6, 46.5)
	Hypokalaemia	11 (11.3)	(5.8, 19.4)
	SOC: Nervous system disorders	48 (49.5)	(39.2, 59.8)
	Headache	20 (20.6)	(13.1, 30.0)
	Dizziness	9 (9.3)	(4.3, 16.9)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Hormone receptors	SOC: Blood and lymphatic system disorders	41 (42.3)	(32.3, 52.7)
Positive (N = 97)	Anaemia	29 (29.9)	(21.0, 40.0)
	Neutropenia	12 (12.4)	(6.6, 20.6)
	SOC: Musculoskeletal and connective tissue disorders	39 (40.2)	(30.4, 50.7)
	Back pain	14 (14.4)	(8.1, 23.0)
	Arthralgia	10 (10.3)	(5.1, 18.1)
	SOC: Eye disorders	38 (39.2)	(29.4, 49.6)
	Dry eye	14 (14.4)	(8.1, 23.0)
	SOC: Injury, poisoning and procedural complications	16 (16.5)	(9.7, 25.4)
	SOC: Cardiac disorders	14 (14.4)	(8.1, 23.0)
	SOC: Ear and labyrinth disorders	14 (14.4)	(8.1, 23.0)
	SOC: Psychiatric disorders	14 (14.4)	(8.1, 23.0)
	SOC: Vascular disorders	13 (13.4)	(7.3, 21.8)
	SOC: Renal and urinary disorders	9 (9.3)	(4.3, 16.9)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Hormone receptors	SOC: Gastrointestinal disorders	77 (92.8)	(84.9, 97.3)
Negative (N = 83)	Nausea	68 (81.9)	(72.0, 89.5)
	Vomiting	35 (42.2)	(31.4, 53.5)
	Diarrhoea	28 (33.7)	(23.7, 44.9)
	Constipation	26 (31.3)	(21.6, 42.4)
	Dyspepsia	13 (15.7)	(8.6, 25.3)
	Stomatitis	12 (14.5)	(7.7, 23.9)
	Abdominal pain	5 (6.0)	(2.0, 13.5)
	SOC: General disorders and administration site conditions	59 (71.1)	(60.1, 80.5)
	Fatigue	41 (49.4)	(38.2, 60.6)
	Asthenia	11 (13.3)	(6.8, 22.5)
	SOC: Skin and subcutaneous tissue disorders	52 (62.7)	(51.3, 73.0)
	Alopecia	37 (44.6)	(33.7, 55.9)
	Rash	8 (9.6)	(4.3, 18.1)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Hormone receptors	SOC: Investigations	50 (60.2)	(48.9, 70.8)
Negative (N = 83)	Aspartate aminotransferase increased	18 (21.7)	(13.4, 32.1)
	Neutrophil count decreased	18 (21.7)	(13.4, 32.1)
	White blood cell count decreased	15 (18.1)	(10.5, 28.0)
	Alanine aminotransferase increased	13 (15.7)	(8.6, 25.3)
	Platelet count decreased	11 (13.3)	(6.8, 22.5)
	Lymphocyte count decreased	6 (7.2)	(2.7, 15.1)
	SOC: Respiratory, thoracic and mediastinal disorders	47 (56.6)	(45.3, 67.5)
	Cough	19 (22.9)	(14.4, 33.4)
	Epistaxis	16 (19.3)	(11.4, 29.4)
	Dyspnoea	13 (15.7)	(8.6, 25.3)
	SOC: Infections and infestations	43 (51.8)	(40.6, 62.9)
	Upper respiratory tract infection	11 (13.3)	(6.8, 22.5)
	Urinary tract infection	11 (13.3)	(6.8, 22.5)
	Nasopharyngitis	8 (9.6)	(4.3, 18.1)
	SOC: Nervous system disorders	42 (50.6)	(39.4, 61.8)
	Headache	20 (24.1)	(15.4, 34.7)
	Dizziness	10 (12.0)	(5.9, 21.0)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Hormone receptors	SOC: Blood and lymphatic system disorders	39 (47.0)	(35.9, 58.3)
Negative (N = 83)	Anaemia	29 (34.9)	(24.8, 46.2)
	Neutropenia	15 (18.1)	(10.5, 28.0)
	SOC: Metabolism and nutrition disorders	35 (42.2)	(31.4, 53.5)
	Decreased appetite	23 (27.7)	(18.4, 38.6)
	Hypokalaemia	11 (13.3)	(6.8, 22.5)
	SOC: Musculoskeletal and connective tissue disorders	30 (36.1)	(25.9, 47.4)
	Arthralgia	14 (16.9)	(9.5, 26.7)
	Back pain	6 (7.2)	(2.7, 15.1)
	SOC: Eye disorders	23 (27.7)	(18.4, 38.6)
	Dry eye	7 (8.4)	(3.5, 16.6)
	SOC: Psychiatric disorders	14 (16.9)	(9.5, 26.7)
	SOC: Vascular disorders	14 (16.9)	(9.5, 26.7)
	SOC: Injury, poisoning and procedural complications	10 (12.0)	(5.9, 21.0)
	SOC: Renal and urinary disorders	10 (12.0)	(5.9, 21.0)
	SOC: Cardiac disorders	8 (9.6)	(4.3, 18.1)
	SOC: Ear and labyrinth disorders	5 (6.0)	(2.0, 13.5)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Lines of prior systemic therapy not including hormone therapy < 3 lines (N = 17)	SOC: Gastrointestinal disorders	15 (88.2)	(63.6, 98.5)
	Nausea	12 (70.6)	(44.0, 89.7)
	Vomiting	7 (41.2)	(18.4, 67.1)
	Constipation	5 (29.4)	(10.3, 56.0)
	Dyspepsia	4 (23.5)	(6.8, 49.9)
	Diarrhoea	3 (17.6)	(3.8, 43.4)
	Stomatitis	2 (11.8)	(1.5, 36.4)
	Abdominal pain	1 (5.9)	(0.1, 28.7)
	SOC: Skin and subcutaneous tissue disorders	14 (82.4)	(56.6, 96.2)
	Alopecia	10 (58.8)	(32.9, 81.6)
	Rash	2 (11.8)	(1.5, 36.4)
	SOC: General disorders and administration site conditions	13 (76.5)	(50.1, 93.2)
	Fatigue	8 (47.1)	(23.0, 72.2)
	Asthenia	1 (5.9)	(0.1, 28.7)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Lines of prior systemic therapy not including hormone therapy < 3 lines (N = 17)	SOC: Investigations	13 (76.5)	(50.1, 93.2)
	Neutrophil count decreased	7 (41.2)	(18.4, 67.1)
	Platelet count decreased	6 (35.3)	(14.2, 61.7)
	White blood cell count decreased	6 (35.3)	(14.2, 61.7)
	Aspartate aminotransferase increased	5 (29.4)	(10.3, 56.0)
	Lymphocyte count decreased	4 (23.5)	(6.8, 49.9)
	Alanine aminotransferase increased	3 (17.6)	(3.8, 43.4)
	SOC: Respiratory, thoracic and mediastinal disorders	13 (76.5)	(50.1, 93.2)
	Cough	6 (35.3)	(14.2, 61.7)
	Epistaxis	6 (35.3)	(14.2, 61.7)
	Dyspnoea	4 (23.5)	(6.8, 49.9)
	SOC: Metabolism and nutrition disorders	11 (64.7)	(38.3, 85.8)
	Decreased appetite	6 (35.3)	(14.2, 61.7)
	SOC: Infections and infestations	10 (58.8)	(32.9, 81.6)
	Upper respiratory tract infection	4 (23.5)	(6.8, 49.9)
	Nasopharyngitis	3 (17.6)	(3.8, 43.4)
	Urinary tract infection	2 (11.8)	(1.5, 36.4)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Lines of prior systemic therapy not including hormone therapy < 3 lines (N = 17)	SOC: Eye disorders	8 (47.1)	(23.0, 72.2)
	Dry eye	3 (17.6)	(3.8, 43.4)
	SOC: Blood and lymphatic system disorders	6 (35.3)	(14.2, 61.7)
	Anaemia	6 (35.3)	(14.2, 61.7)
	Neutropenia	1 (5.9)	(0.1, 28.7)
	SOC: Musculoskeletal and connective tissue disorders	5 (29.4)	(10.3, 56.0)
	Arthralgia	2 (11.8)	(1.5, 36.4)
	Back pain	1 (5.9)	(0.1, 28.7)
	SOC: Injury, poisoning and procedural complications	4 (23.5)	(6.8, 49.9)
	SOC: Nervous system disorders	4 (23.5)	(6.8, 49.9)
	Dizziness	1 (5.9)	(0.1, 28.7)
	Headache	1 (5.9)	(0.1, 28.7)
	SOC: Renal and urinary disorders	4 (23.5)	(6.8, 49.9)
	SOC: Psychiatric disorders	3 (17.6)	(3.8, 43.4)
	SOC: Cardiac disorders	2 (11.8)	(1.5, 36.4)
	SOC: Ear and labyrinth disorders	1 (5.9)	(0.1, 28.7)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

Subgroup	SOC/Preferred Term	Overall 5.4 mg/kg (N = 184) n (%)	95% CI [a]
Lines of prior systemic therapy not including hormone therapy >= 3 lines (N = 167)	SOC: Gastrointestinal disorders	158 (94.6)	(90.0, 97.5)
	Nausea	132 (79.0)	(72.1, 84.9)
	Vomiting	81 (48.5)	(40.7, 56.3)
	Constipation	60 (35.9)	(28.7, 43.7)
	Diarrhoea	55 (32.9)	(25.9, 40.6)
	Dyspepsia	27 (16.2)	(10.9, 22.6)
	Stomatitis	27 (16.2)	(10.9, 22.6)
	Abdominal pain	24 (14.4)	(9.4, 20.6)
	SOC: General disorders and administration site conditions	124 (74.3)	(66.9, 80.7)
	Fatigue	84 (50.3)	(42.5, 58.1)
	Asthenia	25 (15.0)	(9.9, 21.3)
	SOC: Skin and subcutaneous tissue disorders	102 (61.1)	(53.2, 68.5)
	Alopecia	79 (47.3)	(39.5, 55.2)
	Rash	17 (10.2)	(6.0, 15.8)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Lines of prior systemic therapy not including hormone therapy >= 3 lines (N = 167)	SOC: Investigations	93 (55.7)	(47.8, 63.4)
	Neutrophil count decreased	34 (20.4)	(14.5, 27.3)
	White blood cell count decreased	30 (18.0)	(12.5, 24.6)
	Aspartate aminotransferase increased	28 (16.8)	(11.4, 23.3)
	Platelet count decreased	24 (14.4)	(9.4, 20.6)
	Alanine aminotransferase increased	18 (10.8)	(6.5, 16.5)
	Lymphocyte count decreased	15 (9.0)	(5.1, 14.4)
	SOC: Respiratory, thoracic and mediastinal disorders	92 (55.1)	(47.2, 62.8)
	Cough	39 (23.4)	(17.2, 30.5)
	Dyspnoea	27 (16.2)	(10.9, 22.6)
	Epistaxis	20 (12.0)	(7.5, 17.9)
	SOC: Infections and infestations	89 (53.3)	(45.4, 61.0)
	Upper respiratory tract infection	20 (12.0)	(7.5, 17.9)
	Urinary tract infection	20 (12.0)	(7.5, 17.9)
	Nasopharyngitis	17 (10.2)	(6.0, 15.8)
	SOC: Nervous system disorders	87 (52.1)	(44.2, 59.9)
	Headache	39 (23.4)	(17.2, 30.5)
	Dizziness	18 (10.8)	(6.5, 16.5)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

Subgroup	SOC/Preferred Term	Overall 5.4 mg/kg (N = 184) n (%)	95% CI [a]
Lines of prior systemic therapy not including hormone therapy >= 3 lines (N = 167)	SOC: Blood and lymphatic system disorders	74 (44.3)	(36.6, 52.2)
	Anaemia	52 (31.1)	(24.2, 38.8)
	Neutropenia	26 (15.6)	(10.4, 22.0)
	SOC: Metabolism and nutrition disorders	73 (43.7)	(36.1, 51.6)
	Decreased appetite	53 (31.7)	(24.8, 39.4)
	Hypokalaemia	22 (13.2)	(8.4, 19.3)
	SOC: Musculoskeletal and connective tissue disorders	65 (38.9)	(31.5, 46.8)
	Arthralgia	22 (13.2)	(8.4, 19.3)
	Back pain	19 (11.4)	(7.0, 17.2)
	SOC: Eye disorders	53 (31.7)	(24.8, 39.4)
	Dry eye	18 (10.8)	(6.5, 16.5)
	SOC: Vascular disorders	27 (16.2)	(10.9, 22.6)
	SOC: Psychiatric disorders	25 (15.0)	(9.9, 21.3)
	SOC: Injury, poisoning and procedural complications	22 (13.2)	(8.4, 19.3)
	SOC: Cardiac disorders	20 (12.0)	(7.5, 17.9)
	SOC: Ear and labyrinth disorders	18 (10.8)	(6.5, 16.5)
	SOC: Renal and urinary disorders	15 (9.0)	(5.1, 14.4)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Prior pertuzumab	SOC: Gastrointestinal disorders	114 (94.2)	(88.4, 97.6)
Yes (N = 121)	Nausea	90 (74.4)	(65.6, 81.9)
	Vomiting	59 (48.8)	(39.6, 58.0)
	Constipation	45 (37.2)	(28.6, 46.4)
	Diarrhoea	35 (28.9)	(21.0, 37.9)
	Dyspepsia	22 (18.2)	(11.8, 26.2)
	Stomatitis	19 (15.7)	(9.7, 23.4)
	Abdominal pain	13 (10.7)	(5.8, 17.7)
	SOC: General disorders and administration site conditions	86 (71.1)	(62.1, 79.0)
	Fatigue	60 (49.6)	(40.4, 58.8)
	Asthenia	12 (9.9)	(5.2, 16.7)
	SOC: Skin and subcutaneous tissue disorders	75 (62.0)	(52.7, 70.7)
	Alopecia	57 (47.1)	(38.0, 56.4)
	Rash	11 (9.1)	(4.6, 15.7)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

Subgroup	SOC/Preferred Term	Overall 5.4 mg/kg (N = 184) n (%)	95% CI [a]
Prior pertuzumab	SOC: Investigations	72 (59.5)	(50.2, 68.3)
Yes (N = 121)	Neutrophil count decreased	35 (28.9)	(21.0, 37.9)
	White blood cell count decreased	28 (23.1)	(16.0, 31.7)
	Aspartate aminotransferase increased	23 (19.0)	(12.4, 27.1)
	Platelet count decreased	21 (17.4)	(11.1, 25.3)
	Alanine aminotransferase increased	14 (11.6)	(6.5, 18.7)
	Lymphocyte count decreased	14 (11.6)	(6.5, 18.7)
	SOC: Infections and infestations	67 (55.4)	(46.1, 64.4)
	Upper respiratory tract infection	18 (14.9)	(9.1, 22.5)
	Urinary tract infection	15 (12.4)	(7.1, 19.6)
	Nasopharyngitis	14 (11.6)	(6.5, 18.7)
	SOC: Respiratory, thoracic and mediastinal disorders	66 (54.5)	(45.2, 63.6)
	Cough	35 (28.9)	(21.0, 37.9)
	Dyspnoea	17 (14.0)	(8.4, 21.5)
	Epistaxis	16 (13.2)	(7.8, 20.6)
	SOC: Nervous system disorders	57 (47.1)	(38.0, 56.4)
	Headache	29 (24.0)	(16.7, 32.6)
	Dizziness	11 (9.1)	(4.6, 15.7)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Prior pertuzumab	SOC: Metabolism and nutrition disorders	54 (44.6)	(35.6, 53.9)
Yes (N = 121)	Decreased appetite	35 (28.9)	(21.0, 37.9)
	Hypokalaemia	16 (13.2)	(7.8, 20.6)
	SOC: Blood and lymphatic system disorders	49 (40.5)	(31.7, 49.8)
	Anaemia	40 (33.1)	(24.8, 42.2)
	Neutropenia	10 (8.3)	(4.0, 14.7)
	SOC: Musculoskeletal and connective tissue disorders	42 (34.7)	(26.3, 43.9)
	Arthralgia	17 (14.0)	(8.4, 21.5)
	Back pain	14 (11.6)	(6.5, 18.7)
	SOC: Eye disorders	37 (30.6)	(22.5, 39.6)
	Dry eye	16 (13.2)	(7.8, 20.6)
	SOC: Injury, poisoning and procedural complications	20 (16.5)	(10.4, 24.4)
	SOC: Psychiatric disorders	16 (13.2)	(7.8, 20.6)
	SOC: Vascular disorders	16 (13.2)	(7.8, 20.6)
	SOC: Cardiac disorders	13 (10.7)	(5.8, 17.7)
	SOC: Ear and labyrinth disorders	13 (10.7)	(5.8, 17.7)
	SOC: Renal and urinary disorders	12 (9.9)	(5.2, 16.7)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

Subgroup	SOC/Preferred Term	Overall 5.4 mg/kg (N = 184) n (%)	95% CI [a]
Prior pertuzumab	SOC: Gastrointestinal disorders	59 (93.7)	(84.5, 98.2)
No (N = 63)	Nausea	54 (85.7)	(74.6, 93.3)
	Vomiting	29 (46.0)	(33.4, 59.1)
	Diarrhoea	23 (36.5)	(24.7, 49.6)
	Constipation	20 (31.7)	(20.6, 44.7)
	Abdominal pain	12 (19.0)	(10.2, 30.9)
	Stomatitis	10 (15.9)	(7.9, 27.3)
	Dyspepsia	9 (14.3)	(6.7, 25.4)
	SOC: General disorders and administration site conditions	51 (81.0)	(69.1, 89.8)
	Fatigue	32 (50.8)	(37.9, 63.6)
	Asthenia	14 (22.2)	(12.7, 34.5)
	SOC: Skin and subcutaneous tissue disorders	41 (65.1)	(52.0, 76.7)
	Alopecia	32 (50.8)	(37.9, 63.6)
	Rash	8 (12.7)	(5.6, 23.5)
	SOC: Respiratory, thoracic and mediastinal disorders	39 (61.9)	(48.8, 73.9)
	Dyspnoea	14 (22.2)	(12.7, 34.5)
	Cough	10 (15.9)	(7.9, 27.3)
	Epistaxis	10 (15.9)	(7.9, 27.3)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Prior pertuzumab	SOC: Investigations	34 (54.0)	(40.9, 66.6)
No (N = 63)	Aspartate aminotransferase increased	10 (15.9)	(7.9, 27.3)
	Platelet count decreased	9 (14.3)	(6.7, 25.4)
	White blood cell count decreased	8 (12.7)	(5.6, 23.5)
	Alanine aminotransferase increased	7 (11.1)	(4.6, 21.6)
	Neutrophil count decreased	6 (9.5)	(3.6, 19.6)
	Lymphocyte count decreased	5 (7.9)	(2.6, 17.6)
	SOC: Nervous system disorders	34 (54.0)	(40.9, 66.6)
	Headache	11 (17.5)	(9.1, 29.1)
	Dizziness	8 (12.7)	(5.6, 23.5)
	SOC: Infections and infestations	32 (50.8)	(37.9, 63.6)
	Urinary tract infection	7 (11.1)	(4.6, 21.6)
	Nasopharyngitis	6 (9.5)	(3.6, 19.6)
	Upper respiratory tract infection	6 (9.5)	(3.6, 19.6)
	SOC: Blood and lymphatic system disorders	31 (49.2)	(36.4, 62.1)
	Anaemia	18 (28.6)	(17.9, 41.3)
	Neutropenia	17 (27.0)	(16.6, 39.7)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Prior pertuzumab	SOC: Metabolism and nutrition disorders	30 (47.6)	(34.9, 60.6)
No (N = 63)	Decreased appetite	24 (38.1)	(26.1, 51.2)
	Hypokalaemia	6 (9.5)	(3.6, 19.6)
	SOC: Musculoskeletal and connective tissue disorders	28 (44.4)	(31.9, 57.5)
	Arthralgia	7 (11.1)	(4.6, 21.6)
	Back pain	6 (9.5)	(3.6, 19.6)
	SOC: Eye disorders	24 (38.1)	(26.1, 51.2)
	Dry eye	5 (7.9)	(2.6, 17.6)
	SOC: Psychiatric disorders	12 (19.0)	(10.2, 30.9)
	SOC: Vascular disorders	11 (17.5)	(9.1, 29.1)
	SOC: Cardiac disorders	9 (14.3)	(6.7, 25.4)
	SOC: Renal and urinary disorders	7 (11.1)	(4.6, 21.6)
	SOC: Ear and labyrinth disorders	6 (9.5)	(3.6, 19.6)
	SOC: Injury, poisoning and procedural complications	6 (9.5)	(3.6, 19.6)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

Subgroup	SOC/Preferred Term	Overall 5.4 mg/kg (N = 184) n (%)	95% CI [a]
Prior pertuzumab in 1st or 2nd line in advanced/metastatic breast cancer Yes (N = 51)	SOC: Gastrointestinal disorders	47 (92.2)	(81.1, 97.8)
	Nausea	39 (76.5)	(62.5, 87.2)
	Vomiting	28 (54.9)	(40.3, 68.9)
	Constipation	16 (31.4)	(19.1, 45.9)
	Diarrhoea	12 (23.5)	(12.8, 37.5)
	Dyspepsia	11 (21.6)	(11.3, 35.3)
	Stomatitis	4 (7.8)	(2.2, 18.9)
	Abdominal pain	3 (5.9)	(1.2, 16.2)
	SOC: General disorders and administration site conditions	34 (66.7)	(52.1, 79.2)
	Fatigue	22 (43.1)	(29.3, 57.8)
	Asthenia	6 (11.8)	(4.4, 23.9)
	SOC: Skin and subcutaneous tissue disorders	30 (58.8)	(44.2, 72.4)
	Alopecia	22 (43.1)	(29.3, 57.8)
	Rash	2 (3.9)	(0.5, 13.5)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Prior pertuzumab in 1st or 2nd line in advanced/metastatic breast cancer Yes (N = 51)	SOC: Investigations	29 (56.9)	(42.2, 70.7)
	Neutrophil count decreased	12 (23.5)	(12.8, 37.5)
	White blood cell count decreased	9 (17.6)	(8.4, 30.9)
	Aspartate aminotransferase increased	8 (15.7)	(7.0, 28.6)
	Platelet count decreased	7 (13.7)	(5.7, 26.3)
	Alanine aminotransferase increased	6 (11.8)	(4.4, 23.9)
	Lymphocyte count decreased	5 (9.8)	(3.3, 21.4)
	SOC: Infections and infestations	28 (54.9)	(40.3, 68.9)
	Upper respiratory tract infection	9 (17.6)	(8.4, 30.9)
	Nasopharyngitis	5 (9.8)	(3.3, 21.4)
	Urinary tract infection	4 (7.8)	(2.2, 18.9)
	SOC: Respiratory, thoracic and mediastinal disorders	28 (54.9)	(40.3, 68.9)
	Cough	15 (29.4)	(17.5, 43.8)
	Dyspnoea	7 (13.7)	(5.7, 26.3)
	Epistaxis	6 (11.8)	(4.4, 23.9)
	SOC: Metabolism and nutrition disorders	24 (47.1)	(32.9, 61.5)
	Decreased appetite	13 (25.5)	(14.3, 39.6)
	Hypokalaemia	6 (11.8)	(4.4, 23.9)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Prior pertuzumab in 1st or 2nd line in advanced/metastatic breast cancer Yes (N = 51)	SOC: Nervous system disorders	19 (37.3)	(24.1, 51.9)
	Headache	10 (19.6)	(9.8, 33.1)
	Dizziness	4 (7.8)	(2.2, 18.9)
	SOC: Blood and lymphatic system disorders	18 (35.3)	(22.4, 49.9)
	Anaemia	14 (27.5)	(15.9, 41.7)
	Neutropenia	5 (9.8)	(3.3, 21.4)
	SOC: Musculoskeletal and connective tissue disorders	17 (33.3)	(20.8, 47.9)
	Arthralgia	5 (9.8)	(3.3, 21.4)
	Back pain	5 (9.8)	(3.3, 21.4)
	SOC: Eye disorders	16 (31.4)	(19.1, 45.9)
	Dry eye	7 (13.7)	(5.7, 26.3)
	SOC: Injury, poisoning and procedural complications	9 (17.6)	(8.4, 30.9)
	SOC: Vascular disorders	7 (13.7)	(5.7, 26.3)
	SOC: Cardiac disorders	6 (11.8)	(4.4, 23.9)
	SOC: Psychiatric disorders	6 (11.8)	(4.4, 23.9)
	SOC: Renal and urinary disorders	6 (11.8)	(4.4, 23.9)
	SOC: Ear and labyrinth disorders	2 (3.9)	(0.5, 13.5)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

Subgroup	SOC/Preferred Term	Overall 5.4 mg/kg (N = 184) n (%)	95% CI [a]
Prior pertuzumab in 1st or 2nd line in advanced/metastatic breast cancer No (N = 133)	SOC: Gastrointestinal disorders	126 (94.7)	(89.5, 97.9)
	Nausea	105 (78.9)	(71.0, 85.5)
	Vomiting	60 (45.1)	(36.5, 54.0)
	Constipation	49 (36.8)	(28.6, 45.6)
	Diarrhoea	46 (34.6)	(26.6, 43.3)
	Stomatitis	25 (18.8)	(12.5, 26.5)
	Abdominal pain	22 (16.5)	(10.7, 24.0)
	Dyspepsia	20 (15.0)	(9.4, 22.3)
	SOC: General disorders and administration site conditions	103 (77.4)	(69.4, 84.2)
	Fatigue	70 (52.6)	(43.8, 61.3)
	Asthenia	20 (15.0)	(9.4, 22.3)
	SOC: Skin and subcutaneous tissue disorders	86 (64.7)	(55.9, 72.7)
	Alopecia	67 (50.4)	(41.6, 59.2)
	Rash	17 (12.8)	(7.6, 19.7)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Prior pertuzumab in 1st or 2nd line in advanced/metastatic breast cancer	SOC: Investigations	77 (57.9)	(49.0, 66.4)
	Neutrophil count decreased	29 (21.8)	(15.1, 29.8)
No (N = 133)	White blood cell count decreased	27 (20.3)	(13.8, 28.1)
	Aspartate aminotransferase increased	25 (18.8)	(12.5, 26.5)
	Platelet count decreased	23 (17.3)	(11.3, 24.8)
	Alanine aminotransferase increased	15 (11.3)	(6.5, 17.9)
	Lymphocyte count decreased	14 (10.5)	(5.9, 17.0)
	SOC: Respiratory, thoracic and mediastinal disorders	77 (57.9)	(49.0, 66.4)
	Cough	30 (22.6)	(15.8, 30.6)
	Dyspnoea	24 (18.0)	(11.9, 25.6)
	Epistaxis	20 (15.0)	(9.4, 22.3)
	SOC: Nervous system disorders	72 (54.1)	(45.3, 62.8)
	Headache	30 (22.6)	(15.8, 30.6)
	Dizziness	15 (11.3)	(6.5, 17.9)
	SOC: Infections and infestations	71 (53.4)	(44.5, 62.1)
	Urinary tract infection	18 (13.5)	(8.2, 20.5)
	Nasopharyngitis	15 (11.3)	(6.5, 17.9)
	Upper respiratory tract infection	15 (11.3)	(6.5, 17.9)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Prior pertuzumab in 1st or 2nd line in advanced/metastatic breast cancer No (N = 133)	SOC: Blood and lymphatic system disorders	62 (46.6)	(37.9, 55.5)
	Anaemia	44 (33.1)	(25.2, 41.8)
	Neutropenia	22 (16.5)	(10.7, 24.0)
	SOC: Metabolism and nutrition disorders	60 (45.1)	(36.5, 54.0)
	Decreased appetite	46 (34.6)	(26.6, 43.3)
	Hypokalaemia	16 (12.0)	(7.0, 18.8)
	SOC: Musculoskeletal and connective tissue disorders	53 (39.8)	(31.5, 48.7)
	Arthralgia	19 (14.3)	(8.8, 21.4)
	Back pain	15 (11.3)	(6.5, 17.9)
	SOC: Eye disorders	45 (33.8)	(25.9, 42.5)
	Dry eye	14 (10.5)	(5.9, 17.0)
	SOC: Psychiatric disorders	22 (16.5)	(10.7, 24.0)
	SOC: Vascular disorders	20 (15.0)	(9.4, 22.3)
	SOC: Ear and labyrinth disorders	17 (12.8)	(7.6, 19.7)
	SOC: Injury, poisoning and procedural complications	17 (12.8)	(7.6, 19.7)
	SOC: Cardiac disorders	16 (12.0)	(7.0, 18.8)
	SOC: Renal and urinary disorders	13 (9.8)	(5.3, 16.1)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Renal impairment at baseline	SOC: Gastrointestinal disorders	86 (95.6)	(89.0, 98.8)
Within Normal Range (N = 90)	Nausea	74 (82.2)	(72.7, 89.5)
	Vomiting	47 (52.2)	(41.4, 62.9)
	Diarrhoea	30 (33.3)	(23.7, 44.1)
	Constipation	29 (32.2)	(22.8, 42.9)
	Dyspepsia	16 (17.8)	(10.5, 27.3)
	Abdominal pain	13 (14.4)	(7.9, 23.4)
	Stomatitis	11 (12.2)	(6.3, 20.8)
	SOC: General disorders and administration site conditions	70 (77.8)	(67.8, 85.9)
	Fatigue	46 (51.1)	(40.3, 61.8)
	Asthenia	14 (15.6)	(8.8, 24.7)
	SOC: Skin and subcutaneous tissue disorders	57 (63.3)	(52.5, 73.2)
	Alopecia	41 (45.6)	(35.0, 56.4)
	Rash	10 (11.1)	(5.5, 19.5)
	SOC: Infections and infestations	50 (55.6)	(44.7, 66.0)
	Upper respiratory tract infection	16 (17.8)	(10.5, 27.3)
	Nasopharyngitis	11 (12.2)	(6.3, 20.8)
	Urinary tract infection	9 (10.0)	(4.7, 18.1)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Renal impairment at baseline	SOC: Investigations	50 (55.6)	(44.7, 66.0)
Within Normal Range (N = 90)	Neutrophil count decreased	19 (21.1)	(13.2, 31.0)
	Aspartate aminotransferase increased	15 (16.7)	(9.6, 26.0)
	Platelet count decreased	15 (16.7)	(9.6, 26.0)
	White blood cell count decreased	13 (14.4)	(7.9, 23.4)
	Lymphocyte count decreased	9 (10.0)	(4.7, 18.1)
	Alanine aminotransferase increased	8 (8.9)	(3.9, 16.8)
	SOC: Respiratory, thoracic and mediastinal disorders	48 (53.3)	(42.5, 63.9)
	Cough	22 (24.4)	(16.0, 34.6)
	Dyspnoea	14 (15.6)	(8.8, 24.7)
	Epistaxis	12 (13.3)	(7.1, 22.1)
	SOC: Nervous system disorders	47 (52.2)	(41.4, 62.9)
	Headache	21 (23.3)	(15.1, 33.4)
	Dizziness	8 (8.9)	(3.9, 16.8)
	SOC: Metabolism and nutrition disorders	39 (43.3)	(32.9, 54.2)
	Decreased appetite	24 (26.7)	(17.9, 37.0)
	Hypokalaemia	8 (8.9)	(3.9, 16.8)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Renal impairment at baseline	SOC: Musculoskeletal and connective tissue disorders	37 (41.1)	(30.8, 52.0)
Within Normal Range (N = 90)	Arthralgia	16 (17.8)	(10.5, 27.3)
	Back pain	7 (7.8)	(3.2, 15.4)
	SOC: Blood and lymphatic system disorders	31 (34.4)	(24.7, 45.2)
	Anaemia	23 (25.6)	(16.9, 35.8)
	Neutropenia	12 (13.3)	(7.1, 22.1)
	SOC: Eye disorders	31 (34.4)	(24.7, 45.2)
	Dry eye	13 (14.4)	(7.9, 23.4)
	SOC: Psychiatric disorders	18 (20.0)	(12.3, 29.8)
	SOC: Vascular disorders	14 (15.6)	(8.8, 24.7)
	SOC: Injury, poisoning and procedural complications	12 (13.3)	(7.1, 22.1)
	SOC: Renal and urinary disorders	10 (11.1)	(5.5, 19.5)
	SOC: Ear and labyrinth disorders	8 (8.9)	(3.9, 16.8)
	SOC: Cardiac disorders	7 (7.8)	(3.2, 15.4)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Renal impairment at baseline	SOC: Gastrointestinal disorders	66 (95.7)	(87.8, 99.1)
Mild Impairment (N = 69)	Nausea	54 (78.3)	(66.7, 87.3)
	Vomiting	31 (44.9)	(32.9, 57.4)
	Constipation	28 (40.6)	(28.9, 53.1)
	Diarrhoea	21 (30.4)	(19.9, 42.7)
	Dyspepsia	14 (20.3)	(11.6, 31.7)
	Abdominal pain	12 (17.4)	(9.3, 28.4)
	Stomatitis	11 (15.9)	(8.2, 26.7)
	SOC: General disorders and administration site conditions	49 (71.0)	(58.8, 81.3)
	Fatigue	33 (47.8)	(35.6, 60.2)
	Asthenia	8 (11.6)	(5.1, 21.6)
	SOC: Skin and subcutaneous tissue disorders	45 (65.2)	(52.8, 76.3)
	Alopecia	35 (50.7)	(38.4, 63.0)
	Rash	7 (10.1)	(4.2, 19.8)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Renal impairment at baseline	SOC: Investigations	42 (60.9)	(48.4, 72.4)
Mild Impairment (N = 69)	Neutrophil count decreased	16 (23.2)	(13.9, 34.9)
	White blood cell count decreased	15 (21.7)	(12.7, 33.3)
	Aspartate aminotransferase increased	13 (18.8)	(10.4, 30.1)
	Alanine aminotransferase increased	11 (15.9)	(8.2, 26.7)
	Platelet count decreased	9 (13.0)	(6.1, 23.3)
	Lymphocyte count decreased	4 (5.8)	(1.6, 14.2)
	SOC: Infections and infestations	39 (56.5)	(44.0, 68.4)
	Urinary tract infection	10 (14.5)	(7.2, 25.0)
	Nasopharyngitis	8 (11.6)	(5.1, 21.6)
	Upper respiratory tract infection	5 (7.2)	(2.4, 16.1)
	SOC: Respiratory, thoracic and mediastinal disorders	39 (56.5)	(44.0, 68.4)
	Cough	17 (24.6)	(15.1, 36.5)
	Dyspnoea	13 (18.8)	(10.4, 30.1)
	Epistaxis	9 (13.0)	(6.1, 23.3)
	SOC: Blood and lymphatic system disorders	36 (52.2)	(39.8, 64.4)
	Anaemia	23 (33.3)	(22.4, 45.7)
	Neutropenia	13 (18.8)	(10.4, 30.1)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Renal impairment at baseline	SOC: Nervous system disorders	34 (49.3)	(37.0, 61.6)
Mild Impairment (N = 69)	Headache	15 (21.7)	(12.7, 33.3)
	Dizziness	10 (14.5)	(7.2, 25.0)
	SOC: Metabolism and nutrition disorders	31 (44.9)	(32.9, 57.4)
	Decreased appetite	24 (34.8)	(23.7, 47.2)
	Hypokalaemia	11 (15.9)	(8.2, 26.7)
	SOC: Musculoskeletal and connective tissue disorders	28 (40.6)	(28.9, 53.1)
	Back pain	11 (15.9)	(8.2, 26.7)
	Arthralgia	7 (10.1)	(4.2, 19.8)
	SOC: Eye disorders	22 (31.9)	(21.2, 44.2)
	Dry eye	7 (10.1)	(4.2, 19.8)
	SOC: Vascular disorders	12 (17.4)	(9.3, 28.4)
	SOC: Injury, poisoning and procedural complications	11 (15.9)	(8.2, 26.7)
	SOC: Cardiac disorders	10 (14.5)	(7.2, 25.0)
	SOC: Renal and urinary disorders	8 (11.6)	(5.1, 21.6)
	SOC: Ear and labyrinth disorders	7 (10.1)	(4.2, 19.8)
	SOC: Psychiatric disorders	6 (8.7)	(3.3, 18.0)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Renal impairment at baseline	SOC: Gastrointestinal disorders	21 (84.0)	(63.9, 95.5)
Moderate Impairment (N = 25)	Nausea	16 (64.0)	(42.5, 82.0)
	Vomiting	10 (40.0)	(21.1, 61.3)
	Constipation	8 (32.0)	(14.9, 53.5)
	Diarrhoea	7 (28.0)	(12.1, 49.4)
	Stomatitis	7 (28.0)	(12.1, 49.4)
	Dyspepsia	1 (4.0)	(0.1, 20.4)
	SOC: General disorders and administration site conditions	18 (72.0)	(50.6, 87.9)
	Fatigue	13 (52.0)	(31.3, 72.2)
	Asthenia	4 (16.0)	(4.5, 36.1)
	SOC: Respiratory, thoracic and mediastinal disorders	18 (72.0)	(50.6, 87.9)
	Cough	6 (24.0)	(9.4, 45.1)
	Epistaxis	5 (20.0)	(6.8, 40.7)
	Dyspnoea	4 (16.0)	(4.5, 36.1)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Renal impairment at baseline	SOC: Investigations	14 (56.0)	(34.9, 75.6)
Moderate Impairment (N = 25)	White blood cell count decreased	8 (32.0)	(14.9, 53.5)
	Lymphocyte count decreased	6 (24.0)	(9.4, 45.1)
	Neutrophil count decreased	6 (24.0)	(9.4, 45.1)
	Platelet count decreased	6 (24.0)	(9.4, 45.1)
	Aspartate aminotransferase increased	5 (20.0)	(6.8, 40.7)
	Alanine aminotransferase increased	2 (8.0)	(1.0, 26.0)
	SOC: Metabolism and nutrition disorders	14 (56.0)	(34.9, 75.6)
	Decreased appetite	11 (44.0)	(24.4, 65.1)
	Hypokalaemia	3 (12.0)	(2.5, 31.2)
	SOC: Skin and subcutaneous tissue disorders	14 (56.0)	(34.9, 75.6)
	Alopecia	13 (52.0)	(31.3, 72.2)
	Rash	2 (8.0)	(1.0, 26.0)
	SOC: Blood and lymphatic system disorders	13 (52.0)	(31.3, 72.2)
	Anaemia	12 (48.0)	(27.8, 68.7)
	Neutropenia	2 (8.0)	(1.0, 26.0)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Renal impairment at baseline	SOC: Infections and infestations	10 (40.0)	(21.1, 61.3)
Moderate Impairment (N = 25)	Upper respiratory tract infection	3 (12.0)	(2.5, 31.2)
	Urinary tract infection	3 (12.0)	(2.5, 31.2)
	Nasopharyngitis	1 (4.0)	(0.1, 20.4)
	SOC: Nervous system disorders	10 (40.0)	(21.1, 61.3)
	Headache	4 (16.0)	(4.5, 36.1)
	Dizziness	1 (4.0)	(0.1, 20.4)
	SOC: Eye disorders	8 (32.0)	(14.9, 53.5)
	Dry eye	1 (4.0)	(0.1, 20.4)
	SOC: Cardiac disorders	5 (20.0)	(6.8, 40.7)
	SOC: Musculoskeletal and connective tissue disorders	5 (20.0)	(6.8, 40.7)
	Back pain	2 (8.0)	(1.0, 26.0)
	Arthralgia	1 (4.0)	(0.1, 20.4)
	SOC: Ear and labyrinth disorders	4 (16.0)	(4.5, 36.1)
	SOC: Psychiatric disorders	4 (16.0)	(4.5, 36.1)
	SOC: Injury, poisoning and procedural complications	3 (12.0)	(2.5, 31.2)
	SOC: Renal and urinary disorders	1 (4.0)	(0.1, 20.4)
	SOC: Vascular disorders	1 (4.0)	(0.1, 20.4)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Hepatic impairment at baseline	SOC: Gastrointestinal disorders	101 (96.2)	(90.5, 99.0)
Within Normal Range (N = 105)	Nausea	83 (79.0)	(70.0, 86.4)
	Vomiting	57 (54.3)	(44.3, 64.0)
	Diarrhoea	37 (35.2)	(26.2, 45.2)
	Constipation	32 (30.5)	(21.9, 40.2)
	Abdominal pain	18 (17.1)	(10.5, 25.7)
	Stomatitis	18 (17.1)	(10.5, 25.7)
	Dyspepsia	17 (16.2)	(9.7, 24.7)
	SOC: General disorders and administration site conditions	79 (75.2)	(65.9, 83.1)
	Fatigue	54 (51.4)	(41.5, 61.3)
	Asthenia	16 (15.2)	(9.0, 23.6)
	SOC: Respiratory, thoracic and mediastinal disorders	67 (63.8)	(53.9, 73.0)
	Cough	30 (28.6)	(20.2, 38.2)
	Dyspnoea	20 (19.0)	(12.0, 27.9)
	Epistaxis	14 (13.3)	(7.5, 21.4)
	SOC: Skin and subcutaneous tissue disorders	66 (62.9)	(52.9, 72.1)
	Alopecia	52 (49.5)	(39.6, 59.5)
	Rash	10 (9.5)	(4.7, 16.8)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Hepatic impairment at baseline	SOC: Infections and infestations	60 (57.1)	(47.1, 66.8)
Within Normal Range (N = 105)	Nasopharyngitis	16 (15.2)	(9.0, 23.6)
	Urinary tract infection	16 (15.2)	(9.0, 23.6)
	Upper respiratory tract infection	14 (13.3)	(7.5, 21.4)
	SOC: Investigations	60 (57.1)	(47.1, 66.8)
	Neutrophil count decreased	24 (22.9)	(15.2, 32.1)
	White blood cell count decreased	22 (21.0)	(13.6, 30.0)
	Aspartate aminotransferase increased	20 (19.0)	(12.0, 27.9)
	Platelet count decreased	15 (14.3)	(8.2, 22.5)
	Alanine aminotransferase increased	13 (12.4)	(6.8, 20.2)
	Lymphocyte count decreased	11 (10.5)	(5.3, 18.0)
	SOC: Nervous system disorders	50 (47.6)	(37.8, 57.6)
	Headache	25 (23.8)	(16.0, 33.1)
	Dizziness	12 (11.4)	(6.0, 19.1)
	SOC: Blood and lymphatic system disorders	49 (46.7)	(36.9, 56.7)
	Anaemia	35 (33.3)	(24.4, 43.2)
	Neutropenia	16 (15.2)	(9.0, 23.6)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Hepatic impairment at baseline Within Normal Range (N = 105)	SOC: Metabolism and nutrition disorders	44 (41.9)	(32.3, 51.9)
	Decreased appetite	29 (27.6)	(19.3, 37.2)
	Hypokalaemia	12 (11.4)	(6.0, 19.1)
	SOC: Musculoskeletal and connective tissue disorders	39 (37.1)	(27.9, 47.1)
	Arthralgia	14 (13.3)	(7.5, 21.4)
	Back pain	10 (9.5)	(4.7, 16.8)
	SOC: Eye disorders	33 (31.4)	(22.7, 41.2)
	Dry eye	9 (8.6)	(4.0, 15.6)
	SOC: Vascular disorders	20 (19.0)	(12.0, 27.9)
	SOC: Injury, poisoning and procedural complications	17 (16.2)	(9.7, 24.7)
	SOC: Ear and labyrinth disorders	14 (13.3)	(7.5, 21.4)
	SOC: Psychiatric disorders	13 (12.4)	(6.8, 20.2)
	SOC: Cardiac disorders	12 (11.4)	(6.0, 19.1)
	SOC: Renal and urinary disorders	11 (10.5)	(5.3, 18.0)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

Subgroup	SOC/Preferred Term	Overall 5.4 mg/kg (N = 184) n (%)	95% CI [a]
Hepatic impairment at baseline	SOC: Gastrointestinal disorders	69 (90.8)	(81.9, 96.2)
Mild Impairment (N = 76)	Nausea	58 (76.3)	(65.2, 85.3)
	Vomiting	31 (40.8)	(29.6, 52.7)
	Constipation	30 (39.5)	(28.4, 51.4)
	Diarrhoea	21 (27.6)	(18.0, 39.1)
	Dyspepsia	13 (17.1)	(9.4, 27.5)
	Stomatitis	11 (14.5)	(7.5, 24.4)
	Abdominal pain	7 (9.2)	(3.8, 18.1)
	SOC: General disorders and administration site conditions	56 (73.7)	(62.3, 83.1)
	Fatigue	38 (50.0)	(38.3, 61.7)
	Asthenia	8 (10.5)	(4.7, 19.7)
	SOC: Skin and subcutaneous tissue disorders	49 (64.5)	(52.7, 75.1)
	Alopecia	36 (47.4)	(35.8, 59.2)
	Rash	9 (11.8)	(5.6, 21.3)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Hepatic impairment at baseline	SOC: Investigations	44 (57.9)	(46.0, 69.1)
Mild Impairment (N = 76)	Neutrophil count decreased	17 (22.4)	(13.6, 33.4)
	Platelet count decreased	15 (19.7)	(11.5, 30.5)
	White blood cell count decreased	14 (18.4)	(10.5, 29.0)
	Aspartate aminotransferase increased	13 (17.1)	(9.4, 27.5)
	Alanine aminotransferase increased	8 (10.5)	(4.7, 19.7)
	Lymphocyte count decreased	8 (10.5)	(4.7, 19.7)
	SOC: Nervous system disorders	40 (52.6)	(40.8, 64.2)
	Headache	14 (18.4)	(10.5, 29.0)
	Dizziness	7 (9.2)	(3.8, 18.1)
	SOC: Infections and infestations	39 (51.3)	(39.6, 63.0)
	Upper respiratory tract infection	10 (13.2)	(6.5, 22.9)
	Urinary tract infection	6 (7.9)	(3.0, 16.4)
	Nasopharyngitis	4 (5.3)	(1.5, 12.9)
	SOC: Metabolism and nutrition disorders	39 (51.3)	(39.6, 63.0)
	Decreased appetite	30 (39.5)	(28.4, 51.4)
	Hypokalaemia	9 (11.8)	(5.6, 21.3)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Hepatic impairment at baseline	SOC: Respiratory, thoracic and mediastinal disorders	37 (48.7)	(37.0, 60.4)
Mild Impairment (N = 76)	Cough	15 (19.7)	(11.5, 30.5)
	Dyspnoea	11 (14.5)	(7.5, 24.4)
	Epistaxis	11 (14.5)	(7.5, 24.4)
	SOC: Blood and lymphatic system disorders	30 (39.5)	(28.4, 51.4)
	Anaemia	22 (28.9)	(19.1, 40.5)
	Neutropenia	11 (14.5)	(7.5, 24.4)
	SOC: Musculoskeletal and connective tissue disorders	30 (39.5)	(28.4, 51.4)
	Arthralgia	10 (13.2)	(6.5, 22.9)
	Back pain	10 (13.2)	(6.5, 22.9)
	SOC: Eye disorders	27 (35.5)	(24.9, 47.3)
	Dry eye	12 (15.8)	(8.4, 26.0)
	SOC: Psychiatric disorders	14 (18.4)	(10.5, 29.0)
	SOC: Cardiac disorders	10 (13.2)	(6.5, 22.9)
	SOC: Injury, poisoning and procedural complications	8 (10.5)	(4.7, 19.7)
	SOC: Renal and urinary disorders	7 (9.2)	(3.8, 18.1)
	SOC: Vascular disorders	7 (9.2)	(3.8, 18.1)
	SOC: Ear and labyrinth disorders	5 (6.6)	(2.2, 14.7)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Best response to T-DM1 therapy CR/PR/SD (N = 79)	SOC: Gastrointestinal disorders	71 (89.9)	(81.0, 95.5)
	Nausea	62 (78.5)	(67.8, 86.9)
	Constipation	32 (40.5)	(29.6, 52.1)
	Vomiting	29 (36.7)	(26.1, 48.3)
	Diarrhoea	18 (22.8)	(14.1, 33.6)
	Dyspepsia	14 (17.7)	(10.0, 27.9)
	Stomatitis	14 (17.7)	(10.0, 27.9)
	Abdominal pain	8 (10.1)	(4.5, 19.0)
	SOC: General disorders and administration site conditions	56 (70.9)	(59.6, 80.6)
	Fatigue	40 (50.6)	(39.1, 62.1)
	Asthenia	8 (10.1)	(4.5, 19.0)
	SOC: Skin and subcutaneous tissue disorders	54 (68.4)	(56.9, 78.4)
	Alopecia	38 (48.1)	(36.7, 59.6)
	Rash	6 (7.6)	(2.8, 15.8)
	SOC: Infections and infestations	46 (58.2)	(46.6, 69.2)
	Upper respiratory tract infection	10 (12.7)	(6.2, 22.0)
	Urinary tract infection	9 (11.4)	(5.3, 20.5)
	Nasopharyngitis	8 (10.1)	(4.5, 19.0)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Best response to T-DM1 therapy	SOC: Investigations	46 (58.2)	(46.6, 69.2)
CR/PR/SD (N = 79)	Neutrophil count decreased	20 (25.3)	(16.2, 36.4)
	Platelet count decreased	19 (24.1)	(15.1, 35.0)
	White blood cell count decreased	17 (21.5)	(13.1, 32.2)
	Aspartate aminotransferase increased	16 (20.3)	(12.0, 30.8)
	Lymphocyte count decreased	11 (13.9)	(7.2, 23.5)
	Alanine aminotransferase increased	10 (12.7)	(6.2, 22.0)
	SOC: Respiratory, thoracic and mediastinal disorders	46 (58.2)	(46.6, 69.2)
	Cough	16 (20.3)	(12.0, 30.8)
	Dyspnoea	13 (16.5)	(9.1, 26.5)
	Epistaxis	12 (15.2)	(8.1, 25.0)
	SOC: Nervous system disorders	42 (53.2)	(41.6, 64.5)
	Headache	19 (24.1)	(15.1, 35.0)
	Dizziness	6 (7.6)	(2.8, 15.8)
	SOC: Blood and lymphatic system disorders	37 (46.8)	(35.5, 58.4)
	Anaemia	26 (32.9)	(22.7, 44.4)
	Neutropenia	13 (16.5)	(9.1, 26.5)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Best response to T-DM1 therapy CR/PR/SD (N = 79)	SOC: Metabolism and nutrition disorders	37 (46.8)	(35.5, 58.4)
	Decreased appetite	24 (30.4)	(20.5, 41.8)
	Hypokalaemia	9 (11.4)	(5.3, 20.5)
	SOC: Eye disorders	28 (35.4)	(25.0, 47.0)
	Dry eye	8 (10.1)	(4.5, 19.0)
	SOC: Musculoskeletal and connective tissue disorders	27 (34.2)	(23.9, 45.7)
	Arthralgia	8 (10.1)	(4.5, 19.0)
	Back pain	5 (6.3)	(2.1, 14.2)
	SOC: Injury, poisoning and procedural complications	13 (16.5)	(9.1, 26.5)
	SOC: Cardiac disorders	11 (13.9)	(7.2, 23.5)
	SOC: Psychiatric disorders	11 (13.9)	(7.2, 23.5)
	SOC: Ear and labyrinth disorders	10 (12.7)	(6.2, 22.0)
	SOC: Vascular disorders	9 (11.4)	(5.3, 20.5)
	SOC: Renal and urinary disorders	8 (10.1)	(4.5, 19.0)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Best response to T-DM1 therapy PD (N = 66)	SOC: Gastrointestinal disorders	63 (95.5)	(87.3, 99.1)
	Nausea	48 (72.7)	(60.4, 83.0)
	Vomiting	39 (59.1)	(46.3, 71.0)
	Diarrhoea	27 (40.9)	(29.0, 53.7)
	Constipation	19 (28.8)	(18.3, 41.3)
	Abdominal pain	14 (21.2)	(12.1, 33.0)
	Stomatitis	11 (16.7)	(8.6, 27.9)
	Dyspepsia	9 (13.6)	(6.4, 24.3)
	SOC: General disorders and administration site conditions	51 (77.3)	(65.3, 86.7)
	Fatigue	30 (45.5)	(33.1, 58.2)
	Asthenia	14 (21.2)	(12.1, 33.0)
	SOC: Skin and subcutaneous tissue disorders	46 (69.7)	(57.1, 80.4)
	Alopecia	38 (57.6)	(44.8, 69.7)
	Rash	10 (15.2)	(7.5, 26.1)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Best response to T-DM1 therapy	SOC: Investigations	39 (59.1)	(46.3, 71.0)
PD (N = 66)	White blood cell count decreased	17 (25.8)	(15.8, 38.0)
	Neutrophil count decreased	16 (24.2)	(14.5, 36.4)
	Aspartate aminotransferase increased	11 (16.7)	(8.6, 27.9)
	Platelet count decreased	8 (12.1)	(5.4, 22.5)
	Alanine aminotransferase increased	7 (10.6)	(4.4, 20.6)
	Lymphocyte count decreased	6 (9.1)	(3.4, 18.7)
	SOC: Respiratory, thoracic and mediastinal disorders	38 (57.6)	(44.8, 69.7)
	Cough	18 (27.3)	(17.0, 39.6)
	Epistaxis	12 (18.2)	(9.8, 29.6)
	Dyspnoea	11 (16.7)	(8.6, 27.9)
	SOC: Nervous system disorders	35 (53.0)	(40.3, 65.4)
	Headache	14 (21.2)	(12.1, 33.0)
	Dizziness	9 (13.6)	(6.4, 24.3)
	SOC: Infections and infestations	32 (48.5)	(36.0, 61.1)
	Urinary tract infection	10 (15.2)	(7.5, 26.1)
	Nasopharyngitis	9 (13.6)	(6.4, 24.3)
	Upper respiratory tract infection	8 (12.1)	(5.4, 22.5)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Best response to T-DM1 therapy	SOC: Metabolism and nutrition disorders	31 (47.0)	(34.6, 59.7)
PD (N = 66)	Decreased appetite	22 (33.3)	(22.2, 46.0)
	Hypokalaemia	10 (15.2)	(7.5, 26.1)
	SOC: Blood and lymphatic system disorders	28 (42.4)	(30.3, 55.2)
	Anaemia	21 (31.8)	(20.9, 44.4)
	Neutropenia	9 (13.6)	(6.4, 24.3)
	SOC: Musculoskeletal and connective tissue disorders	24 (36.4)	(24.9, 49.1)
	Back pain	9 (13.6)	(6.4, 24.3)
	Arthralgia	8 (12.1)	(5.4, 22.5)
	SOC: Eye disorders	22 (33.3)	(22.2, 46.0)
	Dry eye	7 (10.6)	(4.4, 20.6)
	SOC: Vascular disorders	13 (19.7)	(10.9, 31.3)
	SOC: Psychiatric disorders	12 (18.2)	(9.8, 29.6)
	SOC: Injury, poisoning and procedural complications	11 (16.7)	(8.6, 27.9)
	SOC: Renal and urinary disorders	9 (13.6)	(6.4, 24.3)
	SOC: Cardiac disorders	7 (10.6)	(4.4, 20.6)
	SOC: Ear and labyrinth disorders	5 (7.6)	(2.5, 16.8)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Brain metastases	SOC: Gastrointestinal disorders	22 (91.7)	(73.0, 99.0)
Yes (N = 24)	Nausea	16 (66.7)	(44.7, 84.4)
	Vomiting	11 (45.8)	(25.6, 67.2)
	Diarrhoea	10 (41.7)	(22.1, 63.4)
	Stomatitis	8 (33.3)	(15.6, 55.3)
	Constipation	7 (29.2)	(12.6, 51.1)
	Dyspepsia	4 (16.7)	(4.7, 37.4)
	Abdominal pain	3 (12.5)	(2.7, 32.4)
	SOC: General disorders and administration site conditions	18 (75.0)	(53.3, 90.2)
	Fatigue	14 (58.3)	(36.6, 77.9)
	Asthenia	1 (4.2)	(0.1, 21.1)
	SOC: Investigations	17 (70.8)	(48.9, 87.4)
	Aspartate aminotransferase increased	6 (25.0)	(9.8, 46.7)
	Neutrophil count decreased	6 (25.0)	(9.8, 46.7)
	White blood cell count decreased	6 (25.0)	(9.8, 46.7)
	Platelet count decreased	4 (16.7)	(4.7, 37.4)
	Alanine aminotransferase increased	2 (8.3)	(1.0, 27.0)
	Lymphocyte count decreased	2 (8.3)	(1.0, 27.0)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Brain metastases	SOC: Infections and infestations	15 (62.5)	(40.6, 81.2)
Yes (N = 24)	Urinary tract infection	6 (25.0)	(9.8, 46.7)
	Upper respiratory tract infection	4 (16.7)	(4.7, 37.4)
	Nasopharyngitis	2 (8.3)	(1.0, 27.0)
	SOC: Skin and subcutaneous tissue disorders	15 (62.5)	(40.6, 81.2)
	Alopecia	13 (54.2)	(32.8, 74.4)
	Rash	2 (8.3)	(1.0, 27.0)
	SOC: Nervous system disorders	14 (58.3)	(36.6, 77.9)
	Headache	6 (25.0)	(9.8, 46.7)
	Dizziness	5 (20.8)	(7.1, 42.2)
	SOC: Blood and lymphatic system disorders	13 (54.2)	(32.8, 74.4)
	Anaemia	8 (33.3)	(15.6, 55.3)
	Neutropenia	5 (20.8)	(7.1, 42.2)
	SOC: Respiratory, thoracic and mediastinal disorders	13 (54.2)	(32.8, 74.4)
	Cough	6 (25.0)	(9.8, 46.7)
	Epistaxis	4 (16.7)	(4.7, 37.4)
	Dyspnoea	2 (8.3)	(1.0, 27.0)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Brain metastases	SOC: Metabolism and nutrition disorders	11 (45.8)	(25.6, 67.2)
Yes (N = 24)	Decreased appetite	9 (37.5)	(18.8, 59.4)
	Hypokalaemia	4 (16.7)	(4.7, 37.4)
	SOC: Musculoskeletal and connective tissue disorders	9 (37.5)	(18.8, 59.4)
	Arthralgia	3 (12.5)	(2.7, 32.4)
	Back pain	3 (12.5)	(2.7, 32.4)
	SOC: Eye disorders	6 (25.0)	(9.8, 46.7)
	Dry eye	2 (8.3)	(1.0, 27.0)
	SOC: Injury, poisoning and procedural complications	5 (20.8)	(7.1, 42.2)
	SOC: Vascular disorders	4 (16.7)	(4.7, 37.4)
	SOC: Cardiac disorders	2 (8.3)	(1.0, 27.0)
	SOC: Ear and labyrinth disorders	2 (8.3)	(1.0, 27.0)
	SOC: Psychiatric disorders	2 (8.3)	(1.0, 27.0)
	SOC: Renal and urinary disorders	2 (8.3)	(1.0, 27.0)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Brain metastases	SOC: Gastrointestinal disorders	151 (94.4)	(89.6, 97.4)
No (N = 160)	Nausea	128 (80.0)	(73.0, 85.9)
	Vomiting	77 (48.1)	(40.2, 56.2)
	Constipation	58 (36.3)	(28.8, 44.2)
	Diarrhoea	48 (30.0)	(23.0, 37.7)
	Dyspepsia	27 (16.9)	(11.4, 23.6)
	Abdominal pain	22 (13.8)	(8.8, 20.1)
	Stomatitis	21 (13.1)	(8.3, 19.4)
	SOC: General disorders and administration site conditions	119 (74.4)	(66.9, 80.9)
	Fatigue	78 (48.8)	(40.8, 56.8)
	Asthenia	25 (15.6)	(10.4, 22.2)
	SOC: Skin and subcutaneous tissue disorders	101 (63.1)	(55.1, 70.6)
	Alopecia	76 (47.5)	(39.6, 55.5)
	Rash	17 (10.6)	(6.3, 16.5)
	SOC: Respiratory, thoracic and mediastinal disorders	92 (57.5)	(49.4, 65.3)
	Cough	39 (24.4)	(17.9, 31.8)
	Dyspnoea	29 (18.1)	(12.5, 25.0)
	Epistaxis	22 (13.8)	(8.8, 20.1)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Brain metastases	SOC: Investigations	89 (55.6)	(47.6, 63.5)
No (N = 160)	Neutrophil count decreased	35 (21.9)	(15.7, 29.1)
	White blood cell count decreased	30 (18.8)	(13.0, 25.7)
	Aspartate aminotransferase increased	27 (16.9)	(11.4, 23.6)
	Platelet count decreased	26 (16.3)	(10.9, 22.9)
	Alanine aminotransferase increased	19 (11.9)	(7.3, 17.9)
	Lymphocyte count decreased	17 (10.6)	(6.3, 16.5)
	SOC: Infections and infestations	84 (52.5)	(44.5, 60.4)
	Upper respiratory tract infection	20 (12.5)	(7.8, 18.6)
	Nasopharyngitis	18 (11.3)	(6.8, 17.2)
	Urinary tract infection	16 (10.0)	(5.8, 15.7)
	SOC: Nervous system disorders	77 (48.1)	(40.2, 56.2)
	Headache	34 (21.3)	(15.2, 28.4)
	Dizziness	14 (8.8)	(4.9, 14.2)
	SOC: Metabolism and nutrition disorders	73 (45.6)	(37.7, 53.7)
	Decreased appetite	50 (31.3)	(24.2, 39.0)
	Hypokalaemia	18 (11.3)	(6.8, 17.2)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Brain metastases	SOC: Blood and lymphatic system disorders	67 (41.9)	(34.1, 49.9)
No (N = 160)	Anaemia	50 (31.3)	(24.2, 39.0)
	Neutropenia	22 (13.8)	(8.8, 20.1)
	SOC: Musculoskeletal and connective tissue disorders	61 (38.1)	(30.6, 46.1)
	Arthralgia	21 (13.1)	(8.3, 19.4)
	Back pain	17 (10.6)	(6.3, 16.5)
	SOC: Eye disorders	55 (34.4)	(27.1, 42.3)
	Dry eye	19 (11.9)	(7.3, 17.9)
	SOC: Psychiatric disorders	26 (16.3)	(10.9, 22.9)
	SOC: Vascular disorders	23 (14.4)	(9.3, 20.8)
	SOC: Injury, poisoning and procedural complications	21 (13.1)	(8.3, 19.4)
	SOC: Cardiac disorders	20 (12.5)	(7.8, 18.6)
	SOC: Ear and labyrinth disorders	17 (10.6)	(6.3, 16.5)
	SOC: Renal and urinary disorders	17 (10.6)	(6.3, 16.5)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Bone metastases	SOC: Gastrointestinal disorders	53 (100.0)	(93.3, 100.0)
Yes (N = 53)	Nausea	49 (92.5)	(81.8, 97.9)
	Vomiting	31 (58.5)	(44.1, 71.9)
	Constipation	21 (39.6)	(26.5, 54.0)
	Diarrhoea	20 (37.7)	(24.8, 52.1)
	Abdominal pain	10 (18.9)	(9.4, 32.0)
	Stomatitis	9 (17.0)	(8.1, 29.8)
	Dyspepsia	8 (15.1)	(6.7, 27.6)
	SOC: General disorders and administration site conditions	41 (77.4)	(63.8, 87.7)
	Fatigue	28 (52.8)	(38.6, 66.7)
	Asthenia	10 (18.9)	(9.4, 32.0)
	SOC: Respiratory, thoracic and mediastinal disorders	36 (67.9)	(53.7, 80.1)
	Cough	13 (24.5)	(13.8, 38.3)
	Dyspnoea	12 (22.6)	(12.3, 36.2)
	Epistaxis	8 (15.1)	(6.7, 27.6)
	SOC: Skin and subcutaneous tissue disorders	33 (62.3)	(47.9, 75.2)
	Alopecia	27 (50.9)	(36.8, 64.9)
	Rash	4 (7.5)	(2.1, 18.2)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Bone metastases	SOC: Nervous system disorders	32 (60.4)	(46.0, 73.5)
Yes (N = 53)	Headache	12 (22.6)	(12.3, 36.2)
	Dizziness	7 (13.2)	(5.5, 25.3)
	SOC: Metabolism and nutrition disorders	31 (58.5)	(44.1, 71.9)
	Decreased appetite	23 (43.4)	(29.8, 57.7)
	Hypokalaemia	7 (13.2)	(5.5, 25.3)
	SOC: Investigations	30 (56.6)	(42.3, 70.2)
	Neutrophil count decreased	15 (28.3)	(16.8, 42.3)
	White blood cell count decreased	12 (22.6)	(12.3, 36.2)
	Aspartate aminotransferase increased	11 (20.8)	(10.8, 34.1)
	Platelet count decreased	10 (18.9)	(9.4, 32.0)
	Lymphocyte count decreased	7 (13.2)	(5.5, 25.3)
	Alanine aminotransferase increased	4 (7.5)	(2.1, 18.2)
	SOC: Infections and infestations	29 (54.7)	(40.4, 68.4)
	Urinary tract infection	7 (13.2)	(5.5, 25.3)
	Nasopharyngitis	6 (11.3)	(4.3, 23.0)
	Upper respiratory tract infection	3 (5.7)	(1.2, 15.7)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Bone metastases	SOC: Musculoskeletal and connective tissue disorders	23 (43.4)	(29.8, 57.7)
Yes (N = 53)	Back pain	9 (17.0)	(8.1, 29.8)
	Arthralgia	6 (11.3)	(4.3, 23.0)
	SOC: Blood and lymphatic system disorders	22 (41.5)	(28.1, 55.9)
	Anaemia	18 (34.0)	(21.5, 48.3)
	Neutropenia	6 (11.3)	(4.3, 23.0)
	SOC: Eye disorders	17 (32.1)	(19.9, 46.3)
	Dry eye	6 (11.3)	(4.3, 23.0)
	SOC: Cardiac disorders	10 (18.9)	(9.4, 32.0)
	SOC: Injury, poisoning and procedural complications	9 (17.0)	(8.1, 29.8)
	SOC: Ear and labyrinth disorders	8 (15.1)	(6.7, 27.6)
	SOC: Psychiatric disorders	8 (15.1)	(6.7, 27.6)
	SOC: Vascular disorders	8 (15.1)	(6.7, 27.6)
	SOC: Renal and urinary disorders	5 (9.4)	(3.1, 20.7)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Bone metastases	SOC: Gastrointestinal disorders	120 (91.6)	(85.5, 95.7)
No (N = 131)	Nausea	95 (72.5)	(64.0, 80.0)
	Vomiting	57 (43.5)	(34.9, 52.4)
	Constipation	44 (33.6)	(25.6, 42.4)
	Diarrhoea	38 (29.0)	(21.4, 37.6)
	Dyspepsia	23 (17.6)	(11.5, 25.2)
	Stomatitis	20 (15.3)	(9.6, 22.6)
	Abdominal pain	15 (11.5)	(6.6, 18.2)
	SOC: General disorders and administration site conditions	96 (73.3)	(64.8, 80.6)
	Fatigue	64 (48.9)	(40.0, 57.7)
	Asthenia	16 (12.2)	(7.1, 19.1)
	SOC: Skin and subcutaneous tissue disorders	83 (63.4)	(54.5, 71.6)
	Alopecia	62 (47.3)	(38.5, 56.2)
	Rash	15 (11.5)	(6.6, 18.2)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Bone metastases	SOC: Investigations	76 (58.0)	(49.1, 66.6)
No (N = 131)	Neutrophil count decreased	26 (19.8)	(13.4, 27.7)
	White blood cell count decreased	24 (18.3)	(12.1, 26.0)
	Aspartate aminotransferase increased	22 (16.8)	(10.8, 24.3)
	Platelet count decreased	20 (15.3)	(9.6, 22.6)
	Alanine aminotransferase increased	17 (13.0)	(7.7, 20.0)
	Lymphocyte count decreased	12 (9.2)	(4.8, 15.5)
	SOC: Infections and infestations	70 (53.4)	(44.5, 62.2)
	Upper respiratory tract infection	21 (16.0)	(10.2, 23.5)
	Urinary tract infection	15 (11.5)	(6.6, 18.2)
	Nasopharyngitis	14 (10.7)	(6.0, 17.3)
	SOC: Respiratory, thoracic and mediastinal disorders	69 (52.7)	(43.8, 61.5)
	Cough	32 (24.4)	(17.3, 32.7)
	Dyspnoea	19 (14.5)	(9.0, 21.7)
	Epistaxis	18 (13.7)	(8.4, 20.8)
	SOC: Nervous system disorders	59 (45.0)	(36.3, 54.0)
	Headache	28 (21.4)	(14.7, 29.4)
	Dizziness	12 (9.2)	(4.8, 15.5)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Bone metastases	SOC: Blood and lymphatic system disorders	58 (44.3)	(35.6, 53.2)
No (N = 131)	Anaemia	40 (30.5)	(22.8, 39.2)
	Neutropenia	21 (16.0)	(10.2, 23.5)
	SOC: Metabolism and nutrition disorders	53 (40.5)	(32.0, 49.4)
	Decreased appetite	36 (27.5)	(20.0, 36.0)
	Hypokalaemia	15 (11.5)	(6.6, 18.2)
	SOC: Musculoskeletal and connective tissue disorders	47 (35.9)	(27.7, 44.7)
	Arthralgia	18 (13.7)	(8.4, 20.8)
	Back pain	11 (8.4)	(4.3, 14.5)
	SOC: Eye disorders	44 (33.6)	(25.6, 42.4)
	Dry eye	15 (11.5)	(6.6, 18.2)
	SOC: Psychiatric disorders	20 (15.3)	(9.6, 22.6)
	SOC: Vascular disorders	19 (14.5)	(9.0, 21.7)
	SOC: Injury, poisoning and procedural complications	17 (13.0)	(7.7, 20.0)
	SOC: Renal and urinary disorders	14 (10.7)	(6.0, 17.3)
	SOC: Cardiac disorders	12 (9.2)	(4.8, 15.5)
	SOC: Ear and labyrinth disorders	11 (8.4)	(4.3, 14.5)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
History of visceral disease	SOC: Gastrointestinal disorders	158 (93.5)	(88.7, 96.7)
Yes (N = 169)	Nausea	133 (78.7)	(71.7, 84.6)
	Vomiting	80 (47.3)	(39.6, 55.1)
	Constipation	60 (35.5)	(28.3, 43.2)
	Diarrhoea	53 (31.4)	(24.5, 38.9)
	Dyspepsia	31 (18.3)	(12.8, 25.0)
	Stomatitis	26 (15.4)	(10.3, 21.7)
	Abdominal pain	24 (14.2)	(9.3, 20.4)
	SOC: General disorders and administration site conditions	128 (75.7)	(68.6, 82.0)
	Fatigue	86 (50.9)	(43.1, 58.6)
	Asthenia	24 (14.2)	(9.3, 20.4)
	SOC: Skin and subcutaneous tissue disorders	106 (62.7)	(55.0, 70.0)
	Alopecia	80 (47.3)	(39.6, 55.1)
	Rash	19 (11.2)	(6.9, 17.0)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
History of visceral disease	SOC: Investigations	94 (55.6)	(47.8, 63.2)
Yes (N = 169)	Neutrophil count decreased	35 (20.7)	(14.9, 27.6)
	Aspartate aminotransferase increased	30 (17.8)	(12.3, 24.4)
	White blood cell count decreased	29 (17.2)	(11.8, 23.7)
	Platelet count decreased	24 (14.2)	(9.3, 20.4)
	Alanine aminotransferase increased	19 (11.2)	(6.9, 17.0)
	Lymphocyte count decreased	16 (9.5)	(5.5, 14.9)
	SOC: Infections and infestations	93 (55.0)	(47.2, 62.7)
	Upper respiratory tract infection	22 (13.0)	(8.3, 19.0)
	Urinary tract infection	21 (12.4)	(7.9, 18.4)
	Nasopharyngitis	19 (11.2)	(6.9, 17.0)
	SOC: Respiratory, thoracic and mediastinal disorders	93 (55.0)	(47.2, 62.7)
	Cough	38 (22.5)	(16.4, 29.5)
	Dyspnoea	30 (17.8)	(12.3, 24.4)
	Epistaxis	23 (13.6)	(8.8, 19.7)
	SOC: Nervous system disorders	84 (49.7)	(41.9, 57.5)
	Headache	35 (20.7)	(14.9, 27.6)
	Dizziness	18 (10.7)	(6.4, 16.3)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
History of visceral disease	SOC: Metabolism and nutrition disorders	76 (45.0)	(37.3, 52.8)
Yes (N = 169)	Decreased appetite	56 (33.1)	(26.1, 40.8)
	Hypokalaemia	19 (11.2)	(6.9, 17.0)
	SOC: Blood and lymphatic system disorders	69 (40.8)	(33.3, 48.6)
	Anaemia	48 (28.4)	(21.7, 35.8)
	Neutropenia	23 (13.6)	(8.8, 19.7)
	SOC: Musculoskeletal and connective tissue disorders	64 (37.9)	(30.5, 45.6)
	Arthralgia	23 (13.6)	(8.8, 19.7)
	Back pain	17 (10.1)	(6.0, 15.6)
	SOC: Eye disorders	56 (33.1)	(26.1, 40.8)
	Dry eye	20 (11.8)	(7.4, 17.7)
	SOC: Psychiatric disorders	25 (14.8)	(9.8, 21.1)
	SOC: Vascular disorders	24 (14.2)	(9.3, 20.4)
	SOC: Injury, poisoning and procedural complications	23 (13.6)	(8.8, 19.7)
	SOC: Cardiac disorders	21 (12.4)	(7.9, 18.4)
	SOC: Renal and urinary disorders	18 (10.7)	(6.4, 16.3)
	SOC: Ear and labyrinth disorders	17 (10.1)	(6.0, 15.6)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

Subgroup	SOC/Preferred Term	Overall 5.4 mg/kg (N = 184) n (%)	95% CI [a]
History of visceral disease	SOC: Gastrointestinal disorders	15 (100.0)	(78.2, 100.0)
No (N = 15)	Nausea	11 (73.3)	(44.9, 92.2)
	Vomiting	8 (53.3)	(26.6, 78.7)
	Constipation	5 (33.3)	(11.8, 61.6)
	Diarrhoea	5 (33.3)	(11.8, 61.6)
	Stomatitis	3 (20.0)	(4.3, 48.1)
	Abdominal pain	1 (6.7)	(0.2, 31.9)
	SOC: Investigations	12 (80.0)	(51.9, 95.7)
	White blood cell count decreased	7 (46.7)	(21.3, 73.4)
	Neutrophil count decreased	6 (40.0)	(16.3, 67.7)
	Platelet count decreased	6 (40.0)	(16.3, 67.7)
	Aspartate aminotransferase increased	3 (20.0)	(4.3, 48.1)
	Lymphocyte count decreased	3 (20.0)	(4.3, 48.1)
	Alanine aminotransferase increased	2 (13.3)	(1.7, 40.5)
	SOC: Respiratory, thoracic and mediastinal disorders	12 (80.0)	(51.9, 95.7)
	Cough	7 (46.7)	(21.3, 73.4)
	Epistaxis	3 (20.0)	(4.3, 48.1)
	Dyspnoea	1 (6.7)	(0.2, 31.9)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
History of visceral disease	SOC: Blood and lymphatic system disorders	11 (73.3)	(44.9, 92.2)
No (N = 15)	Anaemia	10 (66.7)	(38.4, 88.2)
	Neutropenia	4 (26.7)	(7.8, 55.1)
	SOC: Skin and subcutaneous tissue disorders	10 (66.7)	(38.4, 88.2)
	Alopecia	9 (60.0)	(32.3, 83.7)
	SOC: General disorders and administration site conditions	9 (60.0)	(32.3, 83.7)
	Fatigue	6 (40.0)	(16.3, 67.7)
	Asthenia	2 (13.3)	(1.7, 40.5)
	SOC: Metabolism and nutrition disorders	8 (53.3)	(26.6, 78.7)
	Decreased appetite	3 (20.0)	(4.3, 48.1)
	Hypokalaemia	3 (20.0)	(4.3, 48.1)
	SOC: Nervous system disorders	7 (46.7)	(21.3, 73.4)
	Headache	5 (33.3)	(11.8, 61.6)
	Dizziness	1 (6.7)	(0.2, 31.9)
	SOC: Infections and infestations	6 (40.0)	(16.3, 67.7)
	Upper respiratory tract infection	2 (13.3)	(1.7, 40.5)
	Nasopharyngitis	1 (6.7)	(0.2, 31.9)
	Urinary tract infection	1 (6.7)	(0.2, 31.9)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
History of visceral disease	SOC: Musculoskeletal and connective tissue disorders	6 (40.0)	(16.3, 67.7)
No (N = 15)	Back pain	3 (20.0)	(4.3, 48.1)
	Arthralgia	1 (6.7)	(0.2, 31.9)
	SOC: Eye disorders	5 (33.3)	(11.8, 61.6)
	Dry eye	1 (6.7)	(0.2, 31.9)
	SOC: Injury, poisoning and procedural complications	3 (20.0)	(4.3, 48.1)
	SOC: Psychiatric disorders	3 (20.0)	(4.3, 48.1)
	SOC: Vascular disorders	3 (20.0)	(4.3, 48.1)
	SOC: Ear and labyrinth disorders	2 (13.3)	(1.7, 40.5)
	SOC: Cardiac disorders	1 (6.7)	(0.2, 31.9)
	SOC: Renal and urinary disorders	1 (6.7)	(0.2, 31.9)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Age	SOC: Gastrointestinal disorders	131 (93.6)	(88.1, 97.0)
<65 years (N = 140)	Nausea	114 (81.4)	(74.0, 87.5)
	Vomiting	68 (48.6)	(40.0, 57.2)
	Constipation	47 (33.6)	(25.8, 42.0)
	Diarrhoea	37 (26.4)	(19.3, 34.5)
	Dyspepsia	28 (20.0)	(13.7, 27.6)
	Abdominal pain	20 (14.3)	(8.9, 21.2)
	Stomatitis	20 (14.3)	(8.9, 21.2)
	SOC: General disorders and administration site conditions	100 (71.4)	(63.2, 78.7)
	Fatigue	65 (46.4)	(38.0, 55.0)
	Asthenia	19 (13.6)	(8.4, 20.4)
	SOC: Skin and subcutaneous tissue disorders	89 (63.6)	(55.0, 71.5)
	Alopecia	69 (49.3)	(40.7, 57.9)
	Rash	16 (11.4)	(6.7, 17.9)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Age	SOC: Investigations	76 (54.3)	(45.7, 62.7)
<65 years (N = 140)	Neutrophil count decreased	27 (19.3)	(13.1, 26.8)
	White blood cell count decreased	23 (16.4)	(10.7, 23.6)
	Aspartate aminotransferase increased	21 (15.0)	(9.5, 22.0)
	Platelet count decreased	19 (13.6)	(8.4, 20.4)
	Alanine aminotransferase increased	15 (10.7)	(6.1, 17.1)
	Lymphocyte count decreased	12 (8.6)	(4.5, 14.5)
	SOC: Infections and infestations	75 (53.6)	(45.0, 62.0)
	Upper respiratory tract infection	19 (13.6)	(8.4, 20.4)
	Nasopharyngitis	15 (10.7)	(6.1, 17.1)
	Urinary tract infection	15 (10.7)	(6.1, 17.1)
	SOC: Nervous system disorders	72 (51.4)	(42.8, 60.0)
	Headache	31 (22.1)	(15.6, 29.9)
	Dizziness	13 (9.3)	(5.0, 15.4)
	SOC: Respiratory, thoracic and mediastinal disorders	72 (51.4)	(42.8, 60.0)
	Cough	33 (23.6)	(16.8, 31.5)
	Dyspnoea	22 (15.7)	(10.1, 22.8)
	Epistaxis	13 (9.3)	(5.0, 15.4)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Age	SOC: Metabolism and nutrition disorders	59 (42.1)	(33.9, 50.8)
<65 years (N = 140)	Decreased appetite	40 (28.6)	(21.3, 36.8)
	Hypokalaemia	10 (7.1)	(3.5, 12.7)
	SOC: Musculoskeletal and connective tissue disorders	55 (39.3)	(31.1, 47.9)
	Arthralgia	17 (12.1)	(7.2, 18.7)
	Back pain	14 (10.0)	(5.6, 16.2)
	SOC: Blood and lymphatic system disorders	53 (37.9)	(29.8, 46.4)
	Anaemia	38 (27.1)	(20.0, 35.3)
	Neutropenia	21 (15.0)	(9.5, 22.0)
	SOC: Eye disorders	42 (30.0)	(22.6, 38.3)
	Dry eye	19 (13.6)	(8.4, 20.4)
	SOC: Psychiatric disorders	23 (16.4)	(10.7, 23.6)
	SOC: Injury, poisoning and procedural complications	19 (13.6)	(8.4, 20.4)
	SOC: Vascular disorders	18 (12.9)	(7.8, 19.6)
	SOC: Renal and urinary disorders	15 (10.7)	(6.1, 17.1)
	SOC: Ear and labyrinth disorders	14 (10.0)	(5.6, 16.2)
	SOC: Cardiac disorders	12 (8.6)	(4.5, 14.5)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Age	SOC: Gastrointestinal disorders	42 (95.5)	(84.5, 99.4)
>=65 years (N = 44)	Nausea	30 (68.2)	(52.4, 81.4)
	Diarrhoea	21 (47.7)	(32.5, 63.3)
	Vomiting	20 (45.5)	(30.4, 61.2)
	Constipation	18 (40.9)	(26.3, 56.8)
	Stomatitis	9 (20.5)	(9.8, 35.3)
	Abdominal pain	5 (11.4)	(3.8, 24.6)
	Dyspepsia	3 (6.8)	(1.4, 18.7)
	SOC: General disorders and administration site conditions	37 (84.1)	(69.9, 93.4)
	Fatigue	27 (61.4)	(45.5, 75.6)
	Asthenia	7 (15.9)	(6.6, 30.1)
	SOC: Respiratory, thoracic and mediastinal disorders	33 (75.0)	(59.7, 86.8)
	Epistaxis	13 (29.5)	(16.8, 45.2)
	Cough	12 (27.3)	(15.0, 42.8)
	Dyspnoea	9 (20.5)	(9.8, 35.3)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Age	SOC: Investigations	30 (68.2)	(52.4, 81.4)
>=65 years (N = 44)	Neutrophil count decreased	14 (31.8)	(18.6, 47.6)
	White blood cell count decreased	13 (29.5)	(16.8, 45.2)
	Aspartate aminotransferase increased	12 (27.3)	(15.0, 42.8)
	Platelet count decreased	11 (25.0)	(13.2, 40.3)
	Lymphocyte count decreased	7 (15.9)	(6.6, 30.1)
	Alanine aminotransferase increased	6 (13.6)	(5.2, 27.4)
	SOC: Blood and lymphatic system disorders	27 (61.4)	(45.5, 75.6)
	Anaemia	20 (45.5)	(30.4, 61.2)
	Neutropenia	6 (13.6)	(5.2, 27.4)
	SOC: Skin and subcutaneous tissue disorders	27 (61.4)	(45.5, 75.6)
	Alopecia	20 (45.5)	(30.4, 61.2)
	Rash	3 (6.8)	(1.4, 18.7)
	SOC: Metabolism and nutrition disorders	25 (56.8)	(41.0, 71.7)
	Decreased appetite	19 (43.2)	(28.3, 59.0)
	Hypokalaemia	12 (27.3)	(15.0, 42.8)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Age	SOC: Infections and infestations	24 (54.5)	(38.8, 69.6)
>=65 years (N = 44)	Urinary tract infection	7 (15.9)	(6.6, 30.1)
	Nasopharyngitis	5 (11.4)	(3.8, 24.6)
	Upper respiratory tract infection	5 (11.4)	(3.8, 24.6)
	SOC: Eye disorders	19 (43.2)	(28.3, 59.0)
	Dry eye	2 (4.5)	(0.6, 15.5)
	SOC: Nervous system disorders	19 (43.2)	(28.3, 59.0)
	Headache	9 (20.5)	(9.8, 35.3)
	Dizziness	6 (13.6)	(5.2, 27.4)
	SOC: Musculoskeletal and connective tissue disorders	15 (34.1)	(20.5, 49.9)
	Arthralgia	7 (15.9)	(6.6, 30.1)
	Back pain	6 (13.6)	(5.2, 27.4)
	SOC: Cardiac disorders	10 (22.7)	(11.5, 37.8)
	SOC: Vascular disorders	9 (20.5)	(9.8, 35.3)
	SOC: Injury, poisoning and procedural complications	7 (15.9)	(6.6, 30.1)
	SOC: Ear and labyrinth disorders	5 (11.4)	(3.8, 24.6)
	SOC: Psychiatric disorders	5 (11.4)	(3.8, 24.6)
	SOC: Renal and urinary disorders	4 (9.1)	(2.5, 21.7)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Region	SOC: Gastrointestinal disorders	57 (90.5)	(80.4, 96.4)
Asia (N = 63)	Nausea	46 (73.0)	(60.3, 83.4)
	Constipation	21 (33.3)	(22.0, 46.3)
	Vomiting	21 (33.3)	(22.0, 46.3)
	Dyspepsia	12 (19.0)	(10.2, 30.9)
	Stomatitis	11 (17.5)	(9.1, 29.1)
	Diarrhoea	10 (15.9)	(7.9, 27.3)
	Abdominal pain	2 (3.2)	(0.4, 11.0)
	SOC: Skin and subcutaneous tissue disorders	43 (68.3)	(55.3, 79.4)
	Alopecia	32 (50.8)	(37.9, 63.6)
	Rash	6 (9.5)	(3.6, 19.6)
	SOC: Investigations	37 (58.7)	(45.6, 71.0)
	Neutrophil count decreased	24 (38.1)	(26.1, 51.2)
	White blood cell count decreased	24 (38.1)	(26.1, 51.2)
	Platelet count decreased	16 (25.4)	(15.3, 37.9)
	Aspartate aminotransferase increased	12 (19.0)	(10.2, 30.9)
	Lymphocyte count decreased	11 (17.5)	(9.1, 29.1)
	Alanine aminotransferase increased	8 (12.7)	(5.6, 23.5)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Region	SOC: General disorders and administration site conditions	34 (54.0)	(40.9, 66.6)
Asia (N = 63)	Fatigue	22 (34.9)	(23.3, 48.0)
	Asthenia	1 (1.6)	(0.0, 8.5)
	SOC: Respiratory, thoracic and mediastinal disorders	34 (54.0)	(40.9, 66.6)
	Epistaxis	11 (17.5)	(9.1, 29.1)
	Cough	9 (14.3)	(6.7, 25.4)
	Dyspnoea	4 (6.3)	(1.8, 15.5)
	SOC: Nervous system disorders	30 (47.6)	(34.9, 60.6)
	Headache	14 (22.2)	(12.7, 34.5)
	Dizziness	4 (6.3)	(1.8, 15.5)
	SOC: Infections and infestations	29 (46.0)	(33.4, 59.1)
	Upper respiratory tract infection	8 (12.7)	(5.6, 23.5)
	Nasopharyngitis	7 (11.1)	(4.6, 21.6)
	Urinary tract infection	3 (4.8)	(1.0, 13.3)
	SOC: Metabolism and nutrition disorders	29 (46.0)	(33.4, 59.1)
	Decreased appetite	23 (36.5)	(24.7, 49.6)
	Hypokalaemia	1 (1.6)	(0.0, 8.5)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Region	SOC: Blood and lymphatic system disorders	28 (44.4)	(31.9, 57.5)
Asia (N = 63)	Anaemia	20 (31.7)	(20.6, 44.7)
	Neutropenia	9 (14.3)	(6.7, 25.4)
	SOC: Musculoskeletal and connective tissue disorders	19 (30.2)	(19.2, 43.0)
	Arthralgia	4 (6.3)	(1.8, 15.5)
	Back pain	2 (3.2)	(0.4, 11.0)
	SOC: Eye disorders	14 (22.2)	(12.7, 34.5)
	Dry eye	6 (9.5)	(3.6, 19.6)
	SOC: Injury, poisoning and procedural complications	10 (15.9)	(7.9, 27.3)
	SOC: Ear and labyrinth disorders	6 (9.5)	(3.6, 19.6)
	SOC: Psychiatric disorders	6 (9.5)	(3.6, 19.6)
	SOC: Cardiac disorders	4 (6.3)	(1.8, 15.5)
	SOC: Renal and urinary disorders	3 (4.8)	(1.0, 13.3)
	SOC: Vascular disorders	1 (1.6)	(0.0, 8.5)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Region	SOC: Gastrointestinal disorders	53 (100.0)	(93.3, 100.0)
North America (N = 53)	Nausea	43 (81.1)	(68.0, 90.6)
	Vomiting	31 (58.5)	(44.1, 71.9)
	Diarrhoea	23 (43.4)	(29.8, 57.7)
	Constipation	18 (34.0)	(21.5, 48.3)
	Abdominal pain	11 (20.8)	(10.8, 34.1)
	Stomatitis	10 (18.9)	(9.4, 32.0)
	Dyspepsia	7 (13.2)	(5.5, 25.3)
	SOC: General disorders and administration site conditions	46 (86.8)	(74.7, 94.5)
	Fatigue	41 (77.4)	(63.8, 87.7)
	Asthenia	2 (3.8)	(0.5, 13.0)
	SOC: Skin and subcutaneous tissue disorders	36 (67.9)	(53.7, 80.1)
	Alopecia	30 (56.6)	(42.3, 70.2)
	Rash	7 (13.2)	(5.5, 25.3)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Region	SOC: Investigations	32 (60.4)	(46.0, 73.5)
North America (N = 53)	Neutrophil count decreased	11 (20.8)	(10.8, 34.1)
	Platelet count decreased	10 (18.9)	(9.4, 32.0)
	White blood cell count decreased	10 (18.9)	(9.4, 32.0)
	Aspartate aminotransferase increased	9 (17.0)	(8.1, 29.8)
	Lymphocyte count decreased	4 (7.5)	(2.1, 18.2)
	Alanine aminotransferase increased	3 (5.7)	(1.2, 15.7)
	SOC: Respiratory, thoracic and mediastinal disorders	32 (60.4)	(46.0, 73.5)
	Cough	21 (39.6)	(26.5, 54.0)
	Dyspnoea	7 (13.2)	(5.5, 25.3)
	Epistaxis	6 (11.3)	(4.3, 23.0)
	SOC: Infections and infestations	31 (58.5)	(44.1, 71.9)
	Upper respiratory tract infection	11 (20.8)	(10.8, 34.1)
	Urinary tract infection	7 (13.2)	(5.5, 25.3)
	Nasopharyngitis	5 (9.4)	(3.1, 20.7)
	SOC: Nervous system disorders	30 (56.6)	(42.3, 70.2)
	Headache	14 (26.4)	(15.3, 40.3)
	Dizziness	10 (18.9)	(9.4, 32.0)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Region	SOC: Metabolism and nutrition disorders	28 (52.8)	(38.6, 66.7)
North America (N = 53)	Decreased appetite	17 (32.1)	(19.9, 46.3)
	Hypokalaemia	12 (22.6)	(12.3, 36.2)
	SOC: Eye disorders	23 (43.4)	(29.8, 57.7)
	Dry eye	8 (15.1)	(6.7, 27.6)
	SOC: Musculoskeletal and connective tissue disorders	21 (39.6)	(26.5, 54.0)
	Arthralgia	13 (24.5)	(13.8, 38.3)
	Back pain	8 (15.1)	(6.7, 27.6)
	SOC: Blood and lymphatic system disorders	20 (37.7)	(24.8, 52.1)
	Anaemia	17 (32.1)	(19.9, 46.3)
	Neutropenia	6 (11.3)	(4.3, 23.0)
	SOC: Psychiatric disorders	13 (24.5)	(13.8, 38.3)
	SOC: Vascular disorders	12 (22.6)	(12.3, 36.2)
	SOC: Injury, poisoning and procedural complications	9 (17.0)	(8.1, 29.8)
	SOC: Ear and labyrinth disorders	8 (15.1)	(6.7, 27.6)
	SOC: Renal and urinary disorders	8 (15.1)	(6.7, 27.6)
	SOC: Cardiac disorders	6 (11.3)	(4.3, 23.0)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Region	SOC: Gastrointestinal disorders	63 (92.6)	(83.7, 97.6)
EU (N = 68)	Nausea	55 (80.9)	(69.5, 89.4)
	Vomiting	36 (52.9)	(40.4, 65.2)
	Constipation	26 (38.2)	(26.7, 50.8)
	Diarrhoea	25 (36.8)	(25.4, 49.3)
	Abdominal pain	12 (17.6)	(9.5, 28.8)
	Dyspepsia	12 (17.6)	(9.5, 28.8)
	Stomatitis	8 (11.8)	(5.2, 21.9)
	SOC: General disorders and administration site conditions	57 (83.8)	(72.9, 91.6)
	Fatigue	29 (42.6)	(30.7, 55.2)
	Asthenia	23 (33.8)	(22.8, 46.3)
	SOC: Infections and infestations	39 (57.4)	(44.8, 69.3)
	Urinary tract infection	12 (17.6)	(9.5, 28.8)
	Nasopharyngitis	8 (11.8)	(5.2, 21.9)
	Upper respiratory tract infection	5 (7.4)	(2.4, 16.3)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Region	SOC: Respiratory, thoracic and mediastinal disorders	39 (57.4)	(44.8, 69.3)
EU (N = 68)	Dyspnoea	20 (29.4)	(19.0, 41.7)
	Cough	15 (22.1)	(12.9, 33.8)
	Epistaxis	9 (13.2)	(6.2, 23.6)
	SOC: Investigations	37 (54.4)	(41.9, 66.5)
	Aspartate aminotransferase increased	12 (17.6)	(9.5, 28.8)
	Alanine aminotransferase increased	10 (14.7)	(7.3, 25.4)
	Neutrophil count decreased	6 (8.8)	(3.3, 18.2)
	Lymphocyte count decreased	4 (5.9)	(1.6, 14.4)
	Platelet count decreased	4 (5.9)	(1.6, 14.4)
	White blood cell count decreased	2 (2.9)	(0.4, 10.2)
	SOC: Skin and subcutaneous tissue disorders	37 (54.4)	(41.9, 66.5)
	Alopecia	27 (39.7)	(28.0, 52.3)
	Rash	6 (8.8)	(3.3, 18.2)
	SOC: Blood and lymphatic system disorders	32 (47.1)	(34.8, 59.6)
	Anaemia	21 (30.9)	(20.2, 43.3)
	Neutropenia	12 (17.6)	(9.5, 28.8)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Region	SOC: Nervous system disorders	31 (45.6)	(33.5, 58.1)
EU (N = 68)	Headache	12 (17.6)	(9.5, 28.8)
	Dizziness	5 (7.4)	(2.4, 16.3)
	SOC: Musculoskeletal and connective tissue disorders	30 (44.1)	(32.1, 56.7)
	Back pain	10 (14.7)	(7.3, 25.4)
	Arthralgia	7 (10.3)	(4.2, 20.1)
	SOC: Metabolism and nutrition disorders	27 (39.7)	(28.0, 52.3)
	Decreased appetite	19 (27.9)	(17.7, 40.1)
	Hypokalaemia	9 (13.2)	(6.2, 23.6)
	SOC: Eye disorders	24 (35.3)	(24.1, 47.8)
	Dry eye	7 (10.3)	(4.2, 20.1)
	SOC: Vascular disorders	14 (20.6)	(11.7, 32.1)
	SOC: Cardiac disorders	12 (17.6)	(9.5, 28.8)
	SOC: Psychiatric disorders	9 (13.2)	(6.2, 23.6)
	SOC: Renal and urinary disorders	8 (11.8)	(5.2, 21.9)
	SOC: Injury, poisoning and procedural complications	7 (10.3)	(4.2, 20.1)
	SOC: Ear and labyrinth disorders	5 (7.4)	(2.4, 16.3)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
ECOG performance status	SOC: Gastrointestinal disorders	97 (95.1)	(88.9, 98.4)
0 (N = 102)	Nausea	79 (77.5)	(68.1, 85.1)
	Vomiting	52 (51.0)	(40.9, 61.0)
	Constipation	43 (42.2)	(32.4, 52.3)
	Diarrhoea	32 (31.4)	(22.5, 41.3)
	Dyspepsia	22 (21.6)	(14.0, 30.8)
	Abdominal pain	19 (18.6)	(11.6, 27.6)
	Stomatitis	19 (18.6)	(11.6, 27.6)
	SOC: General disorders and administration site conditions	80 (78.4)	(69.2, 86.0)
	Fatigue	53 (52.0)	(41.8, 62.0)
	Asthenia	15 (14.7)	(8.5, 23.1)
	SOC: Skin and subcutaneous tissue disorders	65 (63.7)	(53.6, 73.0)
	Alopecia	51 (50.0)	(39.9, 60.1)
	Rash	9 (8.8)	(4.1, 16.1)
	SOC: Respiratory, thoracic and mediastinal disorders	64 (62.7)	(52.6, 72.1)
	Cough	30 (29.4)	(20.8, 39.3)
	Dyspnoea	15 (14.7)	(8.5, 23.1)
	Epistaxis	14 (13.7)	(7.7, 22.0)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
ECOG performance status	SOC: Investigations	63 (61.8)	(51.6, 71.2)
0 (N = 102)	Neutrophil count decreased	24 (23.5)	(15.7, 33.0)
	Aspartate aminotransferase increased	22 (21.6)	(14.0, 30.8)
	White blood cell count decreased	22 (21.6)	(14.0, 30.8)
	Platelet count decreased	17 (16.7)	(10.0, 25.3)
	Alanine aminotransferase increased	14 (13.7)	(7.7, 22.0)
	Lymphocyte count decreased	14 (13.7)	(7.7, 22.0)
	SOC: Infections and infestations	57 (55.9)	(45.7, 65.7)
	Upper respiratory tract infection	15 (14.7)	(8.5, 23.1)
	Urinary tract infection	12 (11.8)	(6.2, 19.6)
	Nasopharyngitis	11 (10.8)	(5.5, 18.5)
	SOC: Metabolism and nutrition disorders	48 (47.1)	(37.1, 57.2)
	Decreased appetite	34 (33.3)	(24.3, 43.4)
	Hypokalaemia	7 (6.9)	(2.8, 13.6)
	SOC: Nervous system disorders	48 (47.1)	(37.1, 57.2)
	Headache	22 (21.6)	(14.0, 30.8)
	Dizziness	12 (11.8)	(6.2, 19.6)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
ECOG performance status	SOC: Blood and lymphatic system disorders	47 (46.1)	(36.2, 56.2)
0 (N = 102)	Anaemia	39 (38.2)	(28.8, 48.4)
	Neutropenia	14 (13.7)	(7.7, 22.0)
	SOC: Musculoskeletal and connective tissue disorders	39 (38.2)	(28.8, 48.4)
	Arthralgia	14 (13.7)	(7.7, 22.0)
	Back pain	12 (11.8)	(6.2, 19.6)
	SOC: Eye disorders	38 (37.3)	(27.9, 47.4)
	Dry eye	14 (13.7)	(7.7, 22.0)
	SOC: Psychiatric disorders	19 (18.6)	(11.6, 27.6)
	SOC: Vascular disorders	18 (17.6)	(10.8, 26.4)
	SOC: Injury, poisoning and procedural complications	15 (14.7)	(8.5, 23.1)
	SOC: Ear and labyrinth disorders	13 (12.7)	(7.0, 20.8)
	SOC: Cardiac disorders	10 (9.8)	(4.8, 17.3)
	SOC: Renal and urinary disorders	9 (8.8)	(4.1, 16.1)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
ECOG performance status	SOC: Gastrointestinal disorders	76 (93.8)	(86.2, 98.0)
1 (N = 81)	Nausea	65 (80.2)	(69.9, 88.3)
	Vomiting	36 (44.4)	(33.4, 55.9)
	Diarrhoea	26 (32.1)	(22.2, 43.4)
	Constipation	22 (27.2)	(17.9, 38.2)
	Stomatitis	10 (12.3)	(6.1, 21.5)
	Dyspepsia	9 (11.1)	(5.2, 20.0)
	Abdominal pain	6 (7.4)	(2.8, 15.4)
	SOC: General disorders and administration site conditions	56 (69.1)	(57.9, 78.9)
	Fatigue	39 (48.1)	(36.9, 59.5)
	Asthenia	11 (13.6)	(7.0, 23.0)
	SOC: Skin and subcutaneous tissue disorders	50 (61.7)	(50.3, 72.3)
	Alopecia	37 (45.7)	(34.6, 57.1)
	Rash	10 (12.3)	(6.1, 21.5)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
ECOG performance status	SOC: Investigations	43 (53.1)	(41.7, 64.3)
1 (N = 81)	Neutrophil count decreased	17 (21.0)	(12.7, 31.5)
	White blood cell count decreased	14 (17.3)	(9.8, 27.3)
	Platelet count decreased	13 (16.0)	(8.8, 25.9)
	Aspartate aminotransferase increased	11 (13.6)	(7.0, 23.0)
	Alanine aminotransferase increased	7 (8.6)	(3.5, 17.0)
	Lymphocyte count decreased	5 (6.2)	(2.0, 13.8)
	SOC: Nervous system disorders	43 (53.1)	(41.7, 64.3)
	Headache	18 (22.2)	(13.7, 32.8)
	Dizziness	7 (8.6)	(3.5, 17.0)
	SOC: Infections and infestations	41 (50.6)	(39.3, 61.9)
	Nasopharyngitis	9 (11.1)	(5.2, 20.0)
	Upper respiratory tract infection	9 (11.1)	(5.2, 20.0)
	Urinary tract infection	9 (11.1)	(5.2, 20.0)
	SOC: Respiratory, thoracic and mediastinal disorders	40 (49.4)	(38.1, 60.7)
	Dyspnoea	15 (18.5)	(10.8, 28.7)
	Cough	14 (17.3)	(9.8, 27.3)
	Epistaxis	12 (14.8)	(7.9, 24.4)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
ECOG performance status	SOC: Metabolism and nutrition disorders	36 (44.4)	(33.4, 55.9)
1 (N = 81)	Decreased appetite	25 (30.9)	(21.1, 42.1)
	Hypokalaemia	15 (18.5)	(10.8, 28.7)
	SOC: Blood and lymphatic system disorders	33 (40.7)	(29.9, 52.2)
	Anaemia	19 (23.5)	(14.8, 34.2)
	Neutropenia	13 (16.0)	(8.8, 25.9)
	SOC: Musculoskeletal and connective tissue disorders	31 (38.3)	(27.7, 49.7)
	Arthralgia	10 (12.3)	(6.1, 21.5)
	Back pain	8 (9.9)	(4.4, 18.5)
	SOC: Eye disorders	23 (28.4)	(18.9, 39.5)
	Dry eye	7 (8.6)	(3.5, 17.0)
	SOC: Cardiac disorders	12 (14.8)	(7.9, 24.4)
	SOC: Injury, poisoning and procedural complications	11 (13.6)	(7.0, 23.0)
	SOC: Renal and urinary disorders	10 (12.3)	(6.1, 21.5)
	SOC: Psychiatric disorders	9 (11.1)	(5.2, 20.0)
	SOC: Vascular disorders	9 (11.1)	(5.2, 20.0)
	SOC: Ear and labyrinth disorders	6 (7.4)	(2.8, 15.4)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Baseline sum of diameters of target lesions <5 cm (N = 74)	SOC: Gastrointestinal disorders	71 (95.9)	(88.6, 99.2)
	Nausea	57 (77.0)	(65.8, 86.0)
	Vomiting	34 (45.9)	(34.3, 57.9)
	Diarrhoea	26 (35.1)	(24.4, 47.1)
	Constipation	24 (32.4)	(22.0, 44.3)
	Dyspepsia	13 (17.6)	(9.7, 28.2)
	Stomatitis	13 (17.6)	(9.7, 28.2)
	Abdominal pain	7 (9.5)	(3.9, 18.5)
	SOC: General disorders and administration site conditions	60 (81.1)	(70.3, 89.3)
	Fatigue	37 (50.0)	(38.1, 61.9)
	Asthenia	14 (18.9)	(10.7, 29.7)
	SOC: Skin and subcutaneous tissue disorders	49 (66.2)	(54.3, 76.8)
	Alopecia	43 (58.1)	(46.1, 69.5)
	Rash	6 (8.1)	(3.0, 16.8)
	SOC: Respiratory, thoracic and mediastinal disorders	48 (64.9)	(52.9, 75.6)
	Cough	20 (27.0)	(17.4, 38.6)
	Dyspnoea	12 (16.2)	(8.7, 26.6)
	Epistaxis	12 (16.2)	(8.7, 26.6)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Baseline sum of diameters of target lesions <5 cm (N = 74)	SOC: Investigations	42 (56.8)	(44.7, 68.2)
	White blood cell count decreased	15 (20.3)	(11.8, 31.2)
	Neutrophil count decreased	14 (18.9)	(10.7, 29.7)
	Platelet count decreased	12 (16.2)	(8.7, 26.6)
	Aspartate aminotransferase increased	10 (13.5)	(6.7, 23.5)
	Alanine aminotransferase increased	8 (10.8)	(4.8, 20.2)
	Lymphocyte count decreased	7 (9.5)	(3.9, 18.5)
	SOC: Infections and infestations	41 (55.4)	(43.4, 67.0)
	Nasopharyngitis	9 (12.2)	(5.7, 21.8)
	Upper respiratory tract infection	8 (10.8)	(4.8, 20.2)
	Urinary tract infection	8 (10.8)	(4.8, 20.2)
	SOC: Nervous system disorders	36 (48.6)	(36.9, 60.6)
	Headache	13 (17.6)	(9.7, 28.2)
	Dizziness	6 (8.1)	(3.0, 16.8)
	SOC: Blood and lymphatic system disorders	33 (44.6)	(33.0, 56.6)
	Anaemia	25 (33.8)	(23.2, 45.7)
	Neutropenia	11 (14.9)	(7.7, 25.0)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Baseline sum of diameters of target lesions <5 cm (N = 74)	SOC: Metabolism and nutrition disorders	32 (43.2)	(31.8, 55.3)
	Decreased appetite	21 (28.4)	(18.5, 40.1)
	Hypokalaemia	8 (10.8)	(4.8, 20.2)
	SOC: Musculoskeletal and connective tissue disorders	29 (39.2)	(28.0, 51.2)
	Arthralgia	11 (14.9)	(7.7, 25.0)
	Back pain	9 (12.2)	(5.7, 21.8)
	SOC: Eye disorders	26 (35.1)	(24.4, 47.1)
	Dry eye	7 (9.5)	(3.9, 18.5)
	SOC: Ear and labyrinth disorders	10 (13.5)	(6.7, 23.5)
	SOC: Injury, poisoning and procedural complications	10 (13.5)	(6.7, 23.5)
	SOC: Psychiatric disorders	10 (13.5)	(6.7, 23.5)
	SOC: Vascular disorders	10 (13.5)	(6.7, 23.5)
	SOC: Cardiac disorders	8 (10.8)	(4.8, 20.2)
	SOC: Renal and urinary disorders	8 (10.8)	(4.8, 20.2)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Baseline sum of diameters of target lesions >=5 cm (N = 96)	SOC: Gastrointestinal disorders	89 (92.7)	(85.6, 97.0)
	Nausea	77 (80.2)	(70.8, 87.6)
	Vomiting	49 (51.0)	(40.6, 61.4)
	Constipation	34 (35.4)	(25.9, 45.8)
	Diarrhoea	30 (31.3)	(22.2, 41.5)
	Dyspepsia	16 (16.7)	(9.8, 25.6)
	Abdominal pain	15 (15.6)	(9.0, 24.5)
	Stomatitis	11 (11.5)	(5.9, 19.6)
	SOC: General disorders and administration site conditions	68 (70.8)	(60.7, 79.7)
	Fatigue	48 (50.0)	(39.6, 60.4)
	Asthenia	9 (9.4)	(4.4, 17.1)
	SOC: Skin and subcutaneous tissue disorders	57 (59.4)	(48.9, 69.3)
	Alopecia	40 (41.7)	(31.7, 52.2)
	Rash	12 (12.5)	(6.6, 20.8)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Baseline sum of diameters of target lesions >=5 cm (N = 96)	SOC: Investigations	56 (58.3)	(47.8, 68.3)
	Neutrophil count decreased	24 (25.0)	(16.7, 34.9)
	Aspartate aminotransferase increased	18 (18.8)	(11.5, 28.0)
	White blood cell count decreased	18 (18.8)	(11.5, 28.0)
	Platelet count decreased	15 (15.6)	(9.0, 24.5)
	Lymphocyte count decreased	10 (10.4)	(5.1, 18.3)
	Alanine aminotransferase increased	9 (9.4)	(4.4, 17.1)
	SOC: Infections and infestations	48 (50.0)	(39.6, 60.4)
	Upper respiratory tract infection	15 (15.6)	(9.0, 24.5)
	Urinary tract infection	13 (13.5)	(7.4, 22.0)
	Nasopharyngitis	8 (8.3)	(3.7, 15.8)
	SOC: Respiratory, thoracic and mediastinal disorders	48 (50.0)	(39.6, 60.4)
	Cough	20 (20.8)	(13.2, 30.3)
	Dyspnoea	15 (15.6)	(9.0, 24.5)
	Epistaxis	14 (14.6)	(8.2, 23.3)
	SOC: Metabolism and nutrition disorders	47 (49.0)	(38.6, 59.4)
	Decreased appetite	35 (36.5)	(26.9, 46.9)
	Hypokalaemia	14 (14.6)	(8.2, 23.3)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Baseline sum of diameters of target lesions >=5 cm (N = 96)	SOC: Nervous system disorders	47 (49.0)	(38.6, 59.4)
	Headache	24 (25.0)	(16.7, 34.9)
	Dizziness	12 (12.5)	(6.6, 20.8)
	SOC: Blood and lymphatic system disorders	41 (42.7)	(32.7, 53.2)
	Anaemia	29 (30.2)	(21.3, 40.4)
	Neutropenia	14 (14.6)	(8.2, 23.3)
	SOC: Musculoskeletal and connective tissue disorders	34 (35.4)	(25.9, 45.8)
	Arthralgia	12 (12.5)	(6.6, 20.8)
	Back pain	8 (8.3)	(3.7, 15.8)
	SOC: Eye disorders	31 (32.3)	(23.1, 42.6)
	Dry eye	13 (13.5)	(7.4, 22.0)
	SOC: Vascular disorders	16 (16.7)	(9.8, 25.6)
	SOC: Injury, poisoning and procedural complications	15 (15.6)	(9.0, 24.5)
	SOC: Psychiatric disorders	15 (15.6)	(9.0, 24.5)
	SOC: Cardiac disorders	11 (11.5)	(5.9, 19.6)
	SOC: Renal and urinary disorders	7 (7.3)	(3.0, 14.4)
	SOC: Ear and labyrinth disorders	5 (5.2)	(1.7, 11.7)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

Subgroup	SOC/Preferred Term	Overall 5.4 mg/kg (N = 184) n (%)	95% CI [a]
DS-8201a immediately following initial T-DM1	SOC: Gastrointestinal disorders	51 (91.1)	(80.4, 97.0)
Yes (N = 56)	Nausea	39 (69.6)	(55.9, 81.2)
	Vomiting	24 (42.9)	(29.7, 56.8)
	Constipation	19 (33.9)	(21.8, 47.8)
	Diarrhoea	12 (21.4)	(11.6, 34.4)
	Dyspepsia	11 (19.6)	(10.2, 32.4)
	Stomatitis	7 (12.5)	(5.2, 24.1)
	Abdominal pain	5 (8.9)	(3.0, 19.6)
	SOC: General disorders and administration site conditions	41 (73.2)	(59.7, 84.2)
	Fatigue	28 (50.0)	(36.3, 63.7)
	Asthenia	3 (5.4)	(1.1, 14.9)
	SOC: Skin and subcutaneous tissue disorders	39 (69.6)	(55.9, 81.2)
	Alopecia	30 (53.6)	(39.7, 67.0)
	Rash	5 (8.9)	(3.0, 19.6)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

Subgroup	SOC/Preferred Term	Overall 5.4 mg/kg (N = 184) n (%)	95% CI [a]
DS-8201a immediately following initial T-DM1 Yes (N = 56)	SOC: Investigations	37 (66.1)	(52.2, 78.2)
	Neutrophil count decreased	15 (26.8)	(15.8, 40.3)
	White blood cell count decreased	14 (25.0)	(14.4, 38.4)
	Aspartate aminotransferase increased	13 (23.2)	(13.0, 36.4)
	Platelet count decreased	12 (21.4)	(11.6, 34.4)
	Alanine aminotransferase increased	9 (16.1)	(7.6, 28.3)
	Lymphocyte count decreased	8 (14.3)	(6.4, 26.2)
	SOC: Infections and infestations	33 (58.9)	(45.0, 71.9)
	Upper respiratory tract infection	10 (17.9)	(8.9, 30.4)
	Nasopharyngitis	7 (12.5)	(5.2, 24.1)
	Urinary tract infection	2 (3.6)	(0.4, 12.3)
	SOC: Respiratory, thoracic and mediastinal disorders	32 (57.1)	(43.2, 70.3)
	Cough	10 (17.9)	(8.9, 30.4)
	Epistaxis	9 (16.1)	(7.6, 28.3)
	Dyspnoea	5 (8.9)	(3.0, 19.6)
	SOC: Nervous system disorders	28 (50.0)	(36.3, 63.7)
	Headache	14 (25.0)	(14.4, 38.4)
	Dizziness	2 (3.6)	(0.4, 12.3)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
DS-8201a immediately following initial T-DM1 Yes (N = 56)	SOC: Blood and lymphatic system disorders	24 (42.9)	(29.7, 56.8)
	Anaemia	21 (37.5)	(24.9, 51.5)
	Neutropenia	4 (7.1)	(2.0, 17.3)
	SOC: Metabolism and nutrition disorders	22 (39.3)	(26.5, 53.2)
	Decreased appetite	12 (21.4)	(11.6, 34.4)
	Hypokalaemia	4 (7.1)	(2.0, 17.3)
	SOC: Musculoskeletal and connective tissue disorders	22 (39.3)	(26.5, 53.2)
	Arthralgia	6 (10.7)	(4.0, 21.9)
	Back pain	5 (8.9)	(3.0, 19.6)
	SOC: Eye disorders	18 (32.1)	(20.3, 46.0)
	Dry eye	6 (10.7)	(4.0, 21.9)
	SOC: Psychiatric disorders	11 (19.6)	(10.2, 32.4)
	SOC: Injury, poisoning and procedural complications	10 (17.9)	(8.9, 30.4)
	SOC: Renal and urinary disorders	7 (12.5)	(5.2, 24.1)
	SOC: Cardiac disorders	3 (5.4)	(1.1, 14.9)
	SOC: Vascular disorders	3 (5.4)	(1.1, 14.9)
	SOC: Ear and labyrinth disorders	2 (3.6)	(0.4, 12.3)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

Subgroup	SOC/Preferred Term	Overall 5.4 mg/kg (N = 184) n (%)	95% CI [a]
DS-8201a immediately following initial T-DM1 No (N = 128)	SOC: Gastrointestinal disorders	122 (95.3)	(90.1, 98.3)
	Nausea	105 (82.0)	(74.3, 88.3)
	Vomiting	64 (50.0)	(41.0, 59.0)
	Constipation	46 (35.9)	(27.7, 44.9)
	Diarrhoea	46 (35.9)	(27.7, 44.9)
	Stomatitis	22 (17.2)	(11.1, 24.9)
	Abdominal pain	20 (15.6)	(9.8, 23.1)
	Dyspepsia	20 (15.6)	(9.8, 23.1)
	SOC: General disorders and administration site conditions	96 (75.0)	(66.6, 82.2)
	Fatigue	64 (50.0)	(41.0, 59.0)
	Asthenia	23 (18.0)	(11.7, 25.7)
	SOC: Skin and subcutaneous tissue disorders	77 (60.2)	(51.1, 68.7)
	Alopecia	59 (46.1)	(37.2, 55.1)
	Rash	14 (10.9)	(6.1, 17.7)
	SOC: Respiratory, thoracic and mediastinal disorders	73 (57.0)	(48.0, 65.7)
	Cough	35 (27.3)	(19.8, 35.9)
	Dyspnoea	26 (20.3)	(13.7, 28.3)
	Epistaxis	17 (13.3)	(7.9, 20.4)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

Subgroup	SOC/Preferred Term	Overall 5.4 mg/kg (N = 184) n (%)	95% CI [a]
DS-8201a immediately following initial T-DM1 No (N = 128)	SOC: Investigations	69 (53.9)	(44.9, 62.8)
	Neutrophil count decreased	26 (20.3)	(13.7, 28.3)
	White blood cell count decreased	22 (17.2)	(11.1, 24.9)
	Aspartate aminotransferase increased	20 (15.6)	(9.8, 23.1)
	Platelet count decreased	18 (14.1)	(8.6, 21.3)
	Alanine aminotransferase increased	12 (9.4)	(4.9, 15.8)
	Lymphocyte count decreased	11 (8.6)	(4.4, 14.9)
	SOC: Infections and infestations	66 (51.6)	(42.6, 60.5)
	Urinary tract infection	20 (15.6)	(9.8, 23.1)
	Upper respiratory tract infection	14 (10.9)	(6.1, 17.7)
	Nasopharyngitis	13 (10.2)	(5.5, 16.7)
	SOC: Nervous system disorders	63 (49.2)	(40.3, 58.2)
	Headache	26 (20.3)	(13.7, 28.3)
	Dizziness	17 (13.3)	(7.9, 20.4)
	SOC: Metabolism and nutrition disorders	62 (48.4)	(39.5, 57.4)
	Decreased appetite	47 (36.7)	(28.4, 45.7)
	Hypokalaemia	18 (14.1)	(8.6, 21.3)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
DS-8201a immediately following initial T-DM1 No (N = 128)	SOC: Blood and lymphatic system disorders	56 (43.8)	(35.0, 52.8)
	Anaemia	37 (28.9)	(21.2, 37.6)
	Neutropenia	23 (18.0)	(11.7, 25.7)
	SOC: Musculoskeletal and connective tissue disorders	48 (37.5)	(29.1, 46.5)
	Arthralgia	18 (14.1)	(8.6, 21.3)
	Back pain	15 (11.7)	(6.7, 18.6)
	SOC: Eye disorders	43 (33.6)	(25.5, 42.5)
	Dry eye	15 (11.7)	(6.7, 18.6)
	SOC: Vascular disorders	24 (18.8)	(12.4, 26.6)
	SOC: Cardiac disorders	19 (14.8)	(9.2, 22.2)
	SOC: Ear and labyrinth disorders	17 (13.3)	(7.9, 20.4)
	SOC: Psychiatric disorders	17 (13.3)	(7.9, 20.4)
	SOC: Injury, poisoning and procedural complications	16 (12.5)	(7.3, 19.5)
	SOC: Renal and urinary disorders	12 (9.4)	(4.9, 15.8)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
HER2 status	SOC: Gastrointestinal disorders	144 (93.5)	(88.4, 96.8)
IHC3+ (N = 154)	Nausea	122 (79.2)	(72.0, 85.3)
	Vomiting	72 (46.8)	(38.7, 55.0)
	Constipation	53 (34.4)	(27.0, 42.5)
	Diarrhoea	48 (31.2)	(24.0, 39.1)
	Dyspepsia	28 (18.2)	(12.4, 25.2)
	Stomatitis	26 (16.9)	(11.3, 23.8)
	Abdominal pain	21 (13.6)	(8.6, 20.1)
	SOC: General disorders and administration site conditions	113 (73.4)	(65.7, 80.2)
	Fatigue	76 (49.4)	(41.2, 57.5)
	Asthenia	24 (15.6)	(10.2, 22.3)
	SOC: Skin and subcutaneous tissue disorders	101 (65.6)	(57.5, 73.0)
	Alopecia	76 (49.4)	(41.2, 57.5)
	Rash	19 (12.3)	(7.6, 18.6)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
HER2 status	SOC: Investigations	93 (60.4)	(52.2, 68.2)
IHC3+ (N = 154)	Neutrophil count decreased	38 (24.7)	(18.1, 32.3)
	White blood cell count decreased	31 (20.1)	(14.1, 27.3)
	Aspartate aminotransferase increased	29 (18.8)	(13.0, 25.9)
	Platelet count decreased	27 (17.5)	(11.9, 24.5)
	Alanine aminotransferase increased	18 (11.7)	(7.1, 17.8)
	Lymphocyte count decreased	16 (10.4)	(6.1, 16.3)
	SOC: Respiratory, thoracic and mediastinal disorders	89 (57.8)	(49.6, 65.7)
	Cough	38 (24.7)	(18.1, 32.3)
	Dyspnoea	24 (15.6)	(10.2, 22.3)
	Epistaxis	24 (15.6)	(10.2, 22.3)
	SOC: Infections and infestations	83 (53.9)	(45.7, 61.9)
	Upper respiratory tract infection	21 (13.6)	(8.6, 20.1)
	Urinary tract infection	20 (13.0)	(8.1, 19.3)
	Nasopharyngitis	17 (11.0)	(6.6, 17.1)
	SOC: Nervous system disorders	77 (50.0)	(41.8, 58.2)
	Headache	31 (20.1)	(14.1, 27.3)
	Dizziness	16 (10.4)	(6.1, 16.3)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
HER2 status	SOC: Metabolism and nutrition disorders	71 (46.1)	(38.1, 54.3)
IHC3+ (N = 154)	Decreased appetite	53 (34.4)	(27.0, 42.5)
	Hypokalaemia	17 (11.0)	(6.6, 17.1)
	SOC: Blood and lymphatic system disorders	70 (45.5)	(37.4, 53.7)
	Anaemia	52 (33.8)	(26.4, 41.8)
	Neutropenia	25 (16.2)	(10.8, 23.0)
	SOC: Musculoskeletal and connective tissue disorders	55 (35.7)	(28.2, 43.8)
	Arthralgia	22 (14.3)	(9.2, 20.8)
	Back pain	14 (9.1)	(5.1, 14.8)
	SOC: Eye disorders	51 (33.1)	(25.8, 41.1)
	Dry eye	17 (11.0)	(6.6, 17.1)
	SOC: Psychiatric disorders	22 (14.3)	(9.2, 20.8)
	SOC: Injury, poisoning and procedural complications	21 (13.6)	(8.6, 20.1)
	SOC: Vascular disorders	20 (13.0)	(8.1, 19.3)
	SOC: Renal and urinary disorders	18 (11.7)	(7.1, 17.8)
	SOC: Cardiac disorders	17 (11.0)	(6.6, 17.1)
	SOC: Ear and labyrinth disorders	15 (9.7)	(5.6, 15.6)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
HER2 status	SOC: Gastrointestinal disorders	27 (96.4)	(81.7, 99.9)
ISH+ except IHC3+ (N = 28)	Nausea	20 (71.4)	(51.3, 86.8)
	Vomiting	14 (50.0)	(30.6, 69.4)
	Constipation	11 (39.3)	(21.5, 59.4)
	Diarrhoea	10 (35.7)	(18.6, 55.9)
	Abdominal pain	4 (14.3)	(4.0, 32.7)
	Stomatitis	3 (10.7)	(2.3, 28.2)
	Dyspepsia	2 (7.1)	(0.9, 23.5)
	SOC: General disorders and administration site conditions	22 (78.6)	(59.0, 91.7)
	Fatigue	14 (50.0)	(30.6, 69.4)
	Asthenia	2 (7.1)	(0.9, 23.5)
	SOC: Respiratory, thoracic and mediastinal disorders	15 (53.6)	(33.9, 72.5)
	Cough	7 (25.0)	(10.7, 44.9)
	Dyspnoea	7 (25.0)	(10.7, 44.9)
	Epistaxis	1 (3.6)	(0.1, 18.3)
	SOC: Skin and subcutaneous tissue disorders	15 (53.6)	(33.9, 72.5)
	Alopecia	13 (46.4)	(27.5, 66.1)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
HER2 status	SOC: Infections and infestations	14 (50.0)	(30.6, 69.4)
ISH+ except IHC3+ (N = 28)	Nasopharyngitis	3 (10.7)	(2.3, 28.2)
	Upper respiratory tract infection	2 (7.1)	(0.9, 23.5)
	Urinary tract infection	2 (7.1)	(0.9, 23.5)
	SOC: Musculoskeletal and connective tissue disorders	14 (50.0)	(30.6, 69.4)
	Back pain	6 (21.4)	(8.3, 41.0)
	Arthralgia	1 (3.6)	(0.1, 18.3)
	SOC: Metabolism and nutrition disorders	13 (46.4)	(27.5, 66.1)
	Decreased appetite	6 (21.4)	(8.3, 41.0)
	Hypokalaemia	5 (17.9)	(6.1, 36.9)
	SOC: Nervous system disorders	13 (46.4)	(27.5, 66.1)
	Headache	8 (28.6)	(13.2, 48.7)
	Dizziness	3 (10.7)	(2.3, 28.2)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 23 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 10%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
HER2 status	SOC: Investigations	12 (42.9)	(24.5, 62.8)
ISH+ except IHC3+ (N = 28)	White blood cell count decreased	5 (17.9)	(6.1, 36.9)
	Aspartate aminotransferase increased	4 (14.3)	(4.0, 32.7)
	Alanine aminotransferase increased	3 (10.7)	(2.3, 28.2)
	Lymphocyte count decreased	3 (10.7)	(2.3, 28.2)
	Platelet count decreased	3 (10.7)	(2.3, 28.2)
	Neutrophil count decreased	2 (7.1)	(0.9, 23.5)
	SOC: Blood and lymphatic system disorders	10 (35.7)	(18.6, 55.9)
	Anaemia	6 (21.4)	(8.3, 41.0)
	Neutropenia	2 (7.1)	(0.9, 23.5)
	SOC: Eye disorders	9 (32.1)	(15.9, 52.4)
	Dry eye	3 (10.7)	(2.3, 28.2)
	SOC: Vascular disorders	7 (25.0)	(10.7, 44.9)
	SOC: Cardiac disorders	5 (17.9)	(6.1, 36.9)
	SOC: Injury, poisoning and procedural complications	5 (17.9)	(6.1, 36.9)
	SOC: Psychiatric disorders	5 (17.9)	(6.1, 36.9)
	SOC: Ear and labyrinth disorders	4 (14.3)	(4.0, 32.7)
	SOC: Renal and urinary disorders	1 (3.6)	(0.1, 18.3)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 25 Serious treatment-emergent adverse events by system organ class, preferred term with incidence >= 5%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Overall	SOC: Infections and infestations	18 (9.8)	(5.9, 15.0)
	SOC: Respiratory, thoracic and mediastinal disorders	14 (7.6)	(4.2, 12.4)
	SOC: Gastrointestinal disorders	13 (7.1)	(3.8, 11.8)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 25 Serious treatment-emergent adverse events by system organ class, preferred term with incidence >= 5%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Estrogen receptors	SOC: Gastrointestinal disorders	10 (10.8)	(5.3, 18.9)
Positive (N = 93)	SOC: Infections and infestations	9 (9.7)	(4.5, 17.6)
	SOC: Respiratory, thoracic and mediastinal disorders	8 (8.6)	(3.8, 16.2)
Negative (N = 88)	SOC: Infections and infestations	8 (9.1)	(4.0, 17.1)
	SOC: Respiratory, thoracic and mediastinal disorders	6 (6.8)	(2.5, 14.3)
	SOC: Gastrointestinal disorders	3 (3.4)	(0.7, 9.6)
Progesterone receptors	SOC: Infections and infestations	5 (9.8)	(3.3, 21.4)
Positive (N = 51)	SOC: Gastrointestinal disorders	3 (5.9)	(1.2, 16.2)
	SOC: Respiratory, thoracic and mediastinal disorders	2 (3.9)	(0.5, 13.5)
Negative (N = 125)	SOC: Infections and infestations	12 (9.6)	(5.1, 16.2)
	SOC: Respiratory, thoracic and mediastinal disorders	12 (9.6)	(5.1, 16.2)
	SOC: Gastrointestinal disorders	9 (7.2)	(3.3, 13.2)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 25 Serious treatment-emergent adverse events by system organ class, preferred term with incidence >= 5%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Hormone receptors	SOC: Gastrointestinal disorders	10 (10.3)	(5.1, 18.1)
Positive (N = 97)	SOC: Infections and infestations	9 (9.3)	(4.3, 16.9)
	SOC: Respiratory, thoracic and mediastinal disorders	8 (8.2)	(3.6, 15.6)
Negative (N = 83)	SOC: Infections and infestations	8 (9.6)	(4.3, 18.1)
	SOC: Respiratory, thoracic and mediastinal disorders	6 (7.2)	(2.7, 15.1)
	SOC: Gastrointestinal disorders	3 (3.6)	(0.8, 10.2)
Lines of prior systemic therapy	SOC: Infections and infestations	18 (10.8)	(6.5, 16.5)
not including hormone therapy	SOC: Respiratory, thoracic and mediastinal disorders	14 (8.4)	(4.7, 13.7)
>= 3 lines (N = 167)	SOC: Gastrointestinal disorders	13 (7.8)	(4.2, 12.9)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 25 Serious treatment-emergent adverse events by system organ class, preferred term with incidence >= 5%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Prior pertuzumab	SOC: Infections and infestations	6 (5.0)	(1.8, 10.5)
Yes (N = 121)	SOC: Gastrointestinal disorders	5 (4.1)	(1.4, 9.4)
	SOC: Respiratory, thoracic and mediastinal disorders	5 (4.1)	(1.4, 9.4)
No (N = 63)	SOC: Infections and infestations	12 (19.0)	(10.2, 30.9)
	SOC: Respiratory, thoracic and mediastinal disorders	9 (14.3)	(6.7, 25.4)
	SOC: Gastrointestinal disorders	8 (12.7)	(5.6, 23.5)
Prior pertuzumab in 1st or 2nd line in	SOC: Gastrointestinal disorders	2 (3.9)	(0.5, 13.5)
advanced/metastatic breast cancer	SOC: Respiratory, thoracic and mediastinal disorders	2 (3.9)	(0.5, 13.5)
Yes (N = 51)	SOC: Infections and infestations	1 (2.0)	(0.0, 10.4)
No (N = 133)	SOC: Infections and infestations	17 (12.8)	(7.6, 19.7)
	SOC: Respiratory, thoracic and mediastinal disorders	12 (9.0)	(4.7, 15.2)
	SOC: Gastrointestinal disorders	11 (8.3)	(4.2, 14.3)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 25 Serious treatment-emergent adverse events by system organ class, preferred term with incidence >= 5%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Renal impairment at baseline	SOC: Gastrointestinal disorders	9 (10.0)	(4.7, 18.1)
Within Normal Range (N = 90)	SOC: Infections and infestations	9 (10.0)	(4.7, 18.1)
	SOC: Respiratory, thoracic and mediastinal disorders	9 (10.0)	(4.7, 18.1)
Mild Impairment (N = 69)	SOC: Infections and infestations	7 (10.1)	(4.2, 19.8)
	SOC: Gastrointestinal disorders	3 (4.3)	(0.9, 12.2)
	SOC: Respiratory, thoracic and mediastinal disorders	3 (4.3)	(0.9, 12.2)
Moderate Impairment (N = 25)	SOC: Infections and infestations	2 (8.0)	(1.0, 26.0)
	SOC: Respiratory, thoracic and mediastinal disorders	2 (8.0)	(1.0, 26.0)
	SOC: Gastrointestinal disorders	1 (4.0)	(0.1, 20.4)
Hepatic impairment at baseline	SOC: Infections and infestations	12 (11.4)	(6.0, 19.1)
Within Normal Range (N = 105)	SOC: Respiratory, thoracic and mediastinal disorders	11 (10.5)	(5.3, 18.0)
	SOC: Gastrointestinal disorders	5 (4.8)	(1.6, 10.8)
Mild Impairment (N = 76)	SOC: Gastrointestinal disorders	8 (10.5)	(4.7, 19.7)
	SOC: Infections and infestations	6 (7.9)	(3.0, 16.4)
	SOC: Respiratory, thoracic and mediastinal disorders	3 (3.9)	(0.8, 11.1)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 25 Serious treatment-emergent adverse events by system organ class, preferred term with incidence >= 5%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Best response to T-DM1 therapy	SOC: Infections and infestations	6 (7.6)	(2.8, 15.8)
CR/PR/SD (N = 79)	SOC: Respiratory, thoracic and mediastinal disorders	5 (6.3)	(2.1, 14.2)
	SOC: Gastrointestinal disorders	4 (5.1)	(1.4, 12.5)
PD (N = 66)	SOC: Infections and infestations	8 (12.1)	(5.4, 22.5)
	SOC: Respiratory, thoracic and mediastinal disorders	5 (7.6)	(2.5, 16.8)
	SOC: Gastrointestinal disorders	4 (6.1)	(1.7, 14.8)
Brain metastases	SOC: Gastrointestinal disorders	2 (8.3)	(1.0, 27.0)
Yes (N = 24)	SOC: Respiratory, thoracic and mediastinal disorders	1 (4.2)	(0.1, 21.1)
No (N = 160)	SOC: Infections and infestations	18 (11.3)	(6.8, 17.2)
	SOC: Respiratory, thoracic and mediastinal disorders	13 (8.1)	(4.4, 13.5)
	SOC: Gastrointestinal disorders	11 (6.9)	(3.5, 12.0)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 25 Serious treatment-emergent adverse events by system organ class, preferred term with incidence >= 5%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Bone metastases	SOC: Infections and infestations	9 (17.0)	(8.1, 29.8)
Yes (N = 53)	SOC: Respiratory, thoracic and mediastinal disorders	7 (13.2)	(5.5, 25.3)
	SOC: Gastrointestinal disorders	6 (11.3)	(4.3, 23.0)
No (N = 131)	SOC: Infections and infestations	9 (6.9)	(3.2, 12.6)
	SOC: Gastrointestinal disorders	7 (5.3)	(2.2, 10.7)
	SOC: Respiratory, thoracic and mediastinal disorders	7 (5.3)	(2.2, 10.7)
History of visceral disease	SOC: Infections and infestations	18 (10.7)	(6.4, 16.3)
Yes (N = 169)	SOC: Gastrointestinal disorders	12 (7.1)	(3.7, 12.1)
	SOC: Respiratory, thoracic and mediastinal disorders	12 (7.1)	(3.7, 12.1)
No (N = 15)	SOC: Respiratory, thoracic and mediastinal disorders	2 (13.3)	(1.7, 40.5)
	SOC: Gastrointestinal disorders	1 (6.7)	(0.2, 31.9)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 25 Serious treatment-emergent adverse events by system organ class, preferred term with incidence >= 5%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Age	SOC: Infections and infestations	15 (10.7)	(6.1, 17.1)
<65 years (N = 140)	SOC: Gastrointestinal disorders	12 (8.6)	(4.5, 14.5)
	SOC: Respiratory, thoracic and mediastinal disorders	10 (7.1)	(3.5, 12.7)
>=65 years (N = 44)	SOC: Respiratory, thoracic and mediastinal disorders	4 (9.1)	(2.5, 21.7)
	SOC: Infections and infestations	3 (6.8)	(1.4, 18.7)
	SOC: Gastrointestinal disorders	1 (2.3)	(0.1, 12.0)
Region	SOC: Infections and infestations	7 (11.1)	(4.6, 21.6)
Asia (N = 63)	SOC: Respiratory, thoracic and mediastinal disorders	2 (3.2)	(0.4, 11.0)
	SOC: Gastrointestinal disorders	1 (1.6)	(0.0, 8.5)
North America (N = 53)	SOC: Gastrointestinal disorders	6 (11.3)	(4.3, 23.0)
	SOC: Infections and infestations	3 (5.7)	(1.2, 15.7)
	SOC: Respiratory, thoracic and mediastinal disorders	3 (5.7)	(1.2, 15.7)
EU (N = 68)	SOC: Respiratory, thoracic and mediastinal disorders	9 (13.2)	(6.2, 23.6)
	SOC: Infections and infestations	8 (11.8)	(5.2, 21.9)
	SOC: Gastrointestinal disorders	6 (8.8)	(3.3, 18.2)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.
[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 25 Serious treatment-emergent adverse events by system organ class, preferred term with incidence >= 5%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
ECOG performance status	SOC: Respiratory, thoracic and mediastinal disorders	8 (7.8)	(3.4, 14.9)
0 (N = 102)	SOC: Gastrointestinal disorders	7 (6.9)	(2.8, 13.6)
	SOC: Infections and infestations	5 (4.9)	(1.6, 11.1)
1 (N = 81)	SOC: Infections and infestations	12 (14.8)	(7.9, 24.4)
	SOC: Gastrointestinal disorders	6 (7.4)	(2.8, 15.4)
	SOC: Respiratory, thoracic and mediastinal disorders	6 (7.4)	(2.8, 15.4)
Baseline sum of diameters of target lesions	SOC: Infections and infestations	8 (10.8)	(4.8, 20.2)
<5 cm (N = 74)	SOC: Respiratory, thoracic and mediastinal disorders	8 (10.8)	(4.8, 20.2)
	SOC: Gastrointestinal disorders	3 (4.1)	(0.8, 11.4)
>=5 cm (N = 96)	SOC: Gastrointestinal disorders	9 (9.4)	(4.4, 17.1)
	SOC: Infections and infestations	8 (8.3)	(3.7, 15.8)
	SOC: Respiratory, thoracic and mediastinal disorders	4 (4.2)	(1.1, 10.3)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 25 Serious treatment-emergent adverse events by system organ class, preferred term with incidence >= 5%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
DS-8201a immediately following initial T-DM1	SOC: Infections and infestations	4 (7.1)	(2.0, 17.3)
Yes (N = 56)	SOC: Gastrointestinal disorders	2 (3.6)	(0.4, 12.3)
	SOC: Respiratory, thoracic and mediastinal disorders	2 (3.6)	(0.4, 12.3)
No (N = 128)	SOC: Infections and infestations	14 (10.9)	(6.1, 17.7)
	SOC: Respiratory, thoracic and mediastinal disorders	12 (9.4)	(4.9, 15.8)
	SOC: Gastrointestinal disorders	11 (8.6)	(4.4, 14.9)
HER2 status	SOC: Infections and infestations	17 (11.0)	(6.6, 17.1)
IHC3+ (N = 154)	SOC: Gastrointestinal disorders	12 (7.8)	(4.1, 13.2)
	SOC: Respiratory, thoracic and mediastinal disorders	12 (7.8)	(4.1, 13.2)
ISH+ except IHC3+ (N = 28)	SOC: Respiratory, thoracic and mediastinal disorders	2 (7.1)	(0.9, 23.5)
	SOC: Gastrointestinal disorders	1 (3.6)	(0.1, 18.3)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 26 Severe (CTCAE Grade >= 3) treatment-emergent adverse events by system organ class, preferred term with incidence >= 5%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Overall	SOC: Investigations	46 (25.0)	(18.9, 31.9)
	Neutrophil count decreased	24 (13.0)	(8.5, 18.8)
	White blood cell count decreased	12 (6.5)	(3.4, 11.1)
	SOC: Blood and lymphatic system disorders	35 (19.0)	(13.6, 25.4)
	Neutropenia	18 (9.8)	(5.9, 15.0)
	Anaemia	17 (9.2)	(5.5, 14.4)
	SOC: Gastrointestinal disorders	30 (16.3)	(11.3, 22.5)
	Nausea	14 (7.6)	(4.2, 12.4)
	SOC: General disorders and administration site conditions	18 (9.8)	(5.9, 15.0)
	Fatigue	14 (7.6)	(4.2, 12.4)
	SOC: Infections and infestations	17 (9.2)	(5.5, 14.4)
	SOC: Metabolism and nutrition disorders	16 (8.7)	(5.1, 13.7)
	SOC: Respiratory, thoracic and mediastinal disorders	14 (7.6)	(4.2, 12.4)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 26 Severe (CTCAE Grade >= 3) treatment-emergent adverse events by system organ class, preferred term with incidence >= 5%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Estrogen receptors	SOC: Investigations	25 (26.9)	(18.2, 37.1)
Positive (N = 93)	Neutrophil count decreased	15 (16.1)	(9.3, 25.2)
	White blood cell count decreased	9 (9.7)	(4.5, 17.6)
	SOC: Gastrointestinal disorders	22 (23.7)	(15.5, 33.6)
	Nausea	10 (10.8)	(5.3, 18.9)
	SOC: Blood and lymphatic system disorders	17 (18.3)	(11.0, 27.6)
	Anaemia	10 (10.8)	(5.3, 18.9)
	Neutropenia	7 (7.5)	(3.1, 14.9)
	SOC: Metabolism and nutrition disorders	10 (10.8)	(5.3, 18.9)
	SOC: Respiratory, thoracic and mediastinal disorders	8 (8.6)	(3.8, 16.2)
	SOC: Infections and infestations	7 (7.5)	(3.1, 14.9)
	SOC: General disorders and administration site conditions	6 (6.5)	(2.4, 13.5)
	Fatigue	4 (4.3)	(1.2, 10.6)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 26 Severe (CTCAE Grade >= 3) treatment-emergent adverse events by system organ class, preferred term with incidence >= 5%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Estrogen receptors	SOC: Investigations	21 (23.9)	(15.4, 34.1)
Negative (N = 88)	Neutrophil count decreased	9 (10.2)	(4.8, 18.5)
	White blood cell count decreased	3 (3.4)	(0.7, 9.6)
	SOC: Blood and lymphatic system disorders	18 (20.5)	(12.6, 30.4)
	Neutropenia	11 (12.5)	(6.4, 21.3)
	Anaemia	7 (8.0)	(3.3, 15.7)
	SOC: General disorders and administration site conditions	12 (13.6)	(7.2, 22.6)
	Fatigue	10 (11.4)	(5.6, 19.9)
	SOC: Infections and infestations	9 (10.2)	(4.8, 18.5)
	SOC: Gastrointestinal disorders	8 (9.1)	(4.0, 17.1)
	Nausea	4 (4.5)	(1.3, 11.2)
	SOC: Metabolism and nutrition disorders	6 (6.8)	(2.5, 14.3)
	SOC: Respiratory, thoracic and mediastinal disorders	6 (6.8)	(2.5, 14.3)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 26 Severe (CTCAE Grade >= 3) treatment-emergent adverse events by system organ class, preferred term with incidence >= 5%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Progesterone receptors	SOC: Investigations	10 (19.6)	(9.8, 33.1)
Positive (N = 51)	Neutrophil count decreased	5 (9.8)	(3.3, 21.4)
	White blood cell count decreased	4 (7.8)	(2.2, 18.9)
	SOC: Blood and lymphatic system disorders	9 (17.6)	(8.4, 30.9)
	Neutropenia	5 (9.8)	(3.3, 21.4)
	Anaemia	2 (3.9)	(0.5, 13.5)
	SOC: Gastrointestinal disorders	9 (17.6)	(8.4, 30.9)
	Nausea	4 (7.8)	(2.2, 18.9)
	SOC: General disorders and administration site conditions	6 (11.8)	(4.4, 23.9)
	Fatigue	5 (9.8)	(3.3, 21.4)
	SOC: Metabolism and nutrition disorders	6 (11.8)	(4.4, 23.9)
	SOC: Infections and infestations	3 (5.9)	(1.2, 16.2)
	SOC: Respiratory, thoracic and mediastinal disorders	3 (5.9)	(1.2, 16.2)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 26 Severe (CTCAE Grade >= 3) treatment-emergent adverse events by system organ class, preferred term with incidence >= 5%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Progesterone receptors	SOC: Investigations	36 (28.8)	(21.1, 37.6)
Negative (N = 125)	Neutrophil count decreased	19 (15.2)	(9.4, 22.7)
	White blood cell count decreased	8 (6.4)	(2.8, 12.2)
	SOC: Blood and lymphatic system disorders	26 (20.8)	(14.1, 29.0)
	Anaemia	15 (12.0)	(6.9, 19.0)
	Neutropenia	13 (10.4)	(5.7, 17.1)
	SOC: Gastrointestinal disorders	19 (15.2)	(9.4, 22.7)
	Nausea	8 (6.4)	(2.8, 12.2)
	SOC: Infections and infestations	13 (10.4)	(5.7, 17.1)
	SOC: General disorders and administration site conditions	12 (9.6)	(5.1, 16.2)
	Fatigue	9 (7.2)	(3.3, 13.2)
	SOC: Respiratory, thoracic and mediastinal disorders	11 (8.8)	(4.5, 15.2)
	SOC: Metabolism and nutrition disorders	10 (8.0)	(3.9, 14.2)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 26 Severe (CTCAE Grade >= 3) treatment-emergent adverse events by system organ class, preferred term with incidence >= 5%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Hormone receptors	SOC: Investigations	25 (25.8)	(17.4, 35.7)
Positive (N = 97)	Neutrophil count decreased	15 (15.5)	(8.9, 24.2)
	White blood cell count decreased	9 (9.3)	(4.3, 16.9)
	SOC: Gastrointestinal disorders	22 (22.7)	(14.8, 32.3)
	Nausea	10 (10.3)	(5.1, 18.1)
	SOC: Blood and lymphatic system disorders	18 (18.6)	(11.4, 27.7)
	Anaemia	10 (10.3)	(5.1, 18.1)
	Neutropenia	8 (8.2)	(3.6, 15.6)
	SOC: Metabolism and nutrition disorders	11 (11.3)	(5.8, 19.4)
	SOC: General disorders and administration site conditions	8 (8.2)	(3.6, 15.6)
	Fatigue	6 (6.2)	(2.3, 13.0)
	SOC: Respiratory, thoracic and mediastinal disorders	8 (8.2)	(3.6, 15.6)
	SOC: Infections and infestations	7 (7.2)	(3.0, 14.3)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 26 Severe (CTCAE Grade >= 3) treatment-emergent adverse events by system organ class, preferred term with incidence >= 5%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Hormone receptors	SOC: Investigations	21 (25.3)	(16.4, 36.0)
Negative (N = 83)	Neutrophil count decreased	9 (10.8)	(5.1, 19.6)
	White blood cell count decreased	3 (3.6)	(0.8, 10.2)
	SOC: Blood and lymphatic system disorders	17 (20.5)	(12.4, 30.8)
	Neutropenia	10 (12.0)	(5.9, 21.0)
	Anaemia	7 (8.4)	(3.5, 16.6)
	SOC: General disorders and administration site conditions	10 (12.0)	(5.9, 21.0)
	Fatigue	8 (9.6)	(4.3, 18.1)
	SOC: Infections and infestations	9 (10.8)	(5.1, 19.6)
	SOC: Gastrointestinal disorders	8 (9.6)	(4.3, 18.1)
	Nausea	4 (4.8)	(1.3, 11.9)
	SOC: Respiratory, thoracic and mediastinal disorders	6 (7.2)	(2.7, 15.1)
	SOC: Metabolism and nutrition disorders	5 (6.0)	(2.0, 13.5)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 26 Severe (CTCAE Grade >= 3) treatment-emergent adverse events by system organ class, preferred term with incidence >= 5%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Lines of prior systemic therapy not including hormone therapy < 3 lines (N = 17)	SOC: Investigations	7 (41.2)	(18.4, 67.1)
	Neutrophil count decreased	4 (23.5)	(6.8, 49.9)
	White blood cell count decreased	3 (17.6)	(3.8, 43.4)
	SOC: Blood and lymphatic system disorders	3 (17.6)	(3.8, 43.4)
	Anaemia	3 (17.6)	(3.8, 43.4)
	Neutropenia	1 (5.9)	(0.1, 28.7)
	SOC: General disorders and administration site conditions	1 (5.9)	(0.1, 28.7)
	Fatigue	1 (5.9)	(0.1, 28.7)
	SOC: Metabolism and nutrition disorders	1 (5.9)	(0.1, 28.7)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 26 Severe (CTCAE Grade >= 3) treatment-emergent adverse events by system organ class, preferred term with incidence >= 5%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Lines of prior systemic therapy not including hormone therapy >= 3 lines (N = 167)	SOC: Investigations	39 (23.4)	(17.2, 30.5)
	Neutrophil count decreased	20 (12.0)	(7.5, 17.9)
	White blood cell count decreased	9 (5.4)	(2.5, 10.0)
	SOC: Blood and lymphatic system disorders	32 (19.2)	(13.5, 26.0)
	Neutropenia	17 (10.2)	(6.0, 15.8)
	Anaemia	14 (8.4)	(4.7, 13.7)
	SOC: Gastrointestinal disorders	30 (18.0)	(12.5, 24.6)
	Nausea	14 (8.4)	(4.7, 13.7)
	SOC: General disorders and administration site conditions	17 (10.2)	(6.0, 15.8)
	Fatigue	13 (7.8)	(4.2, 12.9)
	SOC: Infections and infestations	17 (10.2)	(6.0, 15.8)
	SOC: Metabolism and nutrition disorders	15 (9.0)	(5.1, 14.4)
	SOC: Respiratory, thoracic and mediastinal disorders	14 (8.4)	(4.7, 13.7)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 26 Severe (CTCAE Grade >= 3) treatment-emergent adverse events by system organ class, preferred term with incidence >= 5%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Prior pertuzumab	SOC: Investigations	33 (27.3)	(19.6, 36.1)
Yes (N = 121)	Neutrophil count decreased	21 (17.4)	(11.1, 25.3)
	White blood cell count decreased	9 (7.4)	(3.5, 13.7)
	SOC: Gastrointestinal disorders	19 (15.7)	(9.7, 23.4)
	Nausea	7 (5.8)	(2.4, 11.6)
	SOC: Blood and lymphatic system disorders	17 (14.0)	(8.4, 21.5)
	Anaemia	11 (9.1)	(4.6, 15.7)
	Neutropenia	5 (4.1)	(1.4, 9.4)
	SOC: General disorders and administration site conditions	9 (7.4)	(3.5, 13.7)
	Fatigue	7 (5.8)	(2.4, 11.6)
	SOC: Metabolism and nutrition disorders	9 (7.4)	(3.5, 13.7)
	SOC: Respiratory, thoracic and mediastinal disorders	7 (5.8)	(2.4, 11.6)
	SOC: Infections and infestations	6 (5.0)	(1.8, 10.5)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 26 Severe (CTCAE Grade >= 3) treatment-emergent adverse events by system organ class, preferred term with incidence >= 5%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Prior pertuzumab	SOC: Blood and lymphatic system disorders	18 (28.6)	(17.9, 41.3)
No (N = 63)	Neutropenia	13 (20.6)	(11.5, 32.7)
	Anaemia	6 (9.5)	(3.6, 19.6)
	SOC: Investigations	13 (20.6)	(11.5, 32.7)
	Neutrophil count decreased	3 (4.8)	(1.0, 13.3)
	White blood cell count decreased	3 (4.8)	(1.0, 13.3)
	SOC: Gastrointestinal disorders	11 (17.5)	(9.1, 29.1)
	Nausea	7 (11.1)	(4.6, 21.6)
	SOC: Infections and infestations	11 (17.5)	(9.1, 29.1)
	SOC: General disorders and administration site conditions	9 (14.3)	(6.7, 25.4)
	Fatigue	7 (11.1)	(4.6, 21.6)
	SOC: Metabolism and nutrition disorders	7 (11.1)	(4.6, 21.6)
	SOC: Respiratory, thoracic and mediastinal disorders	7 (11.1)	(4.6, 21.6)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 26 Severe (CTCAE Grade >= 3) treatment-emergent adverse events by system organ class, preferred term with incidence >= 5%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Prior pertuzumab in 1st or 2nd line in advanced/metastatic breast cancer Yes (N = 51)	SOC: Investigations	14 (27.5)	(15.9, 41.7)
	Neutrophil count decreased	8 (15.7)	(7.0, 28.6)
	White blood cell count decreased	3 (5.9)	(1.2, 16.2)
	SOC: Blood and lymphatic system disorders	6 (11.8)	(4.4, 23.9)
	Anaemia	4 (7.8)	(2.2, 18.9)
	Neutropenia	2 (3.9)	(0.5, 13.5)
	SOC: Gastrointestinal disorders	6 (11.8)	(4.4, 23.9)
	Nausea	3 (5.9)	(1.2, 16.2)
	SOC: Metabolism and nutrition disorders	5 (9.8)	(3.3, 21.4)
	SOC: General disorders and administration site conditions	4 (7.8)	(2.2, 18.9)
	Fatigue	3 (5.9)	(1.2, 16.2)
	SOC: Respiratory, thoracic and mediastinal disorders	4 (7.8)	(2.2, 18.9)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 26 Severe (CTCAE Grade >= 3) treatment-emergent adverse events by system organ class, preferred term with incidence >= 5%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Prior pertuzumab in 1st or 2nd line in advanced/metastatic breast cancer No (N = 133)	SOC: Investigations	32 (24.1)	(17.1, 32.2)
	Neutrophil count decreased	16 (12.0)	(7.0, 18.8)
	White blood cell count decreased	9 (6.8)	(3.1, 12.5)
	SOC: Blood and lymphatic system disorders	29 (21.8)	(15.1, 29.8)
	Neutropenia	16 (12.0)	(7.0, 18.8)
	Anaemia	13 (9.8)	(5.3, 16.1)
	SOC: Gastrointestinal disorders	24 (18.0)	(11.9, 25.6)
	Nausea	11 (8.3)	(4.2, 14.3)
	SOC: Infections and infestations	17 (12.8)	(7.6, 19.7)
	SOC: General disorders and administration site conditions	14 (10.5)	(5.9, 17.0)
	Fatigue	11 (8.3)	(4.2, 14.3)
	SOC: Metabolism and nutrition disorders	11 (8.3)	(4.2, 14.3)
	SOC: Respiratory, thoracic and mediastinal disorders	10 (7.5)	(3.7, 13.4)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 26 Severe (CTCAE Grade >= 3) treatment-emergent adverse events by system organ class, preferred term with incidence >= 5%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Renal impairment at baseline	SOC: Investigations	21 (23.3)	(15.1, 33.4)
Within Normal Range (N = 90)	Neutrophil count decreased	12 (13.3)	(7.1, 22.1)
	White blood cell count decreased	4 (4.4)	(1.2, 11.0)
	SOC: Gastrointestinal disorders	17 (18.9)	(11.4, 28.5)
	Nausea	8 (8.9)	(3.9, 16.8)
	SOC: Blood and lymphatic system disorders	16 (17.8)	(10.5, 27.3)
	Anaemia	10 (11.1)	(5.5, 19.5)
	Neutropenia	9 (10.0)	(4.7, 18.1)
	SOC: Respiratory, thoracic and mediastinal disorders	10 (11.1)	(5.5, 19.5)
	SOC: Infections and infestations	8 (8.9)	(3.9, 16.8)
	SOC: Metabolism and nutrition disorders	8 (8.9)	(3.9, 16.8)
	SOC: General disorders and administration site conditions	4 (4.4)	(1.2, 11.0)
	Fatigue	3 (3.3)	(0.7, 9.4)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 26 Severe (CTCAE Grade >= 3) treatment-emergent adverse events by system organ class, preferred term with incidence >= 5%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Renal impairment at baseline	SOC: Investigations	19 (27.5)	(17.5, 39.6)
Mild Impairment (N = 69)	Neutrophil count decreased	9 (13.0)	(6.1, 23.3)
	White blood cell count decreased	6 (8.7)	(3.3, 18.0)
	SOC: Blood and lymphatic system disorders	16 (23.2)	(13.9, 34.9)
	Neutropenia	8 (11.6)	(5.1, 21.6)
	Anaemia	5 (7.2)	(2.4, 16.1)
	SOC: General disorders and administration site conditions	12 (17.4)	(9.3, 28.4)
	Fatigue	10 (14.5)	(7.2, 25.0)
	SOC: Gastrointestinal disorders	10 (14.5)	(7.2, 25.0)
	Nausea	5 (7.2)	(2.4, 16.1)
	SOC: Infections and infestations	7 (10.1)	(4.2, 19.8)
	SOC: Metabolism and nutrition disorders	6 (8.7)	(3.3, 18.0)
	SOC: Respiratory, thoracic and mediastinal disorders	2 (2.9)	(0.4, 10.1)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 26 Severe (CTCAE Grade >= 3) treatment-emergent adverse events by system organ class, preferred term with incidence >= 5%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Renal impairment at baseline	SOC: Investigations	6 (24.0)	(9.4, 45.1)
Moderate Impairment (N = 25)	Neutrophil count decreased	3 (12.0)	(2.5, 31.2)
	White blood cell count decreased	2 (8.0)	(1.0, 26.0)
	SOC: Blood and lymphatic system disorders	3 (12.0)	(2.5, 31.2)
	Anaemia	2 (8.0)	(1.0, 26.0)
	Neutropenia	1 (4.0)	(0.1, 20.4)
	SOC: Gastrointestinal disorders	3 (12.0)	(2.5, 31.2)
	Nausea	1 (4.0)	(0.1, 20.4)
	SOC: General disorders and administration site conditions	2 (8.0)	(1.0, 26.0)
	Fatigue	1 (4.0)	(0.1, 20.4)
	SOC: Infections and infestations	2 (8.0)	(1.0, 26.0)
	SOC: Metabolism and nutrition disorders	2 (8.0)	(1.0, 26.0)
	SOC: Respiratory, thoracic and mediastinal disorders	2 (8.0)	(1.0, 26.0)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 26 Severe (CTCAE Grade >= 3) treatment-emergent adverse events by system organ class, preferred term with incidence >= 5%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Hepatic impairment at baseline	SOC: Investigations	28 (26.7)	(18.5, 36.2)
Within Normal Range (N = 105)	Neutrophil count decreased	17 (16.2)	(9.7, 24.7)
	White blood cell count decreased	5 (4.8)	(1.6, 10.8)
	SOC: Blood and lymphatic system disorders	23 (21.9)	(14.4, 31.0)
	Neutropenia	11 (10.5)	(5.3, 18.0)
	Anaemia	10 (9.5)	(4.7, 16.8)
	SOC: Gastrointestinal disorders	19 (18.1)	(11.3, 26.8)
	Nausea	9 (8.6)	(4.0, 15.6)
	SOC: Infections and infestations	12 (11.4)	(6.0, 19.1)
	SOC: General disorders and administration site conditions	10 (9.5)	(4.7, 16.8)
	Fatigue	9 (8.6)	(4.0, 15.6)
	SOC: Respiratory, thoracic and mediastinal disorders	9 (8.6)	(4.0, 15.6)
	SOC: Metabolism and nutrition disorders	8 (7.6)	(3.3, 14.5)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 26 Severe (CTCAE Grade >= 3) treatment-emergent adverse events by system organ class, preferred term with incidence >= 5%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Hepatic impairment at baseline	SOC: Investigations	18 (23.7)	(14.7, 34.8)
Mild Impairment (N = 76)	Neutrophil count decreased	7 (9.2)	(3.8, 18.1)
	White blood cell count decreased	7 (9.2)	(3.8, 18.1)
	SOC: Blood and lymphatic system disorders	12 (15.8)	(8.4, 26.0)
	Anaemia	7 (9.2)	(3.8, 18.1)
	Neutropenia	7 (9.2)	(3.8, 18.1)
	SOC: Gastrointestinal disorders	10 (13.2)	(6.5, 22.9)
	Nausea	5 (6.6)	(2.2, 14.7)
	SOC: Metabolism and nutrition disorders	7 (9.2)	(3.8, 18.1)
	SOC: General disorders and administration site conditions	6 (7.9)	(3.0, 16.4)
	Fatigue	5 (6.6)	(2.2, 14.7)
	SOC: Infections and infestations	5 (6.6)	(2.2, 14.7)
	SOC: Respiratory, thoracic and mediastinal disorders	5 (6.6)	(2.2, 14.7)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 26 Severe (CTCAE Grade >= 3) treatment-emergent adverse events by system organ class, preferred term with incidence >= 5%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Best response to T-DM1 therapy CR/PR/SD (N = 79)	SOC: Investigations	21 (26.6)	(17.3, 37.7)
	Neutrophil count decreased	12 (15.2)	(8.1, 25.0)
	White blood cell count decreased	7 (8.9)	(3.6, 17.4)
	SOC: Blood and lymphatic system disorders	15 (19.0)	(11.0, 29.4)
	Neutropenia	10 (12.7)	(6.2, 22.0)
	Anaemia	5 (6.3)	(2.1, 14.2)
	SOC: Gastrointestinal disorders	11 (13.9)	(7.2, 23.5)
	Nausea	5 (6.3)	(2.1, 14.2)
	SOC: General disorders and administration site conditions	8 (10.1)	(4.5, 19.0)
	Fatigue	5 (6.3)	(2.1, 14.2)
	SOC: Infections and infestations	6 (7.6)	(2.8, 15.8)
	SOC: Metabolism and nutrition disorders	6 (7.6)	(2.8, 15.8)
	SOC: Respiratory, thoracic and mediastinal disorders	5 (6.3)	(2.1, 14.2)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 26 Severe (CTCAE Grade >= 3) treatment-emergent adverse events by system organ class, preferred term with incidence >= 5%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Best response to T-DM1 therapy	SOC: Investigations	20 (30.3)	(19.6, 42.9)
PD (N = 66)	Neutrophil count decreased	12 (18.2)	(9.8, 29.6)
	White blood cell count decreased	5 (7.6)	(2.5, 16.8)
	SOC: Blood and lymphatic system disorders	15 (22.7)	(13.3, 34.7)
	Anaemia	9 (13.6)	(6.4, 24.3)
	Neutropenia	5 (7.6)	(2.5, 16.8)
	SOC: Gastrointestinal disorders	12 (18.2)	(9.8, 29.6)
	Nausea	5 (7.6)	(2.5, 16.8)
	SOC: Infections and infestations	8 (12.1)	(5.4, 22.5)
	SOC: General disorders and administration site conditions	6 (9.1)	(3.4, 18.7)
	Fatigue	6 (9.1)	(3.4, 18.7)
	SOC: Metabolism and nutrition disorders	6 (9.1)	(3.4, 18.7)
	SOC: Respiratory, thoracic and mediastinal disorders	5 (7.6)	(2.5, 16.8)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 26 Severe (CTCAE Grade >= 3) treatment-emergent adverse events by system organ class, preferred term with incidence >= 5%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Brain metastases	SOC: Blood and lymphatic system disorders	7 (29.2)	(12.6, 51.1)
Yes (N = 24)	Neutropenia	3 (12.5)	(2.7, 32.4)
	Anaemia	2 (8.3)	(1.0, 27.0)
	SOC: Investigations	7 (29.2)	(12.6, 51.1)
	Neutrophil count decreased	4 (16.7)	(4.7, 37.4)
	White blood cell count decreased	2 (8.3)	(1.0, 27.0)
	SOC: General disorders and administration site conditions	6 (25.0)	(9.8, 46.7)
	Fatigue	5 (20.8)	(7.1, 42.2)
	SOC: Gastrointestinal disorders	4 (16.7)	(4.7, 37.4)
	SOC: Infections and infestations	1 (4.2)	(0.1, 21.1)
	SOC: Metabolism and nutrition disorders	1 (4.2)	(0.1, 21.1)
	SOC: Respiratory, thoracic and mediastinal disorders	1 (4.2)	(0.1, 21.1)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 26 Severe (CTCAE Grade >= 3) treatment-emergent adverse events by system organ class, preferred term with incidence >= 5%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Brain metastases	SOC: Investigations	39 (24.4)	(17.9, 31.8)
No (N = 160)	Neutrophil count decreased	20 (12.5)	(7.8, 18.6)
	White blood cell count decreased	10 (6.3)	(3.0, 11.2)
	SOC: Blood and lymphatic system disorders	28 (17.5)	(12.0, 24.3)
	Anaemia	15 (9.4)	(5.3, 15.0)
	Neutropenia	15 (9.4)	(5.3, 15.0)
	SOC: Gastrointestinal disorders	26 (16.3)	(10.9, 22.9)
	Nausea	14 (8.8)	(4.9, 14.2)
	SOC: Infections and infestations	16 (10.0)	(5.8, 15.7)
	SOC: Metabolism and nutrition disorders	15 (9.4)	(5.3, 15.0)
	SOC: Respiratory, thoracic and mediastinal disorders	13 (8.1)	(4.4, 13.5)
	SOC: General disorders and administration site conditions	12 (7.5)	(3.9, 12.7)
	Fatigue	9 (5.6)	(2.6, 10.4)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 26 Severe (CTCAE Grade >= 3) treatment-emergent adverse events by system organ class, preferred term with incidence >= 5%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Bone metastases	SOC: Investigations	16 (30.2)	(18.3, 44.3)
Yes (N = 53)	Neutrophil count decreased	8 (15.1)	(6.7, 27.6)
	White blood cell count decreased	3 (5.7)	(1.2, 15.7)
	SOC: Blood and lymphatic system disorders	11 (20.8)	(10.8, 34.1)
	Anaemia	7 (13.2)	(5.5, 25.3)
	Neutropenia	5 (9.4)	(3.1, 20.7)
	SOC: Gastrointestinal disorders	11 (20.8)	(10.8, 34.1)
	Nausea	6 (11.3)	(4.3, 23.0)
	SOC: Infections and infestations	9 (17.0)	(8.1, 29.8)
	SOC: Respiratory, thoracic and mediastinal disorders	9 (17.0)	(8.1, 29.8)
	SOC: Metabolism and nutrition disorders	8 (15.1)	(6.7, 27.6)
	SOC: General disorders and administration site conditions	6 (11.3)	(4.3, 23.0)
	Fatigue	4 (7.5)	(2.1, 18.2)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 26 Severe (CTCAE Grade >= 3) treatment-emergent adverse events by system organ class, preferred term with incidence >= 5%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Bone metastases	SOC: Investigations	30 (22.9)	(16.0, 31.1)
No (N = 131)	Neutrophil count decreased	16 (12.2)	(7.1, 19.1)
	White blood cell count decreased	9 (6.9)	(3.2, 12.6)
	SOC: Blood and lymphatic system disorders	24 (18.3)	(12.1, 26.0)
	Neutropenia	13 (9.9)	(5.4, 16.4)
	Anaemia	10 (7.6)	(3.7, 13.6)
	SOC: Gastrointestinal disorders	19 (14.5)	(9.0, 21.7)
	Nausea	8 (6.1)	(2.7, 11.7)
	SOC: General disorders and administration site conditions	12 (9.2)	(4.8, 15.5)
	Fatigue	10 (7.6)	(3.7, 13.6)
	SOC: Infections and infestations	8 (6.1)	(2.7, 11.7)
	SOC: Metabolism and nutrition disorders	8 (6.1)	(2.7, 11.7)
	SOC: Respiratory, thoracic and mediastinal disorders	5 (3.8)	(1.3, 8.7)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 26 Severe (CTCAE Grade >= 3) treatment-emergent adverse events by system organ class, preferred term with incidence >= 5%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
History of visceral disease	SOC: Investigations	41 (24.3)	(18.0, 31.4)
Yes (N = 169)	Neutrophil count decreased	23 (13.6)	(8.8, 19.7)
	White blood cell count decreased	12 (7.1)	(3.7, 12.1)
	SOC: Blood and lymphatic system disorders	31 (18.3)	(12.8, 25.0)
	Neutropenia	16 (9.5)	(5.5, 14.9)
	Anaemia	13 (7.7)	(4.2, 12.8)
	SOC: Gastrointestinal disorders	26 (15.4)	(10.3, 21.7)
	Nausea	12 (7.1)	(3.7, 12.1)
	SOC: General disorders and administration site conditions	18 (10.7)	(6.4, 16.3)
	Fatigue	14 (8.3)	(4.6, 13.5)
	SOC: Infections and infestations	16 (9.5)	(5.5, 14.9)
	SOC: Metabolism and nutrition disorders	13 (7.7)	(4.2, 12.8)
	SOC: Respiratory, thoracic and mediastinal disorders	12 (7.1)	(3.7, 12.1)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 26 Severe (CTCAE Grade >= 3) treatment-emergent adverse events by system organ class, preferred term with incidence >= 5%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
History of visceral disease	SOC: Investigations	5 (33.3)	(11.8, 61.6)
No (N = 15)	Neutrophil count decreased	1 (6.7)	(0.2, 31.9)
	SOC: Blood and lymphatic system disorders	4 (26.7)	(7.8, 55.1)
	Anaemia	4 (26.7)	(7.8, 55.1)
	Neutropenia	2 (13.3)	(1.7, 40.5)
	SOC: Gastrointestinal disorders	4 (26.7)	(7.8, 55.1)
	Nausea	2 (13.3)	(1.7, 40.5)
	SOC: Metabolism and nutrition disorders	3 (20.0)	(4.3, 48.1)
	SOC: Respiratory, thoracic and mediastinal disorders	2 (13.3)	(1.7, 40.5)
	SOC: Infections and infestations	1 (6.7)	(0.2, 31.9)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 26 Severe (CTCAE Grade >= 3) treatment-emergent adverse events by system organ class, preferred term with incidence >= 5%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Age	SOC: Investigations	34 (24.3)	(17.4, 32.2)
<65 years (N = 140)	Neutrophil count decreased	14 (10.0)	(5.6, 16.2)
	White blood cell count decreased	6 (4.3)	(1.6, 9.1)
	SOC: Blood and lymphatic system disorders	24 (17.1)	(11.3, 24.4)
	Neutropenia	16 (11.4)	(6.7, 17.9)
	Anaemia	11 (7.9)	(4.0, 13.6)
	SOC: Gastrointestinal disorders	22 (15.7)	(10.1, 22.8)
	Nausea	9 (6.4)	(3.0, 11.9)
	SOC: Infections and infestations	13 (9.3)	(5.0, 15.4)
	SOC: General disorders and administration site conditions	11 (7.9)	(4.0, 13.6)
	Fatigue	7 (5.0)	(2.0, 10.0)
	SOC: Respiratory, thoracic and mediastinal disorders	10 (7.1)	(3.5, 12.7)
	SOC: Metabolism and nutrition disorders	9 (6.4)	(3.0, 11.9)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 26 Severe (CTCAE Grade >= 3) treatment-emergent adverse events by system organ class, preferred term with incidence >= 5%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Age	SOC: Investigations	12 (27.3)	(15.0, 42.8)
>=65 years (N = 44)	Neutrophil count decreased	10 (22.7)	(11.5, 37.8)
	White blood cell count decreased	6 (13.6)	(5.2, 27.4)
	SOC: Blood and lymphatic system disorders	11 (25.0)	(13.2, 40.3)
	Anaemia	6 (13.6)	(5.2, 27.4)
	Neutropenia	2 (4.5)	(0.6, 15.5)
	SOC: Gastrointestinal disorders	8 (18.2)	(8.2, 32.7)
	Nausea	5 (11.4)	(3.8, 24.6)
	SOC: General disorders and administration site conditions	7 (15.9)	(6.6, 30.1)
	Fatigue	7 (15.9)	(6.6, 30.1)
	SOC: Metabolism and nutrition disorders	7 (15.9)	(6.6, 30.1)
	SOC: Infections and infestations	4 (9.1)	(2.5, 21.7)
	SOC: Respiratory, thoracic and mediastinal disorders	4 (9.1)	(2.5, 21.7)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 26 Severe (CTCAE Grade >= 3) treatment-emergent adverse events by system organ class, preferred term with incidence >= 5%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Region	SOC: Investigations	23 (36.5)	(24.7, 49.6)
Asia (N = 63)	Neutrophil count decreased	13 (20.6)	(11.5, 32.7)
	White blood cell count decreased	8 (12.7)	(5.6, 23.5)
	SOC: Blood and lymphatic system disorders	13 (20.6)	(11.5, 32.7)
	Neutropenia	9 (14.3)	(6.7, 25.4)
	Anaemia	4 (6.3)	(1.8, 15.5)
	SOC: General disorders and administration site conditions	6 (9.5)	(3.6, 19.6)
	Fatigue	5 (7.9)	(2.6, 17.6)
	SOC: Infections and infestations	6 (9.5)	(3.6, 19.6)
	SOC: Gastrointestinal disorders	3 (4.8)	(1.0, 13.3)
	Nausea	1 (1.6)	(0.0, 8.5)
	SOC: Metabolism and nutrition disorders	2 (3.2)	(0.4, 11.0)
	SOC: Respiratory, thoracic and mediastinal disorders	1 (1.6)	(0.0, 8.5)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 26 Severe (CTCAE Grade >= 3) treatment-emergent adverse events by system organ class, preferred term with incidence >= 5%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Region	SOC: Gastrointestinal disorders	15 (28.3)	(16.8, 42.3)
North America (N = 53)	Nausea	6 (11.3)	(4.3, 23.0)
	SOC: Investigations	12 (22.6)	(12.3, 36.2)
	Neutrophil count decreased	7 (13.2)	(5.5, 25.3)
	White blood cell count decreased	4 (7.5)	(2.1, 18.2)
	SOC: Blood and lymphatic system disorders	10 (18.9)	(9.4, 32.0)
	Anaemia	9 (17.0)	(8.1, 29.8)
	Neutropenia	4 (7.5)	(2.1, 18.2)
	SOC: Metabolism and nutrition disorders	7 (13.2)	(5.5, 25.3)
	SOC: General disorders and administration site conditions	5 (9.4)	(3.1, 20.7)
	Fatigue	5 (9.4)	(3.1, 20.7)
	SOC: Infections and infestations	5 (9.4)	(3.1, 20.7)
	SOC: Respiratory, thoracic and mediastinal disorders	4 (7.5)	(2.1, 18.2)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 26 Severe (CTCAE Grade >= 3) treatment-emergent adverse events by system organ class, preferred term with incidence >= 5%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Region	SOC: Blood and lymphatic system disorders	12 (17.6)	(9.5, 28.8)
EU (N = 68)	Neutropenia	5 (7.4)	(2.4, 16.3)
	Anaemia	4 (5.9)	(1.6, 14.4)
	SOC: Gastrointestinal disorders	12 (17.6)	(9.5, 28.8)
	Nausea	7 (10.3)	(4.2, 20.1)
	SOC: Investigations	11 (16.2)	(8.4, 27.1)
	Neutrophil count decreased	4 (5.9)	(1.6, 14.4)
	SOC: Respiratory, thoracic and mediastinal disorders	9 (13.2)	(6.2, 23.6)
	SOC: General disorders and administration site conditions	7 (10.3)	(4.2, 20.1)
	Fatigue	4 (5.9)	(1.6, 14.4)
	SOC: Metabolism and nutrition disorders	7 (10.3)	(4.2, 20.1)
	SOC: Infections and infestations	6 (8.8)	(3.3, 18.2)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 26 Severe (CTCAE Grade >= 3) treatment-emergent adverse events by system organ class, preferred term with incidence >= 5%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
ECOG performance status	SOC: Investigations	26 (25.5)	(17.4, 35.1)
0 (N = 102)	Neutrophil count decreased	13 (12.7)	(7.0, 20.8)
	White blood cell count decreased	6 (5.9)	(2.2, 12.4)
	SOC: Gastrointestinal disorders	20 (19.6)	(12.4, 28.6)
	Nausea	9 (8.8)	(4.1, 16.1)
	SOC: Blood and lymphatic system disorders	17 (16.7)	(10.0, 25.3)
	Anaemia	11 (10.8)	(5.5, 18.5)
	Neutropenia	8 (7.8)	(3.4, 14.9)
	SOC: General disorders and administration site conditions	8 (7.8)	(3.4, 14.9)
	Fatigue	6 (5.9)	(2.2, 12.4)
	SOC: Respiratory, thoracic and mediastinal disorders	8 (7.8)	(3.4, 14.9)
	SOC: Infections and infestations	6 (5.9)	(2.2, 12.4)
	SOC: Metabolism and nutrition disorders	5 (4.9)	(1.6, 11.1)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 26 Severe (CTCAE Grade >= 3) treatment-emergent adverse events by system organ class, preferred term with incidence >= 5%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
ECOG performance status	SOC: Investigations	20 (24.7)	(15.8, 35.5)
1 (N = 81)	Neutrophil count decreased	11 (13.6)	(7.0, 23.0)
	White blood cell count decreased	6 (7.4)	(2.8, 15.4)
	SOC: Blood and lymphatic system disorders	18 (22.2)	(13.7, 32.8)
	Neutropenia	10 (12.3)	(6.1, 21.5)
	Anaemia	6 (7.4)	(2.8, 15.4)
	SOC: Metabolism and nutrition disorders	11 (13.6)	(7.0, 23.0)
	SOC: Gastrointestinal disorders	10 (12.3)	(6.1, 21.5)
	Nausea	5 (6.2)	(2.0, 13.8)
	SOC: General disorders and administration site conditions	10 (12.3)	(6.1, 21.5)
	Fatigue	8 (9.9)	(4.4, 18.5)
	SOC: Infections and infestations	10 (12.3)	(6.1, 21.5)
	SOC: Respiratory, thoracic and mediastinal disorders	6 (7.4)	(2.8, 15.4)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 26 Severe (CTCAE Grade >= 3) treatment-emergent adverse events by system organ class, preferred term with incidence >= 5%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Baseline sum of diameters of target lesions	SOC: Investigations	19 (25.7)	(16.2, 37.2)
<5 cm (N = 74)	Neutrophil count decreased	8 (10.8)	(4.8, 20.2)
	White blood cell count decreased	2 (2.7)	(0.3, 9.4)
	SOC: Gastrointestinal disorders	12 (16.2)	(8.7, 26.6)
	Nausea	6 (8.1)	(3.0, 16.8)
	SOC: Blood and lymphatic system disorders	11 (14.9)	(7.7, 25.0)
	Anaemia	7 (9.5)	(3.9, 18.5)
	Neutropenia	7 (9.5)	(3.9, 18.5)
	SOC: Infections and infestations	8 (10.8)	(4.8, 20.2)
	SOC: General disorders and administration site conditions	5 (6.8)	(2.2, 15.1)
	Fatigue	3 (4.1)	(0.8, 11.4)
	SOC: Metabolism and nutrition disorders	5 (6.8)	(2.2, 15.1)
	SOC: Respiratory, thoracic and mediastinal disorders	5 (6.8)	(2.2, 15.1)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 26 Severe (CTCAE Grade >= 3) treatment-emergent adverse events by system organ class, preferred term with incidence >= 5%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Baseline sum of diameters of target lesions >=5 cm (N = 96)	SOC: Investigations	22 (22.9)	(15.0, 32.6)
	Neutrophil count decreased	13 (13.5)	(7.4, 22.0)
	White blood cell count decreased	8 (8.3)	(3.7, 15.8)
	SOC: Blood and lymphatic system disorders	20 (20.8)	(13.2, 30.3)
	Neutropenia	10 (10.4)	(5.1, 18.3)
	Anaemia	8 (8.3)	(3.7, 15.8)
	SOC: Gastrointestinal disorders	16 (16.7)	(9.8, 25.6)
	Nausea	7 (7.3)	(3.0, 14.4)
	SOC: General disorders and administration site conditions	11 (11.5)	(5.9, 19.6)
	Fatigue	9 (9.4)	(4.4, 17.1)
	SOC: Metabolism and nutrition disorders	11 (11.5)	(5.9, 19.6)
	SOC: Respiratory, thoracic and mediastinal disorders	8 (8.3)	(3.7, 15.8)
	SOC: Infections and infestations	7 (7.3)	(3.0, 14.4)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 26 Severe (CTCAE Grade >= 3) treatment-emergent adverse events by system organ class, preferred term with incidence >= 5%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
DS-8201a immediately following initial T-DM1	SOC: Investigations	15 (26.8)	(15.8, 40.3)
Yes (N = 56)	Neutrophil count decreased	7 (12.5)	(5.2, 24.1)
	White blood cell count decreased	4 (7.1)	(2.0, 17.3)
	SOC: Blood and lymphatic system disorders	6 (10.7)	(4.0, 21.9)
	Anaemia	5 (8.9)	(3.0, 19.6)
	Neutropenia	3 (5.4)	(1.1, 14.9)
	SOC: Gastrointestinal disorders	5 (8.9)	(3.0, 19.6)
	Nausea	2 (3.6)	(0.4, 12.3)
	SOC: Infections and infestations	4 (7.1)	(2.0, 17.3)
	SOC: General disorders and administration site conditions	3 (5.4)	(1.1, 14.9)
	Fatigue	3 (5.4)	(1.1, 14.9)
	SOC: Metabolism and nutrition disorders	3 (5.4)	(1.1, 14.9)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 26 Severe (CTCAE Grade >= 3) treatment-emergent adverse events by system organ class, preferred term with incidence >= 5%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
DS-8201a immediately following initial T-DM1	SOC: Investigations	31 (24.2)	(17.1, 32.6)
No (N = 128)	Neutrophil count decreased	17 (13.3)	(7.9, 20.4)
	White blood cell count decreased	8 (6.3)	(2.7, 11.9)
	SOC: Blood and lymphatic system disorders	29 (22.7)	(15.7, 30.9)
	Neutropenia	15 (11.7)	(6.7, 18.6)
	Anaemia	12 (9.4)	(4.9, 15.8)
	SOC: Gastrointestinal disorders	25 (19.5)	(13.1, 27.5)
	Nausea	12 (9.4)	(4.9, 15.8)
	SOC: General disorders and administration site conditions	15 (11.7)	(6.7, 18.6)
	Fatigue	11 (8.6)	(4.4, 14.9)
	SOC: Respiratory, thoracic and mediastinal disorders	14 (10.9)	(6.1, 17.7)
	SOC: Infections and infestations	13 (10.2)	(5.5, 16.7)
	SOC: Metabolism and nutrition disorders	13 (10.2)	(5.5, 16.7)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 26 Severe (CTCAE Grade >= 3) treatment-emergent adverse events by system organ class, preferred term with incidence >= 5%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
HER2 status	SOC: Investigations	42 (27.3)	(20.4, 35.0)
IHC3+ (N = 154)	Neutrophil count decreased	22 (14.3)	(9.2, 20.8)
	White blood cell count decreased	12 (7.8)	(4.1, 13.2)
	SOC: Blood and lymphatic system disorders	32 (20.8)	(14.7, 28.0)
	Neutropenia	17 (11.0)	(6.6, 17.1)
	Anaemia	16 (10.4)	(6.1, 16.3)
	SOC: Gastrointestinal disorders	26 (16.9)	(11.3, 23.8)
	Nausea	12 (7.8)	(4.1, 13.2)
	SOC: General disorders and administration site conditions	16 (10.4)	(6.1, 16.3)
	Fatigue	12 (7.8)	(4.1, 13.2)
	SOC: Infections and infestations	16 (10.4)	(6.1, 16.3)
	SOC: Metabolism and nutrition disorders	13 (8.4)	(4.6, 14.0)
	SOC: Respiratory, thoracic and mediastinal disorders	11 (7.1)	(3.6, 12.4)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 26 Severe (CTCAE Grade >= 3) treatment-emergent adverse events by system organ class, preferred term with incidence >= 5%, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
HER2 status	SOC: Gastrointestinal disorders	4 (14.3)	(4.0, 32.7)
ISH+ except IHC3+ (N = 28)	Nausea	2 (7.1)	(0.9, 23.5)
	SOC: Blood and lymphatic system disorders	3 (10.7)	(2.3, 28.2)
	Anaemia	1 (3.6)	(0.1, 18.3)
	Neutropenia	1 (3.6)	(0.1, 18.3)
	SOC: Investigations	3 (10.7)	(2.3, 28.2)
	Neutrophil count decreased	2 (7.1)	(0.9, 23.5)
	SOC: Metabolism and nutrition disorders	3 (10.7)	(2.3, 28.2)
	SOC: Respiratory, thoracic and mediastinal disorders	3 (10.7)	(2.3, 28.2)
	SOC: General disorders and administration site conditions	2 (7.1)	(0.9, 23.5)
	Fatigue	2 (7.1)	(0.9, 23.5)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Overall	SOC: Gastrointestinal disorders	173 (94.0)	(89.6, 97.0)
	Nausea	144 (78.3)	(71.6, 84.0)
	Vomiting	88 (47.8)	(40.4, 55.3)
	Constipation	65 (35.3)	(28.4, 42.7)
	Diarrhoea	58 (31.5)	(24.9, 38.8)
	Dyspepsia	31 (16.8)	(11.7, 23.1)
	Stomatitis	29 (15.8)	(10.8, 21.8)
	Abdominal pain	25 (13.6)	(9.0, 19.4)
	Gastrooesophageal reflux disease	18 (9.8)	(5.9, 15.0)
	Abdominal pain upper	16 (8.7)	(5.1, 13.7)
	Haemorrhoids	11 (6.0)	(3.0, 10.4)
	SOC: General disorders and administration site conditions	137 (74.5)	(67.5, 80.6)
	Fatigue	92 (50.0)	(42.6, 57.4)
	Asthenia	26 (14.1)	(9.4, 20.0)
	Oedema peripheral	17 (9.2)	(5.5, 14.4)
	Pyrexia	17 (9.2)	(5.5, 14.4)
	Mucosal inflammation	16 (8.7)	(5.1, 13.7)
	Influenza like illness	12 (6.5)	(3.4, 11.1)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Overall	SOC: Skin and subcutaneous tissue disorders	116 (63.0)	(55.6, 70.0)
	Alopecia	89 (48.4)	(41.0, 55.8)
	Rash	19 (10.3)	(6.3, 15.7)
	Dry skin	11 (6.0)	(3.0, 10.4)
	Nail disorder	10 (5.4)	(2.6, 9.8)
	SOC: Investigations	106 (57.6)	(50.1, 64.8)
	Neutrophil count decreased	41 (22.3)	(16.5, 29.0)
	White blood cell count decreased	36 (19.6)	(14.1, 26.0)
	Aspartate aminotransferase increased	33 (17.9)	(12.7, 24.3)
	Platelet count decreased	30 (16.3)	(11.3, 22.5)
	Alanine aminotransferase increased	21 (11.4)	(7.2, 16.9)
	Lymphocyte count decreased	19 (10.3)	(6.3, 15.7)
	Blood bilirubin increased	15 (8.2)	(4.6, 13.1)
	Weight decreased	15 (8.2)	(4.6, 13.1)
	Blood alkaline phosphatase increased	11 (6.0)	(3.0, 10.4)
	Electrocardiogram QT prolonged	10 (5.4)	(2.6, 9.8)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Overall	SOC: Respiratory, thoracic and mediastinal disorders	105 (57.1)	(49.6, 64.3)
	Cough	45 (24.5)	(18.4, 31.3)
	Dyspnoea	31 (16.8)	(11.7, 23.1)
	Epistaxis	26 (14.1)	(9.4, 20.0)
	Pneumonitis	16 (8.7)	(5.1, 13.7)
	Interstitial lung disease	11 (6.0)	(3.0, 10.4)
	SOC: Infections and infestations	99 (53.8)	(46.3, 61.2)
	Upper respiratory tract infection	24 (13.0)	(8.5, 18.8)
	Urinary tract infection	22 (12.0)	(7.6, 17.5)
	Nasopharyngitis	20 (10.9)	(6.8, 16.3)
	Pneumonia	10 (5.4)	(2.6, 9.8)
	SOC: Nervous system disorders	91 (49.5)	(42.0, 56.9)
	Headache	40 (21.7)	(16.0, 28.4)
	Dizziness	19 (10.3)	(6.3, 15.7)
	Peripheral sensory neuropathy	16 (8.7)	(5.1, 13.7)
	Dysgeusia	13 (7.1)	(3.8, 11.8)
	Neuropathy peripheral	12 (6.5)	(3.4, 11.1)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Overall	SOC: Metabolism and nutrition disorders	84 (45.7)	(38.3, 53.1)
	Decreased appetite	59 (32.1)	(25.4, 39.3)
	Hypokalaemia	22 (12.0)	(7.6, 17.5)
	SOC: Blood and lymphatic system disorders	80 (43.5)	(36.2, 51.0)
	Anaemia	58 (31.5)	(24.9, 38.8)
	Neutropenia	27 (14.7)	(9.9, 20.6)
	Thrombocytopenia	14 (7.6)	(4.2, 12.4)
	Lymphopenia	11 (6.0)	(3.0, 10.4)
	SOC: Musculoskeletal and connective tissue disorders	70 (38.0)	(31.0, 45.5)
	Arthralgia	24 (13.0)	(8.5, 18.8)
	Back pain	20 (10.9)	(6.8, 16.3)
	Myalgia	18 (9.8)	(5.9, 15.0)
	Muscle spasms	15 (8.2)	(4.6, 13.1)
	Pain in extremity	12 (6.5)	(3.4, 11.1)
	SOC: Eye disorders	61 (33.2)	(26.4, 40.5)
	Dry eye	21 (11.4)	(7.2, 16.9)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Overall	SOC: Psychiatric disorders	28 (15.2)	(10.4, 21.2)
	Insomnia	13 (7.1)	(3.8, 11.8)
	Anxiety	12 (6.5)	(3.4, 11.1)
	SOC: Vascular disorders	27 (14.7)	(9.9, 20.6)
	SOC: Injury, poisoning and procedural complications	26 (14.1)	(9.4, 20.0)
	SOC: Cardiac disorders	22 (12.0)	(7.6, 17.5)
	SOC: Ear and labyrinth disorders	19 (10.3)	(6.3, 15.7)
	SOC: Renal and urinary disorders	19 (10.3)	(6.3, 15.7)
	SOC: Reproductive system and breast disorders	12 (6.5)	(3.4, 11.1)
	SOC: Hepatobiliary disorders	10 (5.4)	(2.6, 9.8)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Estrogen receptors	SOC: Gastrointestinal disorders	90 (96.8)	(90.9, 99.3)
Positive (N = 93)	Nausea	72 (77.4)	(67.6, 85.4)
	Vomiting	52 (55.9)	(45.2, 66.2)
	Constipation	39 (41.9)	(31.8, 52.6)
	Diarrhoea	30 (32.3)	(22.9, 42.7)
	Abdominal pain	20 (21.5)	(13.7, 31.2)
	Dyspepsia	18 (19.4)	(11.9, 28.9)
	Stomatitis	16 (17.2)	(10.2, 26.4)
	Abdominal pain upper	9 (9.7)	(4.5, 17.6)
	Gastrooesophageal reflux disease	9 (9.7)	(4.5, 17.6)
	Haemorrhoids	8 (8.6)	(3.8, 16.2)
	SOC: General disorders and administration site conditions	73 (78.5)	(68.8, 86.3)
	Fatigue	49 (52.7)	(42.1, 63.1)
	Asthenia	14 (15.1)	(8.5, 24.0)
	Mucosal inflammation	11 (11.8)	(6.1, 20.2)
	Oedema peripheral	11 (11.8)	(6.1, 20.2)
	Pyrexia	10 (10.8)	(5.3, 18.9)
	Influenza like illness	6 (6.5)	(2.4, 13.5)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Estrogen receptors	SOC: Skin and subcutaneous tissue disorders	56 (60.2)	(49.5, 70.2)
Positive (N = 93)	Alopecia	46 (49.5)	(38.9, 60.0)
	Rash	10 (10.8)	(5.3, 18.9)
	Dry skin	8 (8.6)	(3.8, 16.2)
	Nail disorder	5 (5.4)	(1.8, 12.1)
	SOC: Respiratory, thoracic and mediastinal disorders	54 (58.1)	(47.4, 68.2)
	Cough	24 (25.8)	(17.3, 35.9)
	Dyspnoea	15 (16.1)	(9.3, 25.2)
	Epistaxis	10 (10.8)	(5.3, 18.9)
	Pneumonitis	8 (8.6)	(3.8, 16.2)
	Interstitial lung disease	6 (6.5)	(2.4, 13.5)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Estrogen receptors	SOC: Investigations	53 (57.0)	(46.3, 67.2)
Positive (N = 93)	Neutrophil count decreased	22 (23.7)	(15.5, 33.6)
	White blood cell count decreased	20 (21.5)	(13.7, 31.2)
	Platelet count decreased	18 (19.4)	(11.9, 28.9)
	Aspartate aminotransferase increased	15 (16.1)	(9.3, 25.2)
	Lymphocyte count decreased	13 (14.0)	(7.7, 22.7)
	Weight decreased	9 (9.7)	(4.5, 17.6)
	Alanine aminotransferase increased	8 (8.6)	(3.8, 16.2)
	Blood alkaline phosphatase increased	7 (7.5)	(3.1, 14.9)
	Blood bilirubin increased	6 (6.5)	(2.4, 13.5)
	Electrocardiogram QT prolonged	5 (5.4)	(1.8, 12.1)
	SOC: Infections and infestations	51 (54.8)	(44.2, 65.2)
	Upper respiratory tract infection	12 (12.9)	(6.8, 21.5)
	Nasopharyngitis	11 (11.8)	(6.1, 20.2)
	Urinary tract infection	8 (8.6)	(3.8, 16.2)
	Pneumonia	7 (7.5)	(3.1, 14.9)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Estrogen receptors	SOC: Nervous system disorders	47 (50.5)	(40.0, 61.1)
Positive (N = 93)	Headache	20 (21.5)	(13.7, 31.2)
	Dizziness	9 (9.7)	(4.5, 17.6)
	Neuropathy peripheral	9 (9.7)	(4.5, 17.6)
	Peripheral sensory neuropathy	9 (9.7)	(4.5, 17.6)
	Dysgeusia	8 (8.6)	(3.8, 16.2)
	SOC: Metabolism and nutrition disorders	46 (49.5)	(38.9, 60.0)
	Decreased appetite	33 (35.5)	(25.8, 46.1)
	Hypokalaemia	10 (10.8)	(5.3, 18.9)
	SOC: Blood and lymphatic system disorders	39 (41.9)	(31.8, 52.6)
	Anaemia	29 (31.2)	(22.0, 41.6)
	Neutropenia	11 (11.8)	(6.1, 20.2)
	Thrombocytopenia	5 (5.4)	(1.8, 12.1)
	Lymphopenia	4 (4.3)	(1.2, 10.6)
	SOC: Eye disorders	38 (40.9)	(30.8, 51.5)
	Dry eye	14 (15.1)	(8.5, 24.0)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Estrogen receptors	SOC: Musculoskeletal and connective tissue disorders	37 (39.8)	(29.8, 50.5)
Positive (N = 93)	Back pain	12 (12.9)	(6.8, 21.5)
	Muscle spasms	10 (10.8)	(5.3, 18.9)
	Arthralgia	9 (9.7)	(4.5, 17.6)
	Myalgia	7 (7.5)	(3.1, 14.9)
	Pain in extremity	7 (7.5)	(3.1, 14.9)
	SOC: Injury, poisoning and procedural complications	15 (16.1)	(9.3, 25.2)
	SOC: Cardiac disorders	14 (15.1)	(8.5, 24.0)
	SOC: Psychiatric disorders	14 (15.1)	(8.5, 24.0)
	Anxiety	7 (7.5)	(3.1, 14.9)
	Insomnia	7 (7.5)	(3.1, 14.9)
	SOC: Ear and labyrinth disorders	13 (14.0)	(7.7, 22.7)
	SOC: Vascular disorders	13 (14.0)	(7.7, 22.7)
	SOC: Renal and urinary disorders	8 (8.6)	(3.8, 16.2)
	SOC: Reproductive system and breast disorders	4 (4.3)	(1.2, 10.6)
	SOC: Hepatobiliary disorders	3 (3.2)	(0.7, 9.1)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Estrogen receptors	SOC: Gastrointestinal disorders	81 (92.0)	(84.3, 96.7)
Negative (N = 88)	Nausea	70 (79.5)	(69.6, 87.4)
	Vomiting	35 (39.8)	(29.5, 50.8)
	Diarrhoea	28 (31.8)	(22.3, 42.6)
	Constipation	26 (29.5)	(20.3, 40.2)
	Dyspepsia	13 (14.8)	(8.1, 23.9)
	Stomatitis	13 (14.8)	(8.1, 23.9)
	Gastrooesophageal reflux disease	9 (10.2)	(4.8, 18.5)
	Abdominal pain upper	7 (8.0)	(3.3, 15.7)
	Abdominal pain	5 (5.7)	(1.9, 12.8)
	Haemorrhoids	3 (3.4)	(0.7, 9.6)
	SOC: General disorders and administration site conditions	63 (71.6)	(61.0, 80.7)
	Fatigue	43 (48.9)	(38.1, 59.8)
	Asthenia	12 (13.6)	(7.2, 22.6)
	Influenza like illness	6 (6.8)	(2.5, 14.3)
	Oedema peripheral	6 (6.8)	(2.5, 14.3)
	Pyrexia	6 (6.8)	(2.5, 14.3)
	Mucosal inflammation	5 (5.7)	(1.9, 12.8)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Estrogen receptors	SOC: Skin and subcutaneous tissue disorders	57 (64.8)	(53.9, 74.7)
Negative (N = 88)	Alopecia	40 (45.5)	(34.8, 56.4)
	Rash	9 (10.2)	(4.8, 18.5)
	Nail disorder	5 (5.7)	(1.9, 12.8)
	Dry skin	3 (3.4)	(0.7, 9.6)
	SOC: Investigations	53 (60.2)	(49.2, 70.5)
	Neutrophil count decreased	19 (21.6)	(13.5, 31.6)
	Aspartate aminotransferase increased	18 (20.5)	(12.6, 30.4)
	White blood cell count decreased	16 (18.2)	(10.8, 27.8)
	Alanine aminotransferase increased	13 (14.8)	(8.1, 23.9)
	Platelet count decreased	12 (13.6)	(7.2, 22.6)
	Blood bilirubin increased	9 (10.2)	(4.8, 18.5)
	Lymphocyte count decreased	6 (6.8)	(2.5, 14.3)
	Weight decreased	6 (6.8)	(2.5, 14.3)
	Electrocardiogram QT prolonged	5 (5.7)	(1.9, 12.8)
	Blood alkaline phosphatase increased	4 (4.5)	(1.3, 11.2)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Estrogen receptors	SOC: Respiratory, thoracic and mediastinal disorders	49 (55.7)	(44.7, 66.3)
Negative (N = 88)	Cough	20 (22.7)	(14.5, 32.9)
	Epistaxis	16 (18.2)	(10.8, 27.8)
	Dyspnoea	14 (15.9)	(9.0, 25.2)
	Pneumonitis	8 (9.1)	(4.0, 17.1)
	Interstitial lung disease	5 (5.7)	(1.9, 12.8)
	SOC: Infections and infestations	46 (52.3)	(41.4, 63.0)
	Upper respiratory tract infection	12 (13.6)	(7.2, 22.6)
	Urinary tract infection	12 (13.6)	(7.2, 22.6)
	Nasopharyngitis	9 (10.2)	(4.8, 18.5)
	Pneumonia	3 (3.4)	(0.7, 9.6)
	SOC: Nervous system disorders	44 (50.0)	(39.1, 60.9)
	Headache	20 (22.7)	(14.5, 32.9)
	Dizziness	10 (11.4)	(5.6, 19.9)
	Peripheral sensory neuropathy	7 (8.0)	(3.3, 15.7)
	Dysgeusia	5 (5.7)	(1.9, 12.8)
	Neuropathy peripheral	3 (3.4)	(0.7, 9.6)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Estrogen receptors	SOC: Blood and lymphatic system disorders	41 (46.6)	(35.9, 57.5)
Negative (N = 88)	Anaemia	29 (33.0)	(23.3, 43.8)
	Neutropenia	16 (18.2)	(10.8, 27.8)
	Thrombocytopenia	9 (10.2)	(4.8, 18.5)
	Lymphopenia	7 (8.0)	(3.3, 15.7)
	SOC: Metabolism and nutrition disorders	38 (43.2)	(32.7, 54.2)
	Decreased appetite	26 (29.5)	(20.3, 40.2)
	Hypokalaemia	12 (13.6)	(7.2, 22.6)
	SOC: Musculoskeletal and connective tissue disorders	32 (36.4)	(26.4, 47.3)
	Arthralgia	15 (17.0)	(9.9, 26.6)
	Myalgia	11 (12.5)	(6.4, 21.3)
	Back pain	8 (9.1)	(4.0, 17.1)
	Pain in extremity	5 (5.7)	(1.9, 12.8)
	Muscle spasms	4 (4.5)	(1.3, 11.2)
	SOC: Eye disorders	23 (26.1)	(17.3, 36.6)
	Dry eye	7 (8.0)	(3.3, 15.7)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Estrogen receptors	SOC: Psychiatric disorders	14 (15.9)	(9.0, 25.2)
Negative (N = 88)	Insomnia	6 (6.8)	(2.5, 14.3)
	Anxiety	5 (5.7)	(1.9, 12.8)
	SOC: Vascular disorders	14 (15.9)	(9.0, 25.2)
	SOC: Injury, poisoning and procedural complications	11 (12.5)	(6.4, 21.3)
	SOC: Renal and urinary disorders	11 (12.5)	(6.4, 21.3)
	SOC: Cardiac disorders	8 (9.1)	(4.0, 17.1)
	SOC: Reproductive system and breast disorders	8 (9.1)	(4.0, 17.1)
	SOC: Hepatobiliary disorders	7 (8.0)	(3.3, 15.7)
	SOC: Ear and labyrinth disorders	6 (6.8)	(2.5, 14.3)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Progesterone receptors	SOC: Gastrointestinal disorders	48 (94.1)	(83.8, 98.8)
Positive (N = 51)	Nausea	36 (70.6)	(56.2, 82.5)
	Vomiting	26 (51.0)	(36.6, 65.2)
	Constipation	16 (31.4)	(19.1, 45.9)
	Diarrhoea	13 (25.5)	(14.3, 39.6)
	Abdominal pain	10 (19.6)	(9.8, 33.1)
	Dyspepsia	8 (15.7)	(7.0, 28.6)
	Stomatitis	8 (15.7)	(7.0, 28.6)
	Abdominal pain upper	5 (9.8)	(3.3, 21.4)
	Gastrooesophageal reflux disease	5 (9.8)	(3.3, 21.4)
	Haemorrhoids	3 (5.9)	(1.2, 16.2)
	SOC: General disorders and administration site conditions	41 (80.4)	(66.9, 90.2)
	Fatigue	25 (49.0)	(34.8, 63.4)
	Asthenia	9 (17.6)	(8.4, 30.9)
	Pyrexia	8 (15.7)	(7.0, 28.6)
	Mucosal inflammation	6 (11.8)	(4.4, 23.9)
	Oedema peripheral	6 (11.8)	(4.4, 23.9)
	Influenza like illness	5 (9.8)	(3.3, 21.4)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

Subgroup	SOC/Preferred Term	Overall 5.4 mg/kg (N = 184) n (%)	95% CI [a]
Progesterone receptors	SOC: Infections and infestations	34 (66.7)	(52.1, 79.2)
Positive (N = 51)	Nasopharyngitis	9 (17.6)	(8.4, 30.9)
	Upper respiratory tract infection	8 (15.7)	(7.0, 28.6)
	Urinary tract infection	6 (11.8)	(4.4, 23.9)
	Pneumonia	4 (7.8)	(2.2, 18.9)
	SOC: Skin and subcutaneous tissue disorders	32 (62.7)	(48.1, 75.9)
	Alopecia	23 (45.1)	(31.1, 59.7)
	Rash	7 (13.7)	(5.7, 26.3)
	Dry skin	6 (11.8)	(4.4, 23.9)
	Nail disorder	3 (5.9)	(1.2, 16.2)
	SOC: Respiratory, thoracic and mediastinal disorders	30 (58.8)	(44.2, 72.4)
	Cough	15 (29.4)	(17.5, 43.8)
	Dyspnoea	9 (17.6)	(8.4, 30.9)
	Epistaxis	5 (9.8)	(3.3, 21.4)
	Interstitial lung disease	5 (9.8)	(3.3, 21.4)
	Pneumonitis	5 (9.8)	(3.3, 21.4)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Progesterone receptors	SOC: Investigations	25 (49.0)	(34.8, 63.4)
Positive (N = 51)	Neutrophil count decreased	9 (17.6)	(8.4, 30.9)
	White blood cell count decreased	9 (17.6)	(8.4, 30.9)
	Aspartate aminotransferase increased	7 (13.7)	(5.7, 26.3)
	Platelet count decreased	7 (13.7)	(5.7, 26.3)
	Lymphocyte count decreased	6 (11.8)	(4.4, 23.9)
	Alanine aminotransferase increased	5 (9.8)	(3.3, 21.4)
	Weight decreased	5 (9.8)	(3.3, 21.4)
	Blood alkaline phosphatase increased	4 (7.8)	(2.2, 18.9)
	Blood bilirubin increased	2 (3.9)	(0.5, 13.5)
	Electrocardiogram QT prolonged	2 (3.9)	(0.5, 13.5)
	SOC: Musculoskeletal and connective tissue disorders	24 (47.1)	(32.9, 61.5)
	Back pain	12 (23.5)	(12.8, 37.5)
	Muscle spasms	6 (11.8)	(4.4, 23.9)
	Arthralgia	5 (9.8)	(3.3, 21.4)
	Pain in extremity	4 (7.8)	(2.2, 18.9)
	Myalgia	3 (5.9)	(1.2, 16.2)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Progesterone receptors	SOC: Metabolism and nutrition disorders	23 (45.1)	(31.1, 59.7)
Positive (N = 51)	Decreased appetite	16 (31.4)	(19.1, 45.9)
	Hypokalaemia	6 (11.8)	(4.4, 23.9)
	SOC: Nervous system disorders	23 (45.1)	(31.1, 59.7)
	Headache	11 (21.6)	(11.3, 35.3)
	Peripheral sensory neuropathy	5 (9.8)	(3.3, 21.4)
	Dizziness	3 (5.9)	(1.2, 16.2)
	Dysgeusia	3 (5.9)	(1.2, 16.2)
	Neuropathy peripheral	3 (5.9)	(1.2, 16.2)
	SOC: Blood and lymphatic system disorders	21 (41.2)	(27.6, 55.8)
	Anaemia	12 (23.5)	(12.8, 37.5)
	Neutropenia	7 (13.7)	(5.7, 26.3)
	Thrombocytopenia	5 (9.8)	(3.3, 21.4)
	Lymphopenia	4 (7.8)	(2.2, 18.9)
	SOC: Eye disorders	20 (39.2)	(25.8, 53.9)
	Dry eye	8 (15.7)	(7.0, 28.6)
	SOC: Injury, poisoning and procedural complications	10 (19.6)	(9.8, 33.1)
	SOC: Cardiac disorders	8 (15.7)	(7.0, 28.6)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Progesterone receptors	SOC: Psychiatric disorders	7 (13.7)	(5.7, 26.3)
Positive (N = 51)	Anxiety	4 (7.8)	(2.2, 18.9)
	Insomnia	4 (7.8)	(2.2, 18.9)
	SOC: Ear and labyrinth disorders	6 (11.8)	(4.4, 23.9)
	SOC: Vascular disorders	6 (11.8)	(4.4, 23.9)
	SOC: Renal and urinary disorders	5 (9.8)	(3.3, 21.4)
	SOC: Reproductive system and breast disorders	4 (7.8)	(2.2, 18.9)
	SOC: Hepatobiliary disorders	2 (3.9)	(0.5, 13.5)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Progesterone receptors	SOC: Gastrointestinal disorders	118 (94.4)	(88.8, 97.7)
Negative (N = 125)	Nausea	104 (83.2)	(75.5, 89.3)
	Vomiting	58 (46.4)	(37.4, 55.5)
	Constipation	48 (38.4)	(29.8, 47.5)
	Diarrhoea	42 (33.6)	(25.4, 42.6)
	Dyspepsia	22 (17.6)	(11.4, 25.4)
	Stomatitis	21 (16.8)	(10.7, 24.5)
	Abdominal pain	14 (11.2)	(6.3, 18.1)
	Gastrooesophageal reflux disease	13 (10.4)	(5.7, 17.1)
	Abdominal pain upper	11 (8.8)	(4.5, 15.2)
	Haemorrhoids	8 (6.4)	(2.8, 12.2)
	SOC: General disorders and administration site conditions	91 (72.8)	(64.1, 80.4)
	Fatigue	65 (52.0)	(42.9, 61.0)
	Asthenia	15 (12.0)	(6.9, 19.0)
	Oedema peripheral	11 (8.8)	(4.5, 15.2)
	Mucosal inflammation	9 (7.2)	(3.3, 13.2)
	Influenza like illness	7 (5.6)	(2.3, 11.2)
	Pyrexia	7 (5.6)	(2.3, 11.2)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Progesterone receptors	SOC: Skin and subcutaneous tissue disorders	79 (63.2)	(54.1, 71.6)
Negative (N = 125)	Alopecia	62 (49.6)	(40.5, 58.7)
	Rash	12 (9.6)	(5.1, 16.2)
	Nail disorder	6 (4.8)	(1.8, 10.2)
	Dry skin	5 (4.0)	(1.3, 9.1)
	SOC: Investigations	78 (62.4)	(53.3, 70.9)
	Neutrophil count decreased	31 (24.8)	(17.5, 33.3)
	Aspartate aminotransferase increased	26 (20.8)	(14.1, 29.0)
	White blood cell count decreased	26 (20.8)	(14.1, 29.0)
	Platelet count decreased	21 (16.8)	(10.7, 24.5)
	Alanine aminotransferase increased	16 (12.8)	(7.5, 20.0)
	Blood bilirubin increased	13 (10.4)	(5.7, 17.1)
	Lymphocyte count decreased	12 (9.6)	(5.1, 16.2)
	Weight decreased	9 (7.2)	(3.3, 13.2)
	Electrocardiogram QT prolonged	8 (6.4)	(2.8, 12.2)
	Blood alkaline phosphatase increased	7 (5.6)	(2.3, 11.2)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Progesterone receptors	SOC: Respiratory, thoracic and mediastinal disorders	71 (56.8)	(47.6, 65.6)
Negative (N = 125)	Cough	28 (22.4)	(15.4, 30.7)
	Dyspnoea	20 (16.0)	(10.1, 23.6)
	Epistaxis	20 (16.0)	(10.1, 23.6)
	Pneumonitis	11 (8.8)	(4.5, 15.2)
	Interstitial lung disease	6 (4.8)	(1.8, 10.2)
	SOC: Nervous system disorders	65 (52.0)	(42.9, 61.0)
	Headache	29 (23.2)	(16.1, 31.6)
	Dizziness	16 (12.8)	(7.5, 20.0)
	Peripheral sensory neuropathy	11 (8.8)	(4.5, 15.2)
	Dysgeusia	10 (8.0)	(3.9, 14.2)
	Neuropathy peripheral	8 (6.4)	(2.8, 12.2)
	SOC: Infections and infestations	60 (48.0)	(39.0, 57.1)
	Upper respiratory tract infection	16 (12.8)	(7.5, 20.0)
	Urinary tract infection	13 (10.4)	(5.7, 17.1)
	Nasopharyngitis	11 (8.8)	(4.5, 15.2)
	Pneumonia	5 (4.0)	(1.3, 9.1)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Progesterone receptors	SOC: Metabolism and nutrition disorders	59 (47.2)	(38.2, 56.3)
Negative (N = 125)	Decreased appetite	41 (32.8)	(24.7, 41.8)
	Hypokalaemia	16 (12.8)	(7.5, 20.0)
	SOC: Blood and lymphatic system disorders	56 (44.8)	(35.9, 54.0)
	Anaemia	43 (34.4)	(26.1, 43.4)
	Neutropenia	19 (15.2)	(9.4, 22.7)
	Thrombocytopenia	9 (7.2)	(3.3, 13.2)
	Lymphopenia	7 (5.6)	(2.3, 11.2)
	SOC: Musculoskeletal and connective tissue disorders	45 (36.0)	(27.6, 45.1)
	Arthralgia	19 (15.2)	(9.4, 22.7)
	Myalgia	15 (12.0)	(6.9, 19.0)
	Back pain	8 (6.4)	(2.8, 12.2)
	Muscle spasms	8 (6.4)	(2.8, 12.2)
	Pain in extremity	8 (6.4)	(2.8, 12.2)
	SOC: Eye disorders	40 (32.0)	(23.9, 40.9)
	Dry eye	13 (10.4)	(5.7, 17.1)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Progesterone receptors	SOC: Psychiatric disorders	20 (16.0)	(10.1, 23.6)
Negative (N = 125)	Anxiety	8 (6.4)	(2.8, 12.2)
	Insomnia	8 (6.4)	(2.8, 12.2)
	SOC: Vascular disorders	20 (16.0)	(10.1, 23.6)
	SOC: Injury, poisoning and procedural complications	16 (12.8)	(7.5, 20.0)
	SOC: Cardiac disorders	14 (11.2)	(6.3, 18.1)
	SOC: Renal and urinary disorders	14 (11.2)	(6.3, 18.1)
	SOC: Ear and labyrinth disorders	13 (10.4)	(5.7, 17.1)
	SOC: Hepatobiliary disorders	8 (6.4)	(2.8, 12.2)
	SOC: Reproductive system and breast disorders	8 (6.4)	(2.8, 12.2)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Hormone receptors	SOC: Gastrointestinal disorders	93 (95.9)	(89.8, 98.9)
Positive (N = 97)	Nausea	74 (76.3)	(66.6, 84.3)
	Vomiting	52 (53.6)	(43.2, 63.8)
	Constipation	39 (40.2)	(30.4, 50.7)
	Diarrhoea	30 (30.9)	(21.9, 41.1)
	Abdominal pain	20 (20.6)	(13.1, 30.0)
	Dyspepsia	18 (18.6)	(11.4, 27.7)
	Stomatitis	17 (17.5)	(10.6, 26.6)
	Abdominal pain upper	9 (9.3)	(4.3, 16.9)
	Gastrooesophageal reflux disease	9 (9.3)	(4.3, 16.9)
	Haemorrhoids	8 (8.2)	(3.6, 15.6)
	SOC: General disorders and administration site conditions	77 (79.4)	(70.0, 86.9)
	Fatigue	51 (52.6)	(42.2, 62.8)
	Asthenia	15 (15.5)	(8.9, 24.2)
	Oedema peripheral	12 (12.4)	(6.6, 20.6)
	Mucosal inflammation	11 (11.3)	(5.8, 19.4)
	Pyrexia	11 (11.3)	(5.8, 19.4)
	Influenza like illness	6 (6.2)	(2.3, 13.0)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Hormone receptors	SOC: Skin and subcutaneous tissue disorders	60 (61.9)	(51.4, 71.5)
Positive (N = 97)	Alopecia	49 (50.5)	(40.2, 60.8)
	Rash	11 (11.3)	(5.8, 19.4)
	Dry skin	8 (8.2)	(3.6, 15.6)
	Nail disorder	5 (5.2)	(1.7, 11.6)
	SOC: Respiratory, thoracic and mediastinal disorders	56 (57.7)	(47.3, 67.7)
	Cough	25 (25.8)	(17.4, 35.7)
	Dyspnoea	16 (16.5)	(9.7, 25.4)
	Epistaxis	10 (10.3)	(5.1, 18.1)
	Pneumonitis	8 (8.2)	(3.6, 15.6)
	Interstitial lung disease	7 (7.2)	(3.0, 14.3)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Hormone receptors	SOC: Investigations	55 (56.7)	(46.3, 66.7)
Positive (N = 97)	Neutrophil count decreased	23 (23.7)	(15.7, 33.4)
	White blood cell count decreased	21 (21.6)	(13.9, 31.2)
	Platelet count decreased	19 (19.6)	(12.2, 28.9)
	Aspartate aminotransferase increased	15 (15.5)	(8.9, 24.2)
	Lymphocyte count decreased	13 (13.4)	(7.3, 21.8)
	Weight decreased	9 (9.3)	(4.3, 16.9)
	Alanine aminotransferase increased	8 (8.2)	(3.6, 15.6)
	Blood alkaline phosphatase increased	7 (7.2)	(3.0, 14.3)
	Blood bilirubin increased	7 (7.2)	(3.0, 14.3)
	Electrocardiogram QT prolonged	5 (5.2)	(1.7, 11.6)
	SOC: Infections and infestations	53 (54.6)	(44.2, 64.8)
	Upper respiratory tract infection	13 (13.4)	(7.3, 21.8)
	Nasopharyngitis	12 (12.4)	(6.6, 20.6)
	Urinary tract infection	9 (9.3)	(4.3, 16.9)
	Pneumonia	7 (7.2)	(3.0, 14.3)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Hormone receptors	SOC: Metabolism and nutrition disorders	48 (49.5)	(39.2, 59.8)
Positive (N = 97)	Decreased appetite	35 (36.1)	(26.6, 46.5)
	Hypokalaemia	11 (11.3)	(5.8, 19.4)
	SOC: Nervous system disorders	48 (49.5)	(39.2, 59.8)
	Headache	20 (20.6)	(13.1, 30.0)
	Peripheral sensory neuropathy	10 (10.3)	(5.1, 18.1)
	Dizziness	9 (9.3)	(4.3, 16.9)
	Neuropathy peripheral	9 (9.3)	(4.3, 16.9)
	Dysgeusia	8 (8.2)	(3.6, 15.6)
	SOC: Blood and lymphatic system disorders	41 (42.3)	(32.3, 52.7)
	Anaemia	29 (29.9)	(21.0, 40.0)
	Neutropenia	12 (12.4)	(6.6, 20.6)
	Thrombocytopenia	7 (7.2)	(3.0, 14.3)
	Lymphopenia	4 (4.1)	(1.1, 10.2)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Hormone receptors	SOC: Musculoskeletal and connective tissue disorders	39 (40.2)	(30.4, 50.7)
Positive (N = 97)	Back pain	14 (14.4)	(8.1, 23.0)
	Arthralgia	10 (10.3)	(5.1, 18.1)
	Muscle spasms	10 (10.3)	(5.1, 18.1)
	Myalgia	8 (8.2)	(3.6, 15.6)
	Pain in extremity	7 (7.2)	(3.0, 14.3)
	SOC: Eye disorders	38 (39.2)	(29.4, 49.6)
	Dry eye	14 (14.4)	(8.1, 23.0)
	SOC: Injury, poisoning and procedural complications	16 (16.5)	(9.7, 25.4)
	SOC: Cardiac disorders	14 (14.4)	(8.1, 23.0)
	SOC: Ear and labyrinth disorders	14 (14.4)	(8.1, 23.0)
	SOC: Psychiatric disorders	14 (14.4)	(8.1, 23.0)
	Anxiety	7 (7.2)	(3.0, 14.3)
	Insomnia	7 (7.2)	(3.0, 14.3)
	SOC: Vascular disorders	13 (13.4)	(7.3, 21.8)
	SOC: Renal and urinary disorders	9 (9.3)	(4.3, 16.9)
	SOC: Reproductive system and breast disorders	4 (4.1)	(1.1, 10.2)
	SOC: Hepatobiliary disorders	3 (3.1)	(0.6, 8.8)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Hormone receptors	SOC: Gastrointestinal disorders	77 (92.8)	(84.9, 97.3)
Negative (N = 83)	Nausea	68 (81.9)	(72.0, 89.5)
	Vomiting	35 (42.2)	(31.4, 53.5)
	Diarrhoea	28 (33.7)	(23.7, 44.9)
	Constipation	26 (31.3)	(21.6, 42.4)
	Dyspepsia	13 (15.7)	(8.6, 25.3)
	Stomatitis	12 (14.5)	(7.7, 23.9)
	Gastrooesophageal reflux disease	9 (10.8)	(5.1, 19.6)
	Abdominal pain upper	7 (8.4)	(3.5, 16.6)
	Abdominal pain	5 (6.0)	(2.0, 13.5)
	Haemorrhoids	3 (3.6)	(0.8, 10.2)
	SOC: General disorders and administration site conditions	59 (71.1)	(60.1, 80.5)
	Fatigue	41 (49.4)	(38.2, 60.6)
	Asthenia	11 (13.3)	(6.8, 22.5)
	Influenza like illness	6 (7.2)	(2.7, 15.1)
	Mucosal inflammation	5 (6.0)	(2.0, 13.5)
	Oedema peripheral	5 (6.0)	(2.0, 13.5)
	Pyrexia	5 (6.0)	(2.0, 13.5)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Hormone receptors	SOC: Skin and subcutaneous tissue disorders	52 (62.7)	(51.3, 73.0)
Negative (N = 83)	Alopecia	37 (44.6)	(33.7, 55.9)
	Rash	8 (9.6)	(4.3, 18.1)
	Nail disorder	4 (4.8)	(1.3, 11.9)
	Dry skin	3 (3.6)	(0.8, 10.2)
	SOC: Investigations	50 (60.2)	(48.9, 70.8)
	Aspartate aminotransferase increased	18 (21.7)	(13.4, 32.1)
	Neutrophil count decreased	18 (21.7)	(13.4, 32.1)
	White blood cell count decreased	15 (18.1)	(10.5, 28.0)
	Alanine aminotransferase increased	13 (15.7)	(8.6, 25.3)
	Platelet count decreased	11 (13.3)	(6.8, 22.5)
	Blood bilirubin increased	8 (9.6)	(4.3, 18.1)
	Lymphocyte count decreased	6 (7.2)	(2.7, 15.1)
	Weight decreased	6 (7.2)	(2.7, 15.1)
	Electrocardiogram QT prolonged	5 (6.0)	(2.0, 13.5)
	Blood alkaline phosphatase increased	4 (4.8)	(1.3, 11.9)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Hormone receptors	SOC: Respiratory, thoracic and mediastinal disorders	47 (56.6)	(45.3, 67.5)
Negative (N = 83)	Cough	19 (22.9)	(14.4, 33.4)
	Epistaxis	16 (19.3)	(11.4, 29.4)
	Dyspnoea	13 (15.7)	(8.6, 25.3)
	Pneumonitis	8 (9.6)	(4.3, 18.1)
	Interstitial lung disease	4 (4.8)	(1.3, 11.9)
	SOC: Infections and infestations	43 (51.8)	(40.6, 62.9)
	Upper respiratory tract infection	11 (13.3)	(6.8, 22.5)
	Urinary tract infection	11 (13.3)	(6.8, 22.5)
	Nasopharyngitis	8 (9.6)	(4.3, 18.1)
	Pneumonia	3 (3.6)	(0.8, 10.2)
	SOC: Nervous system disorders	42 (50.6)	(39.4, 61.8)
	Headache	20 (24.1)	(15.4, 34.7)
	Dizziness	10 (12.0)	(5.9, 21.0)
	Peripheral sensory neuropathy	6 (7.2)	(2.7, 15.1)
	Dysgeusia	5 (6.0)	(2.0, 13.5)
	Neuropathy peripheral	3 (3.6)	(0.8, 10.2)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Hormone receptors	SOC: Blood and lymphatic system disorders	39 (47.0)	(35.9, 58.3)
Negative (N = 83)	Anaemia	29 (34.9)	(24.8, 46.2)
	Neutropenia	15 (18.1)	(10.5, 28.0)
	Lymphopenia	7 (8.4)	(3.5, 16.6)
	Thrombocytopenia	7 (8.4)	(3.5, 16.6)
	SOC: Metabolism and nutrition disorders	35 (42.2)	(31.4, 53.5)
	Decreased appetite	23 (27.7)	(18.4, 38.6)
	Hypokalaemia	11 (13.3)	(6.8, 22.5)
	SOC: Musculoskeletal and connective tissue disorders	30 (36.1)	(25.9, 47.4)
	Arthralgia	14 (16.9)	(9.5, 26.7)
	Myalgia	10 (12.0)	(5.9, 21.0)
	Back pain	6 (7.2)	(2.7, 15.1)
	Pain in extremity	5 (6.0)	(2.0, 13.5)
	Muscle spasms	4 (4.8)	(1.3, 11.9)
	SOC: Eye disorders	23 (27.7)	(18.4, 38.6)
	Dry eye	7 (8.4)	(3.5, 16.6)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Hormone receptors	SOC: Psychiatric disorders	14 (16.9)	(9.5, 26.7)
Negative (N = 83)	Insomnia	6 (7.2)	(2.7, 15.1)
	Anxiety	5 (6.0)	(2.0, 13.5)
	SOC: Vascular disorders	14 (16.9)	(9.5, 26.7)
	SOC: Injury, poisoning and procedural complications	10 (12.0)	(5.9, 21.0)
	SOC: Renal and urinary disorders	10 (12.0)	(5.9, 21.0)
	SOC: Cardiac disorders	8 (9.6)	(4.3, 18.1)
	SOC: Reproductive system and breast disorders	8 (9.6)	(4.3, 18.1)
	SOC: Hepatobiliary disorders	7 (8.4)	(3.5, 16.6)
	SOC: Ear and labyrinth disorders	5 (6.0)	(2.0, 13.5)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Lines of prior systemic therapy not including hormone therapy < 3 lines (N = 17)	SOC: Gastrointestinal disorders	15 (88.2)	(63.6, 98.5)
	Nausea	12 (70.6)	(44.0, 89.7)
	Vomiting	7 (41.2)	(18.4, 67.1)
	Constipation	5 (29.4)	(10.3, 56.0)
	Dyspepsia	4 (23.5)	(6.8, 49.9)
	Diarrhoea	3 (17.6)	(3.8, 43.4)
	Gastrooesophageal reflux disease	3 (17.6)	(3.8, 43.4)
	Stomatitis	2 (11.8)	(1.5, 36.4)
	Abdominal pain	1 (5.9)	(0.1, 28.7)
	Abdominal pain upper	1 (5.9)	(0.1, 28.7)
	SOC: Skin and subcutaneous tissue disorders	14 (82.4)	(56.6, 96.2)
	Alopecia	10 (58.8)	(32.9, 81.6)
	Dry skin	3 (17.6)	(3.8, 43.4)
	Rash	2 (11.8)	(1.5, 36.4)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Lines of prior systemic therapy not including hormone therapy < 3 lines (N = 17)	SOC: General disorders and administration site conditions	13 (76.5)	(50.1, 93.2)
	Fatigue	8 (47.1)	(23.0, 72.2)
	Pyrexia	4 (23.5)	(6.8, 49.9)
	Oedema peripheral	2 (11.8)	(1.5, 36.4)
	Asthenia	1 (5.9)	(0.1, 28.7)
	Influenza like illness	1 (5.9)	(0.1, 28.7)
	SOC: Investigations	13 (76.5)	(50.1, 93.2)
	Neutrophil count decreased	7 (41.2)	(18.4, 67.1)
	Platelet count decreased	6 (35.3)	(14.2, 61.7)
	White blood cell count decreased	6 (35.3)	(14.2, 61.7)
	Aspartate aminotransferase increased	5 (29.4)	(10.3, 56.0)
	Blood bilirubin increased	4 (23.5)	(6.8, 49.9)
	Lymphocyte count decreased	4 (23.5)	(6.8, 49.9)
	Alanine aminotransferase increased	3 (17.6)	(3.8, 43.4)
	Blood alkaline phosphatase increased	3 (17.6)	(3.8, 43.4)
	Weight decreased	2 (11.8)	(1.5, 36.4)
	Electrocardiogram QT prolonged	1 (5.9)	(0.1, 28.7)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Lines of prior systemic therapy not including hormone therapy < 3 lines (N = 17)	SOC: Respiratory, thoracic and mediastinal disorders	13 (76.5)	(50.1, 93.2)
	Cough	6 (35.3)	(14.2, 61.7)
	Epistaxis	6 (35.3)	(14.2, 61.7)
	Dyspnoea	4 (23.5)	(6.8, 49.9)
	Interstitial lung disease	1 (5.9)	(0.1, 28.7)
	Pneumonitis	1 (5.9)	(0.1, 28.7)
	SOC: Metabolism and nutrition disorders	11 (64.7)	(38.3, 85.8)
	Decreased appetite	6 (35.3)	(14.2, 61.7)
	SOC: Infections and infestations	10 (58.8)	(32.9, 81.6)
	Upper respiratory tract infection	4 (23.5)	(6.8, 49.9)
	Nasopharyngitis	3 (17.6)	(3.8, 43.4)
	Pneumonia	2 (11.8)	(1.5, 36.4)
	Urinary tract infection	2 (11.8)	(1.5, 36.4)
	SOC: Eye disorders	8 (47.1)	(23.0, 72.2)
	Dry eye	3 (17.6)	(3.8, 43.4)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Lines of prior systemic therapy not including hormone therapy < 3 lines (N = 17)	SOC: Blood and lymphatic system disorders	6 (35.3)	(14.2, 61.7)
	Anaemia	6 (35.3)	(14.2, 61.7)
	Lymphopenia	1 (5.9)	(0.1, 28.7)
	Neutropenia	1 (5.9)	(0.1, 28.7)
	Thrombocytopenia	1 (5.9)	(0.1, 28.7)
	SOC: Musculoskeletal and connective tissue disorders	5 (29.4)	(10.3, 56.0)
	Arthralgia	2 (11.8)	(1.5, 36.4)
	Myalgia	2 (11.8)	(1.5, 36.4)
	Pain in extremity	2 (11.8)	(1.5, 36.4)
	Back pain	1 (5.9)	(0.1, 28.7)
	SOC: Injury, poisoning and procedural complications	4 (23.5)	(6.8, 49.9)
	SOC: Nervous system disorders	4 (23.5)	(6.8, 49.9)
	Dizziness	1 (5.9)	(0.1, 28.7)
	Dysgeusia	1 (5.9)	(0.1, 28.7)
	Headache	1 (5.9)	(0.1, 28.7)
	Peripheral sensory neuropathy	1 (5.9)	(0.1, 28.7)
	SOC: Renal and urinary disorders	4 (23.5)	(6.8, 49.9)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Lines of prior systemic therapy not including hormone therapy < 3 lines (N = 17)	SOC: Psychiatric disorders	3 (17.6)	(3.8, 43.4)
	Anxiety	2 (11.8)	(1.5, 36.4)
	Insomnia	1 (5.9)	(0.1, 28.7)
	SOC: Cardiac disorders	2 (11.8)	(1.5, 36.4)
	SOC: Hepatobiliary disorders	2 (11.8)	(1.5, 36.4)
	SOC: Ear and labyrinth disorders	1 (5.9)	(0.1, 28.7)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

Subgroup	SOC/Preferred Term	Overall 5.4 mg/kg (N = 184) n (%)	95% CI [a]
Lines of prior systemic therapy not including hormone therapy >= 3 lines (N = 167)	SOC: Gastrointestinal disorders	158 (94.6)	(90.0, 97.5)
	Nausea	132 (79.0)	(72.1, 84.9)
	Vomiting	81 (48.5)	(40.7, 56.3)
	Constipation	60 (35.9)	(28.7, 43.7)
	Diarrhoea	55 (32.9)	(25.9, 40.6)
	Dyspepsia	27 (16.2)	(10.9, 22.6)
	Stomatitis	27 (16.2)	(10.9, 22.6)
	Abdominal pain	24 (14.4)	(9.4, 20.6)
	Abdominal pain upper	15 (9.0)	(5.1, 14.4)
	Gastrooesophageal reflux disease	15 (9.0)	(5.1, 14.4)
	Haemorrhoids	11 (6.6)	(3.3, 11.5)
	SOC: General disorders and administration site conditions	124 (74.3)	(66.9, 80.7)
	Fatigue	84 (50.3)	(42.5, 58.1)
	Asthenia	25 (15.0)	(9.9, 21.3)
	Mucosal inflammation	16 (9.6)	(5.6, 15.1)
	Oedema peripheral	15 (9.0)	(5.1, 14.4)
	Pyrexia	13 (7.8)	(4.2, 12.9)
	Influenza like illness	11 (6.6)	(3.3, 11.5)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Lines of prior systemic therapy not including hormone therapy >= 3 lines (N = 167)	SOC: Skin and subcutaneous tissue disorders	102 (61.1)	(53.2, 68.5)
	Alopecia	79 (47.3)	(39.5, 55.2)
	Rash	17 (10.2)	(6.0, 15.8)
	Nail disorder	10 (6.0)	(2.9, 10.7)
	Dry skin	8 (4.8)	(2.1, 9.2)
	SOC: Investigations	93 (55.7)	(47.8, 63.4)
	Neutrophil count decreased	34 (20.4)	(14.5, 27.3)
	White blood cell count decreased	30 (18.0)	(12.5, 24.6)
	Aspartate aminotransferase increased	28 (16.8)	(11.4, 23.3)
	Platelet count decreased	24 (14.4)	(9.4, 20.6)
	Alanine aminotransferase increased	18 (10.8)	(6.5, 16.5)
	Lymphocyte count decreased	15 (9.0)	(5.1, 14.4)
	Weight decreased	13 (7.8)	(4.2, 12.9)
	Blood bilirubin increased	11 (6.6)	(3.3, 11.5)
	Electrocardiogram QT prolonged	9 (5.4)	(2.5, 10.0)
	Blood alkaline phosphatase increased	8 (4.8)	(2.1, 9.2)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Lines of prior systemic therapy not including hormone therapy >= 3 lines (N = 167)	SOC: Respiratory, thoracic and mediastinal disorders	92 (55.1)	(47.2, 62.8)
	Cough	39 (23.4)	(17.2, 30.5)
	Dyspnoea	27 (16.2)	(10.9, 22.6)
	Epistaxis	20 (12.0)	(7.5, 17.9)
	Pneumonitis	15 (9.0)	(5.1, 14.4)
	Interstitial lung disease	10 (6.0)	(2.9, 10.7)
	SOC: Infections and infestations	89 (53.3)	(45.4, 61.0)
	Upper respiratory tract infection	20 (12.0)	(7.5, 17.9)
	Urinary tract infection	20 (12.0)	(7.5, 17.9)
	Nasopharyngitis	17 (10.2)	(6.0, 15.8)
	Pneumonia	8 (4.8)	(2.1, 9.2)
	SOC: Nervous system disorders	87 (52.1)	(44.2, 59.9)
	Headache	39 (23.4)	(17.2, 30.5)
	Dizziness	18 (10.8)	(6.5, 16.5)
	Peripheral sensory neuropathy	15 (9.0)	(5.1, 14.4)
	Dysgeusia	12 (7.2)	(3.8, 12.2)
	Neuropathy peripheral	12 (7.2)	(3.8, 12.2)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Lines of prior systemic therapy not including hormone therapy >= 3 lines (N = 167)	SOC: Blood and lymphatic system disorders	74 (44.3)	(36.6, 52.2)
	Anaemia	52 (31.1)	(24.2, 38.8)
	Neutropenia	26 (15.6)	(10.4, 22.0)
	Thrombocytopenia	13 (7.8)	(4.2, 12.9)
	Lymphopenia	10 (6.0)	(2.9, 10.7)
	SOC: Metabolism and nutrition disorders	73 (43.7)	(36.1, 51.6)
	Decreased appetite	53 (31.7)	(24.8, 39.4)
	Hypokalaemia	22 (13.2)	(8.4, 19.3)
	SOC: Musculoskeletal and connective tissue disorders	65 (38.9)	(31.5, 46.8)
	Arthralgia	22 (13.2)	(8.4, 19.3)
	Back pain	19 (11.4)	(7.0, 17.2)
	Myalgia	16 (9.6)	(5.6, 15.1)
	Muscle spasms	15 (9.0)	(5.1, 14.4)
	Pain in extremity	10 (6.0)	(2.9, 10.7)
	SOC: Eye disorders	53 (31.7)	(24.8, 39.4)
	Dry eye	18 (10.8)	(6.5, 16.5)
	SOC: Vascular disorders	27 (16.2)	(10.9, 22.6)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Lines of prior systemic therapy not including hormone therapy >= 3 lines (N = 167)	SOC: Psychiatric disorders	25 (15.0)	(9.9, 21.3)
	Insomnia	12 (7.2)	(3.8, 12.2)
	Anxiety	10 (6.0)	(2.9, 10.7)
	SOC: Injury, poisoning and procedural complications	22 (13.2)	(8.4, 19.3)
	SOC: Cardiac disorders	20 (12.0)	(7.5, 17.9)
	SOC: Ear and labyrinth disorders	18 (10.8)	(6.5, 16.5)
	SOC: Renal and urinary disorders	15 (9.0)	(5.1, 14.4)
	SOC: Reproductive system and breast disorders	12 (7.2)	(3.8, 12.2)
	SOC: Hepatobiliary disorders	8 (4.8)	(2.1, 9.2)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

Subgroup	SOC/Preferred Term	Overall 5.4 mg/kg (N = 184) n (%)	95% CI [a]
Prior pertuzumab	SOC: Gastrointestinal disorders	114 (94.2)	(88.4, 97.6)
Yes (N = 121)	Nausea	90 (74.4)	(65.6, 81.9)
	Vomiting	59 (48.8)	(39.6, 58.0)
	Constipation	45 (37.2)	(28.6, 46.4)
	Diarrhoea	35 (28.9)	(21.0, 37.9)
	Dyspepsia	22 (18.2)	(11.8, 26.2)
	Stomatitis	19 (15.7)	(9.7, 23.4)
	Abdominal pain	13 (10.7)	(5.8, 17.7)
	Gastrooesophageal reflux disease	13 (10.7)	(5.8, 17.7)
	Abdominal pain upper	9 (7.4)	(3.5, 13.7)
	Haemorrhoids	8 (6.6)	(2.9, 12.6)
	SOC: General disorders and administration site conditions	86 (71.1)	(62.1, 79.0)
	Fatigue	60 (49.6)	(40.4, 58.8)
	Asthenia	12 (9.9)	(5.2, 16.7)
	Pyrexia	9 (7.4)	(3.5, 13.7)
	Mucosal inflammation	8 (6.6)	(2.9, 12.6)
	Oedema peripheral	8 (6.6)	(2.9, 12.6)
	Influenza like illness	6 (5.0)	(1.8, 10.5)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Prior pertuzumab	SOC: Skin and subcutaneous tissue disorders	75 (62.0)	(52.7, 70.7)
Yes (N = 121)	Alopecia	57 (47.1)	(38.0, 56.4)
	Rash	11 (9.1)	(4.6, 15.7)
	Dry skin	8 (6.6)	(2.9, 12.6)
	Nail disorder	7 (5.8)	(2.4, 11.6)
	SOC: Investigations	72 (59.5)	(50.2, 68.3)
	Neutrophil count decreased	35 (28.9)	(21.0, 37.9)
	White blood cell count decreased	28 (23.1)	(16.0, 31.7)
	Aspartate aminotransferase increased	23 (19.0)	(12.4, 27.1)
	Platelet count decreased	21 (17.4)	(11.1, 25.3)
	Alanine aminotransferase increased	14 (11.6)	(6.5, 18.7)
	Lymphocyte count decreased	14 (11.6)	(6.5, 18.7)
	Weight decreased	14 (11.6)	(6.5, 18.7)
	Blood bilirubin increased	10 (8.3)	(4.0, 14.7)
	Electrocardiogram QT prolonged	7 (5.8)	(2.4, 11.6)
	Blood alkaline phosphatase increased	6 (5.0)	(1.8, 10.5)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Prior pertuzumab	SOC: Infections and infestations	67 (55.4)	(46.1, 64.4)
Yes (N = 121)	Upper respiratory tract infection	18 (14.9)	(9.1, 22.5)
	Urinary tract infection	15 (12.4)	(7.1, 19.6)
	Nasopharyngitis	14 (11.6)	(6.5, 18.7)
	Pneumonia	6 (5.0)	(1.8, 10.5)
	SOC: Respiratory, thoracic and mediastinal disorders	66 (54.5)	(45.2, 63.6)
	Cough	35 (28.9)	(21.0, 37.9)
	Dyspnoea	17 (14.0)	(8.4, 21.5)
	Epistaxis	16 (13.2)	(7.8, 20.6)
	Pneumonitis	10 (8.3)	(4.0, 14.7)
	Interstitial lung disease	9 (7.4)	(3.5, 13.7)
	SOC: Nervous system disorders	57 (47.1)	(38.0, 56.4)
	Headache	29 (24.0)	(16.7, 32.6)
	Dizziness	11 (9.1)	(4.6, 15.7)
	Dysgeusia	11 (9.1)	(4.6, 15.7)
	Peripheral sensory neuropathy	11 (9.1)	(4.6, 15.7)
	Neuropathy peripheral	6 (5.0)	(1.8, 10.5)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Prior pertuzumab	SOC: Metabolism and nutrition disorders	54 (44.6)	(35.6, 53.9)
Yes (N = 121)	Decreased appetite	35 (28.9)	(21.0, 37.9)
	Hypokalaemia	16 (13.2)	(7.8, 20.6)
	SOC: Blood and lymphatic system disorders	49 (40.5)	(31.7, 49.8)
	Anaemia	40 (33.1)	(24.8, 42.2)
	Neutropenia	10 (8.3)	(4.0, 14.7)
	Thrombocytopenia	8 (6.6)	(2.9, 12.6)
	Lymphopenia	7 (5.8)	(2.4, 11.6)
	SOC: Musculoskeletal and connective tissue disorders	42 (34.7)	(26.3, 43.9)
	Arthralgia	17 (14.0)	(8.4, 21.5)
	Back pain	14 (11.6)	(6.5, 18.7)
	Muscle spasms	9 (7.4)	(3.5, 13.7)
	Myalgia	6 (5.0)	(1.8, 10.5)
	Pain in extremity	6 (5.0)	(1.8, 10.5)
	SOC: Eye disorders	37 (30.6)	(22.5, 39.6)
	Dry eye	16 (13.2)	(7.8, 20.6)
	SOC: Injury, poisoning and procedural complications	20 (16.5)	(10.4, 24.4)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Prior pertuzumab	SOC: Psychiatric disorders	16 (13.2)	(7.8, 20.6)
Yes (N = 121)	Anxiety	8 (6.6)	(2.9, 12.6)
	Insomnia	5 (4.1)	(1.4, 9.4)
	SOC: Vascular disorders	16 (13.2)	(7.8, 20.6)
	SOC: Cardiac disorders	13 (10.7)	(5.8, 17.7)
	SOC: Ear and labyrinth disorders	13 (10.7)	(5.8, 17.7)
	SOC: Renal and urinary disorders	12 (9.9)	(5.2, 16.7)
	SOC: Reproductive system and breast disorders	9 (7.4)	(3.5, 13.7)
	SOC: Hepatobiliary disorders	4 (3.3)	(0.9, 8.2)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Prior pertuzumab	SOC: Gastrointestinal disorders	59 (93.7)	(84.5, 98.2)
No (N = 63)	Nausea	54 (85.7)	(74.6, 93.3)
	Vomiting	29 (46.0)	(33.4, 59.1)
	Diarrhoea	23 (36.5)	(24.7, 49.6)
	Constipation	20 (31.7)	(20.6, 44.7)
	Abdominal pain	12 (19.0)	(10.2, 30.9)
	Stomatitis	10 (15.9)	(7.9, 27.3)
	Dyspepsia	9 (14.3)	(6.7, 25.4)
	Abdominal pain upper	7 (11.1)	(4.6, 21.6)
	Gastrooesophageal reflux disease	5 (7.9)	(2.6, 17.6)
	Haemorrhoids	3 (4.8)	(1.0, 13.3)
	SOC: General disorders and administration site conditions	51 (81.0)	(69.1, 89.8)
	Fatigue	32 (50.8)	(37.9, 63.6)
	Asthenia	14 (22.2)	(12.7, 34.5)
	Oedema peripheral	9 (14.3)	(6.7, 25.4)
	Mucosal inflammation	8 (12.7)	(5.6, 23.5)
	Pyrexia	8 (12.7)	(5.6, 23.5)
	Influenza like illness	6 (9.5)	(3.6, 19.6)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Prior pertuzumab	SOC: Skin and subcutaneous tissue disorders	41 (65.1)	(52.0, 76.7)
No (N = 63)	Alopecia	32 (50.8)	(37.9, 63.6)
	Rash	8 (12.7)	(5.6, 23.5)
	Dry skin	3 (4.8)	(1.0, 13.3)
	Nail disorder	3 (4.8)	(1.0, 13.3)
	SOC: Respiratory, thoracic and mediastinal disorders	39 (61.9)	(48.8, 73.9)
	Dyspnoea	14 (22.2)	(12.7, 34.5)
	Cough	10 (15.9)	(7.9, 27.3)
	Epistaxis	10 (15.9)	(7.9, 27.3)
	Pneumonitis	6 (9.5)	(3.6, 19.6)
	Interstitial lung disease	2 (3.2)	(0.4, 11.0)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Prior pertuzumab	SOC: Investigations	34 (54.0)	(40.9, 66.6)
No (N = 63)	Aspartate aminotransferase increased	10 (15.9)	(7.9, 27.3)
	Platelet count decreased	9 (14.3)	(6.7, 25.4)
	White blood cell count decreased	8 (12.7)	(5.6, 23.5)
	Alanine aminotransferase increased	7 (11.1)	(4.6, 21.6)
	Neutrophil count decreased	6 (9.5)	(3.6, 19.6)
	Blood alkaline phosphatase increased	5 (7.9)	(2.6, 17.6)
	Blood bilirubin increased	5 (7.9)	(2.6, 17.6)
	Lymphocyte count decreased	5 (7.9)	(2.6, 17.6)
	Electrocardiogram QT prolonged	3 (4.8)	(1.0, 13.3)
	Weight decreased	1 (1.6)	(0.0, 8.5)
	SOC: Nervous system disorders	34 (54.0)	(40.9, 66.6)
	Headache	11 (17.5)	(9.1, 29.1)
	Dizziness	8 (12.7)	(5.6, 23.5)
	Neuropathy peripheral	6 (9.5)	(3.6, 19.6)
	Peripheral sensory neuropathy	5 (7.9)	(2.6, 17.6)
	Dysgeusia	2 (3.2)	(0.4, 11.0)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Prior pertuzumab	SOC: Infections and infestations	32 (50.8)	(37.9, 63.6)
No (N = 63)	Urinary tract infection	7 (11.1)	(4.6, 21.6)
	Nasopharyngitis	6 (9.5)	(3.6, 19.6)
	Upper respiratory tract infection	6 (9.5)	(3.6, 19.6)
	Pneumonia	4 (6.3)	(1.8, 15.5)
	SOC: Blood and lymphatic system disorders	31 (49.2)	(36.4, 62.1)
	Anaemia	18 (28.6)	(17.9, 41.3)
	Neutropenia	17 (27.0)	(16.6, 39.7)
	Thrombocytopenia	6 (9.5)	(3.6, 19.6)
	Lymphopenia	4 (6.3)	(1.8, 15.5)
	SOC: Metabolism and nutrition disorders	30 (47.6)	(34.9, 60.6)
	Decreased appetite	24 (38.1)	(26.1, 51.2)
	Hypokalaemia	6 (9.5)	(3.6, 19.6)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

Subgroup	SOC/Preferred Term	Overall 5.4 mg/kg (N = 184) n (%)	95% CI [a]
Prior pertuzumab	SOC: Musculoskeletal and connective tissue disorders	28 (44.4)	(31.9, 57.5)
No (N = 63)	Myalgia	12 (19.0)	(10.2, 30.9)
	Arthralgia	7 (11.1)	(4.6, 21.6)
	Back pain	6 (9.5)	(3.6, 19.6)
	Muscle spasms	6 (9.5)	(3.6, 19.6)
	Pain in extremity	6 (9.5)	(3.6, 19.6)
	SOC: Eye disorders	24 (38.1)	(26.1, 51.2)
	Dry eye	5 (7.9)	(2.6, 17.6)
	SOC: Psychiatric disorders	12 (19.0)	(10.2, 30.9)
	Insomnia	8 (12.7)	(5.6, 23.5)
	Anxiety	4 (6.3)	(1.8, 15.5)
	SOC: Vascular disorders	11 (17.5)	(9.1, 29.1)
	SOC: Cardiac disorders	9 (14.3)	(6.7, 25.4)
	SOC: Renal and urinary disorders	7 (11.1)	(4.6, 21.6)
	SOC: Ear and labyrinth disorders	6 (9.5)	(3.6, 19.6)
	SOC: Hepatobiliary disorders	6 (9.5)	(3.6, 19.6)
	SOC: Injury, poisoning and procedural complications	6 (9.5)	(3.6, 19.6)
	SOC: Reproductive system and breast disorders	3 (4.8)	(1.0, 13.3)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

Subgroup	SOC/Preferred Term	Overall 5.4 mg/kg (N = 184) n (%)	95% CI [a]
Prior pertuzumab in 1st or 2nd line in advanced/metastatic breast cancer Yes (N = 51)	SOC: Gastrointestinal disorders	47 (92.2)	(81.1, 97.8)
	Nausea	39 (76.5)	(62.5, 87.2)
	Vomiting	28 (54.9)	(40.3, 68.9)
	Constipation	16 (31.4)	(19.1, 45.9)
	Diarrhoea	12 (23.5)	(12.8, 37.5)
	Dyspepsia	11 (21.6)	(11.3, 35.3)
	Gastrooesophageal reflux disease	4 (7.8)	(2.2, 18.9)
	Stomatitis	4 (7.8)	(2.2, 18.9)
	Abdominal pain	3 (5.9)	(1.2, 16.2)
	Abdominal pain upper	3 (5.9)	(1.2, 16.2)
	Haemorrhoids	2 (3.9)	(0.5, 13.5)
	SOC: General disorders and administration site conditions	34 (66.7)	(52.1, 79.2)
	Fatigue	22 (43.1)	(29.3, 57.8)
	Asthenia	6 (11.8)	(4.4, 23.9)
	Pyrexia	5 (9.8)	(3.3, 21.4)
	Influenza like illness	2 (3.9)	(0.5, 13.5)
	Mucosal inflammation	2 (3.9)	(0.5, 13.5)
	Oedema peripheral	2 (3.9)	(0.5, 13.5)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Prior pertuzumab in 1st or 2nd line in advanced/metastatic breast cancer Yes (N = 51)	SOC: Skin and subcutaneous tissue disorders	30 (58.8)	(44.2, 72.4)
	Alopecia	22 (43.1)	(29.3, 57.8)
	Dry skin	4 (7.8)	(2.2, 18.9)
	Nail disorder	3 (5.9)	(1.2, 16.2)
	Rash	2 (3.9)	(0.5, 13.5)
	SOC: Investigations	29 (56.9)	(42.2, 70.7)
	Neutrophil count decreased	12 (23.5)	(12.8, 37.5)
	White blood cell count decreased	9 (17.6)	(8.4, 30.9)
	Aspartate aminotransferase increased	8 (15.7)	(7.0, 28.6)
	Platelet count decreased	7 (13.7)	(5.7, 26.3)
	Weight decreased	7 (13.7)	(5.7, 26.3)
	Alanine aminotransferase increased	6 (11.8)	(4.4, 23.9)
	Blood bilirubin increased	6 (11.8)	(4.4, 23.9)
	Lymphocyte count decreased	5 (9.8)	(3.3, 21.4)
	Blood alkaline phosphatase increased	3 (5.9)	(1.2, 16.2)
	Electrocardiogram QT prolonged	1 (2.0)	(0.0, 10.4)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Prior pertuzumab in 1st or 2nd line in advanced/metastatic breast cancer Yes (N = 51)	SOC: Infections and infestations	28 (54.9)	(40.3, 68.9)
	Upper respiratory tract infection	9 (17.6)	(8.4, 30.9)
	Nasopharyngitis	5 (9.8)	(3.3, 21.4)
	Urinary tract infection	4 (7.8)	(2.2, 18.9)
	Pneumonia	2 (3.9)	(0.5, 13.5)
	SOC: Respiratory, thoracic and mediastinal disorders	28 (54.9)	(40.3, 68.9)
	Cough	15 (29.4)	(17.5, 43.8)
	Dyspnoea	7 (13.7)	(5.7, 26.3)
	Epistaxis	6 (11.8)	(4.4, 23.9)
	Interstitial lung disease	4 (7.8)	(2.2, 18.9)
	Pneumonitis	3 (5.9)	(1.2, 16.2)
	SOC: Metabolism and nutrition disorders	24 (47.1)	(32.9, 61.5)
	Decreased appetite	13 (25.5)	(14.3, 39.6)
	Hypokalaemia	6 (11.8)	(4.4, 23.9)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Prior pertuzumab in 1st or 2nd line in advanced/metastatic breast cancer Yes (N = 51)	SOC: Nervous system disorders	19 (37.3)	(24.1, 51.9)
	Headache	10 (19.6)	(9.8, 33.1)
	Dizziness	4 (7.8)	(2.2, 18.9)
	Dysgeusia	4 (7.8)	(2.2, 18.9)
	Peripheral sensory neuropathy	4 (7.8)	(2.2, 18.9)
	Neuropathy peripheral	1 (2.0)	(0.0, 10.4)
	SOC: Blood and lymphatic system disorders	18 (35.3)	(22.4, 49.9)
	Anaemia	14 (27.5)	(15.9, 41.7)
	Thrombocytopenia	6 (11.8)	(4.4, 23.9)
	Lymphopenia	5 (9.8)	(3.3, 21.4)
	Neutropenia	5 (9.8)	(3.3, 21.4)
	SOC: Musculoskeletal and connective tissue disorders	17 (33.3)	(20.8, 47.9)
	Arthralgia	5 (9.8)	(3.3, 21.4)
	Back pain	5 (9.8)	(3.3, 21.4)
	Muscle spasms	4 (7.8)	(2.2, 18.9)
	Pain in extremity	4 (7.8)	(2.2, 18.9)
	Myalgia	2 (3.9)	(0.5, 13.5)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Prior pertuzumab in 1st or 2nd line in advanced/metastatic breast cancer Yes (N = 51)	SOC: Eye disorders	16 (31.4)	(19.1, 45.9)
	Dry eye	7 (13.7)	(5.7, 26.3)
	SOC: Injury, poisoning and procedural complications	9 (17.6)	(8.4, 30.9)
	SOC: Vascular disorders	7 (13.7)	(5.7, 26.3)
	SOC: Cardiac disorders	6 (11.8)	(4.4, 23.9)
	SOC: Psychiatric disorders	6 (11.8)	(4.4, 23.9)
	Anxiety	2 (3.9)	(0.5, 13.5)
	Insomnia	1 (2.0)	(0.0, 10.4)
	SOC: Renal and urinary disorders	6 (11.8)	(4.4, 23.9)
	SOC: Hepatobiliary disorders	3 (5.9)	(1.2, 16.2)
	SOC: Ear and labyrinth disorders	2 (3.9)	(0.5, 13.5)
	SOC: Reproductive system and breast disorders	2 (3.9)	(0.5, 13.5)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

Subgroup	SOC/Preferred Term	Overall 5.4 mg/kg (N = 184) n (%)	95% CI [a]
Prior pertuzumab in 1st or 2nd line in advanced/metastatic breast cancer No (N = 133)	SOC: Gastrointestinal disorders	126 (94.7)	(89.5, 97.9)
	Nausea	105 (78.9)	(71.0, 85.5)
	Vomiting	60 (45.1)	(36.5, 54.0)
	Constipation	49 (36.8)	(28.6, 45.6)
	Diarrhoea	46 (34.6)	(26.6, 43.3)
	Stomatitis	25 (18.8)	(12.5, 26.5)
	Abdominal pain	22 (16.5)	(10.7, 24.0)
	Dyspepsia	20 (15.0)	(9.4, 22.3)
	Gastrooesophageal reflux disease	14 (10.5)	(5.9, 17.0)
	Abdominal pain upper	13 (9.8)	(5.3, 16.1)
	Haemorrhoids	9 (6.8)	(3.1, 12.5)
	SOC: General disorders and administration site conditions	103 (77.4)	(69.4, 84.2)
	Fatigue	70 (52.6)	(43.8, 61.3)
	Asthenia	20 (15.0)	(9.4, 22.3)
	Oedema peripheral	15 (11.3)	(6.5, 17.9)
	Mucosal inflammation	14 (10.5)	(5.9, 17.0)
	Pyrexia	12 (9.0)	(4.7, 15.2)
	Influenza like illness	10 (7.5)	(3.7, 13.4)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Prior pertuzumab in 1st or 2nd line in advanced/metastatic breast cancer	SOC: Skin and subcutaneous tissue disorders	86 (64.7)	(55.9, 72.7)
	Alopecia	67 (50.4)	(41.6, 59.2)
No (N = 133)	Rash	17 (12.8)	(7.6, 19.7)
	Dry skin	7 (5.3)	(2.1, 10.5)
	Nail disorder	7 (5.3)	(2.1, 10.5)
	SOC: Investigations	77 (57.9)	(49.0, 66.4)
	Neutrophil count decreased	29 (21.8)	(15.1, 29.8)
	White blood cell count decreased	27 (20.3)	(13.8, 28.1)
	Aspartate aminotransferase increased	25 (18.8)	(12.5, 26.5)
	Platelet count decreased	23 (17.3)	(11.3, 24.8)
	Alanine aminotransferase increased	15 (11.3)	(6.5, 17.9)
	Lymphocyte count decreased	14 (10.5)	(5.9, 17.0)
	Blood bilirubin increased	9 (6.8)	(3.1, 12.5)
	Electrocardiogram QT prolonged	9 (6.8)	(3.1, 12.5)
	Blood alkaline phosphatase increased	8 (6.0)	(2.6, 11.5)
	Weight decreased	8 (6.0)	(2.6, 11.5)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Prior pertuzumab in 1st or 2nd line in advanced/metastatic breast cancer	SOC: Respiratory, thoracic and mediastinal disorders	77 (57.9)	(49.0, 66.4)
	Cough	30 (22.6)	(15.8, 30.6)
No (N = 133)	Dyspnoea	24 (18.0)	(11.9, 25.6)
	Epistaxis	20 (15.0)	(9.4, 22.3)
	Pneumonitis	13 (9.8)	(5.3, 16.1)
	Interstitial lung disease	7 (5.3)	(2.1, 10.5)
	SOC: Nervous system disorders	72 (54.1)	(45.3, 62.8)
	Headache	30 (22.6)	(15.8, 30.6)
	Dizziness	15 (11.3)	(6.5, 17.9)
	Peripheral sensory neuropathy	12 (9.0)	(4.7, 15.2)
	Neuropathy peripheral	11 (8.3)	(4.2, 14.3)
	Dysgeusia	9 (6.8)	(3.1, 12.5)
	SOC: Infections and infestations	71 (53.4)	(44.5, 62.1)
	Urinary tract infection	18 (13.5)	(8.2, 20.5)
	Nasopharyngitis	15 (11.3)	(6.5, 17.9)
	Upper respiratory tract infection	15 (11.3)	(6.5, 17.9)
	Pneumonia	8 (6.0)	(2.6, 11.5)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Prior pertuzumab in 1st or 2nd line in advanced/metastatic breast cancer No (N = 133)	SOC: Blood and lymphatic system disorders	62 (46.6)	(37.9, 55.5)
	Anaemia	44 (33.1)	(25.2, 41.8)
	Neutropenia	22 (16.5)	(10.7, 24.0)
	Thrombocytopenia	8 (6.0)	(2.6, 11.5)
	Lymphopenia	6 (4.5)	(1.7, 9.6)
	SOC: Metabolism and nutrition disorders	60 (45.1)	(36.5, 54.0)
	Decreased appetite	46 (34.6)	(26.6, 43.3)
	Hypokalaemia	16 (12.0)	(7.0, 18.8)
	SOC: Musculoskeletal and connective tissue disorders	53 (39.8)	(31.5, 48.7)
	Arthralgia	19 (14.3)	(8.8, 21.4)
	Myalgia	16 (12.0)	(7.0, 18.8)
	Back pain	15 (11.3)	(6.5, 17.9)
	Muscle spasms	11 (8.3)	(4.2, 14.3)
	Pain in extremity	8 (6.0)	(2.6, 11.5)
	SOC: Eye disorders	45 (33.8)	(25.9, 42.5)
	Dry eye	14 (10.5)	(5.9, 17.0)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Prior pertuzumab in 1st or 2nd line in advanced/metastatic breast cancer No (N = 133)	SOC: Psychiatric disorders	22 (16.5)	(10.7, 24.0)
	Insomnia	12 (9.0)	(4.7, 15.2)
	Anxiety	10 (7.5)	(3.7, 13.4)
	SOC: Vascular disorders	20 (15.0)	(9.4, 22.3)
	SOC: Ear and labyrinth disorders	17 (12.8)	(7.6, 19.7)
	SOC: Injury, poisoning and procedural complications	17 (12.8)	(7.6, 19.7)
	SOC: Cardiac disorders	16 (12.0)	(7.0, 18.8)
	SOC: Renal and urinary disorders	13 (9.8)	(5.3, 16.1)
	SOC: Reproductive system and breast disorders	10 (7.5)	(3.7, 13.4)
	SOC: Hepatobiliary disorders	7 (5.3)	(2.1, 10.5)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Renal impairment at baseline	SOC: Gastrointestinal disorders	86 (95.6)	(89.0, 98.8)
Within Normal Range (N = 90)	Nausea	74 (82.2)	(72.7, 89.5)
	Vomiting	47 (52.2)	(41.4, 62.9)
	Diarrhoea	30 (33.3)	(23.7, 44.1)
	Constipation	29 (32.2)	(22.8, 42.9)
	Dyspepsia	16 (17.8)	(10.5, 27.3)
	Abdominal pain	13 (14.4)	(7.9, 23.4)
	Stomatitis	11 (12.2)	(6.3, 20.8)
	Gastrooesophageal reflux disease	10 (11.1)	(5.5, 19.5)
	Abdominal pain upper	9 (10.0)	(4.7, 18.1)
	Haemorrhoids	8 (8.9)	(3.9, 16.8)
	SOC: General disorders and administration site conditions	70 (77.8)	(67.8, 85.9)
	Fatigue	46 (51.1)	(40.3, 61.8)
	Asthenia	14 (15.6)	(8.8, 24.7)
	Mucosal inflammation	9 (10.0)	(4.7, 18.1)
	Pyrexia	9 (10.0)	(4.7, 18.1)
	Oedema peripheral	7 (7.8)	(3.2, 15.4)
	Influenza like illness	5 (5.6)	(1.8, 12.5)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Renal impairment at baseline	SOC: Skin and subcutaneous tissue disorders	57 (63.3)	(52.5, 73.2)
Within Normal Range (N = 90)	Alopecia	41 (45.6)	(35.0, 56.4)
	Rash	10 (11.1)	(5.5, 19.5)
	Dry skin	6 (6.7)	(2.5, 13.9)
	Nail disorder	2 (2.2)	(0.3, 7.8)
	SOC: Infections and infestations	50 (55.6)	(44.7, 66.0)
	Upper respiratory tract infection	16 (17.8)	(10.5, 27.3)
	Nasopharyngitis	11 (12.2)	(6.3, 20.8)
	Urinary tract infection	9 (10.0)	(4.7, 18.1)
	Pneumonia	4 (4.4)	(1.2, 11.0)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Renal impairment at baseline	SOC: Investigations	50 (55.6)	(44.7, 66.0)
Within Normal Range (N = 90)	Neutrophil count decreased	19 (21.1)	(13.2, 31.0)
	Aspartate aminotransferase increased	15 (16.7)	(9.6, 26.0)
	Platelet count decreased	15 (16.7)	(9.6, 26.0)
	White blood cell count decreased	13 (14.4)	(7.9, 23.4)
	Blood bilirubin increased	11 (12.2)	(6.3, 20.8)
	Lymphocyte count decreased	9 (10.0)	(4.7, 18.1)
	Alanine aminotransferase increased	8 (8.9)	(3.9, 16.8)
	Blood alkaline phosphatase increased	7 (7.8)	(3.2, 15.4)
	Electrocardiogram QT prolonged	4 (4.4)	(1.2, 11.0)
	Weight decreased	3 (3.3)	(0.7, 9.4)
	SOC: Respiratory, thoracic and mediastinal disorders	48 (53.3)	(42.5, 63.9)
	Cough	22 (24.4)	(16.0, 34.6)
	Dyspnoea	14 (15.6)	(8.8, 24.7)
	Epistaxis	12 (13.3)	(7.1, 22.1)
	Pneumonitis	6 (6.7)	(2.5, 13.9)
	Interstitial lung disease	4 (4.4)	(1.2, 11.0)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Renal impairment at baseline	SOC: Nervous system disorders	47 (52.2)	(41.4, 62.9)
Within Normal Range (N = 90)	Headache	21 (23.3)	(15.1, 33.4)
	Dizziness	8 (8.9)	(3.9, 16.8)
	Peripheral sensory neuropathy	8 (8.9)	(3.9, 16.8)
	Dysgeusia	7 (7.8)	(3.2, 15.4)
	Neuropathy peripheral	6 (6.7)	(2.5, 13.9)
	SOC: Metabolism and nutrition disorders	39 (43.3)	(32.9, 54.2)
	Decreased appetite	24 (26.7)	(17.9, 37.0)
	Hypokalaemia	8 (8.9)	(3.9, 16.8)
	SOC: Musculoskeletal and connective tissue disorders	37 (41.1)	(30.8, 52.0)
	Arthralgia	16 (17.8)	(10.5, 27.3)
	Myalgia	10 (11.1)	(5.5, 19.5)
	Muscle spasms	8 (8.9)	(3.9, 16.8)
	Back pain	7 (7.8)	(3.2, 15.4)
	Pain in extremity	6 (6.7)	(2.5, 13.9)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Renal impairment at baseline	SOC: Blood and lymphatic system disorders	31 (34.4)	(24.7, 45.2)
Within Normal Range (N = 90)	Anaemia	23 (25.6)	(16.9, 35.8)
	Neutropenia	12 (13.3)	(7.1, 22.1)
	Thrombocytopenia	7 (7.8)	(3.2, 15.4)
	Lymphopenia	5 (5.6)	(1.8, 12.5)
	SOC: Eye disorders	31 (34.4)	(24.7, 45.2)
	Dry eye	13 (14.4)	(7.9, 23.4)
	SOC: Psychiatric disorders	18 (20.0)	(12.3, 29.8)
	Anxiety	7 (7.8)	(3.2, 15.4)
	Insomnia	6 (6.7)	(2.5, 13.9)
	SOC: Vascular disorders	14 (15.6)	(8.8, 24.7)
	SOC: Injury, poisoning and procedural complications	12 (13.3)	(7.1, 22.1)
	SOC: Renal and urinary disorders	10 (11.1)	(5.5, 19.5)
	SOC: Ear and labyrinth disorders	8 (8.9)	(3.9, 16.8)
	SOC: Reproductive system and breast disorders	8 (8.9)	(3.9, 16.8)
	SOC: Cardiac disorders	7 (7.8)	(3.2, 15.4)
	SOC: Hepatobiliary disorders	3 (3.3)	(0.7, 9.4)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

Subgroup	SOC/Preferred Term	Overall 5.4 mg/kg (N = 184) n (%)	95% CI [a]
Renal impairment at baseline	SOC: Gastrointestinal disorders	66 (95.7)	(87.8, 99.1)
Mild Impairment (N = 69)	Nausea	54 (78.3)	(66.7, 87.3)
	Vomiting	31 (44.9)	(32.9, 57.4)
	Constipation	28 (40.6)	(28.9, 53.1)
	Diarrhoea	21 (30.4)	(19.9, 42.7)
	Dyspepsia	14 (20.3)	(11.6, 31.7)
	Abdominal pain	12 (17.4)	(9.3, 28.4)
	Stomatitis	11 (15.9)	(8.2, 26.7)
	Abdominal pain upper	6 (8.7)	(3.3, 18.0)
	Gastrooesophageal reflux disease	6 (8.7)	(3.3, 18.0)
	Haemorrhoids	3 (4.3)	(0.9, 12.2)
	SOC: General disorders and administration site conditions	49 (71.0)	(58.8, 81.3)
	Fatigue	33 (47.8)	(35.6, 60.2)
	Asthenia	8 (11.6)	(5.1, 21.6)
	Oedema peripheral	8 (11.6)	(5.1, 21.6)
	Influenza like illness	7 (10.1)	(4.2, 19.8)
	Pyrexia	5 (7.2)	(2.4, 16.1)
	Mucosal inflammation	4 (5.8)	(1.6, 14.2)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Renal impairment at baseline	SOC: Skin and subcutaneous tissue disorders	45 (65.2)	(52.8, 76.3)
Mild Impairment (N = 69)	Alopecia	35 (50.7)	(38.4, 63.0)
	Nail disorder	7 (10.1)	(4.2, 19.8)
	Rash	7 (10.1)	(4.2, 19.8)
	Dry skin	3 (4.3)	(0.9, 12.2)
	SOC: Investigations	42 (60.9)	(48.4, 72.4)
	Neutrophil count decreased	16 (23.2)	(13.9, 34.9)
	White blood cell count decreased	15 (21.7)	(12.7, 33.3)
	Aspartate aminotransferase increased	13 (18.8)	(10.4, 30.1)
	Alanine aminotransferase increased	11 (15.9)	(8.2, 26.7)
	Platelet count decreased	9 (13.0)	(6.1, 23.3)
	Weight decreased	9 (13.0)	(6.1, 23.3)
	Blood bilirubin increased	4 (5.8)	(1.6, 14.2)
	Lymphocyte count decreased	4 (5.8)	(1.6, 14.2)
	Blood alkaline phosphatase increased	3 (4.3)	(0.9, 12.2)
	Electrocardiogram QT prolonged	3 (4.3)	(0.9, 12.2)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

Subgroup	SOC/Preferred Term	Overall 5.4 mg/kg (N = 184) n (%)	95% CI [a]
Renal impairment at baseline	SOC: Infections and infestations	39 (56.5)	(44.0, 68.4)
Mild Impairment (N = 69)	Urinary tract infection	10 (14.5)	(7.2, 25.0)
	Nasopharyngitis	8 (11.6)	(5.1, 21.6)
	Pneumonia	5 (7.2)	(2.4, 16.1)
	Upper respiratory tract infection	5 (7.2)	(2.4, 16.1)
	SOC: Respiratory, thoracic and mediastinal disorders	39 (56.5)	(44.0, 68.4)
	Cough	17 (24.6)	(15.1, 36.5)
	Dyspnoea	13 (18.8)	(10.4, 30.1)
	Epistaxis	9 (13.0)	(6.1, 23.3)
	Pneumonitis	5 (7.2)	(2.4, 16.1)
	Interstitial lung disease	4 (5.8)	(1.6, 14.2)
	SOC: Blood and lymphatic system disorders	36 (52.2)	(39.8, 64.4)
	Anaemia	23 (33.3)	(22.4, 45.7)
	Neutropenia	13 (18.8)	(10.4, 30.1)
	Thrombocytopenia	7 (10.1)	(4.2, 19.8)
	Lymphopenia	5 (7.2)	(2.4, 16.1)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

Subgroup	SOC/Preferred Term	Overall 5.4 mg/kg (N = 184) n (%)	95% CI [a]
Renal impairment at baseline	SOC: Nervous system disorders	34 (49.3)	(37.0, 61.6)
Mild Impairment (N = 69)	Headache	15 (21.7)	(12.7, 33.3)
	Dizziness	10 (14.5)	(7.2, 25.0)
	Dysgeusia	6 (8.7)	(3.3, 18.0)
	Neuropathy peripheral	6 (8.7)	(3.3, 18.0)
	Peripheral sensory neuropathy	5 (7.2)	(2.4, 16.1)
	SOC: Metabolism and nutrition disorders	31 (44.9)	(32.9, 57.4)
	Decreased appetite	24 (34.8)	(23.7, 47.2)
	Hypokalaemia	11 (15.9)	(8.2, 26.7)
	SOC: Musculoskeletal and connective tissue disorders	28 (40.6)	(28.9, 53.1)
	Back pain	11 (15.9)	(8.2, 26.7)
	Arthralgia	7 (10.1)	(4.2, 19.8)
	Muscle spasms	7 (10.1)	(4.2, 19.8)
	Myalgia	6 (8.7)	(3.3, 18.0)
	Pain in extremity	5 (7.2)	(2.4, 16.1)
	SOC: Eye disorders	22 (31.9)	(21.2, 44.2)
	Dry eye	7 (10.1)	(4.2, 19.8)
	SOC: Vascular disorders	12 (17.4)	(9.3, 28.4)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Renal impairment at baseline	SOC: Injury, poisoning and procedural complications	11 (15.9)	(8.2, 26.7)
Mild Impairment (N = 69)	SOC: Cardiac disorders	10 (14.5)	(7.2, 25.0)
	SOC: Renal and urinary disorders	8 (11.6)	(5.1, 21.6)
	SOC: Ear and labyrinth disorders	7 (10.1)	(4.2, 19.8)
	SOC: Hepatobiliary disorders	7 (10.1)	(4.2, 19.8)
	SOC: Psychiatric disorders	6 (8.7)	(3.3, 18.0)
	Anxiety	3 (4.3)	(0.9, 12.2)
	Insomnia	3 (4.3)	(0.9, 12.2)
	SOC: Reproductive system and breast disorders	4 (5.8)	(1.6, 14.2)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Renal impairment at baseline	SOC: Gastrointestinal disorders	21 (84.0)	(63.9, 95.5)
Moderate Impairment (N = 25)	Nausea	16 (64.0)	(42.5, 82.0)
	Vomiting	10 (40.0)	(21.1, 61.3)
	Constipation	8 (32.0)	(14.9, 53.5)
	Diarrhoea	7 (28.0)	(12.1, 49.4)
	Stomatitis	7 (28.0)	(12.1, 49.4)
	Gastrooesophageal reflux disease	2 (8.0)	(1.0, 26.0)
	Abdominal pain upper	1 (4.0)	(0.1, 20.4)
	Dyspepsia	1 (4.0)	(0.1, 20.4)
	SOC: General disorders and administration site conditions	18 (72.0)	(50.6, 87.9)
	Fatigue	13 (52.0)	(31.3, 72.2)
	Asthenia	4 (16.0)	(4.5, 36.1)
	Mucosal inflammation	3 (12.0)	(2.5, 31.2)
	Pyrexia	3 (12.0)	(2.5, 31.2)
	Oedema peripheral	2 (8.0)	(1.0, 26.0)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Renal impairment at baseline	SOC: Respiratory, thoracic and mediastinal disorders	18 (72.0)	(50.6, 87.9)
Moderate Impairment (N = 25)	Cough	6 (24.0)	(9.4, 45.1)
	Epistaxis	5 (20.0)	(6.8, 40.7)
	Pneumonitis	5 (20.0)	(6.8, 40.7)
	Dyspnoea	4 (16.0)	(4.5, 36.1)
	Interstitial lung disease	3 (12.0)	(2.5, 31.2)
	SOC: Investigations	14 (56.0)	(34.9, 75.6)
	White blood cell count decreased	8 (32.0)	(14.9, 53.5)
	Lymphocyte count decreased	6 (24.0)	(9.4, 45.1)
	Neutrophil count decreased	6 (24.0)	(9.4, 45.1)
	Platelet count decreased	6 (24.0)	(9.4, 45.1)
	Aspartate aminotransferase increased	5 (20.0)	(6.8, 40.7)
	Electrocardiogram QT prolonged	3 (12.0)	(2.5, 31.2)
	Weight decreased	3 (12.0)	(2.5, 31.2)
	Alanine aminotransferase increased	2 (8.0)	(1.0, 26.0)
	Blood alkaline phosphatase increased	1 (4.0)	(0.1, 20.4)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Renal impairment at baseline	SOC: Metabolism and nutrition disorders	14 (56.0)	(34.9, 75.6)
Moderate Impairment (N = 25)	Decreased appetite	11 (44.0)	(24.4, 65.1)
	Hypokalaemia	3 (12.0)	(2.5, 31.2)
	SOC: Skin and subcutaneous tissue disorders	14 (56.0)	(34.9, 75.6)
	Alopecia	13 (52.0)	(31.3, 72.2)
	Dry skin	2 (8.0)	(1.0, 26.0)
	Rash	2 (8.0)	(1.0, 26.0)
	Nail disorder	1 (4.0)	(0.1, 20.4)
	SOC: Blood and lymphatic system disorders	13 (52.0)	(31.3, 72.2)
	Anaemia	12 (48.0)	(27.8, 68.7)
	Neutropenia	2 (8.0)	(1.0, 26.0)
	Lymphopenia	1 (4.0)	(0.1, 20.4)
	SOC: Infections and infestations	10 (40.0)	(21.1, 61.3)
	Upper respiratory tract infection	3 (12.0)	(2.5, 31.2)
	Urinary tract infection	3 (12.0)	(2.5, 31.2)
	Nasopharyngitis	1 (4.0)	(0.1, 20.4)
	Pneumonia	1 (4.0)	(0.1, 20.4)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Renal impairment at baseline	SOC: Nervous system disorders	10 (40.0)	(21.1, 61.3)
Moderate Impairment (N = 25)	Headache	4 (16.0)	(4.5, 36.1)
	Peripheral sensory neuropathy	3 (12.0)	(2.5, 31.2)
	Dizziness	1 (4.0)	(0.1, 20.4)
	SOC: Eye disorders	8 (32.0)	(14.9, 53.5)
	Dry eye	1 (4.0)	(0.1, 20.4)
	SOC: Cardiac disorders	5 (20.0)	(6.8, 40.7)
	SOC: Musculoskeletal and connective tissue disorders	5 (20.0)	(6.8, 40.7)
	Back pain	2 (8.0)	(1.0, 26.0)
	Myalgia	2 (8.0)	(1.0, 26.0)
	Arthralgia	1 (4.0)	(0.1, 20.4)
	Pain in extremity	1 (4.0)	(0.1, 20.4)
	SOC: Ear and labyrinth disorders	4 (16.0)	(4.5, 36.1)
	SOC: Psychiatric disorders	4 (16.0)	(4.5, 36.1)
	Insomnia	4 (16.0)	(4.5, 36.1)
	Anxiety	2 (8.0)	(1.0, 26.0)
	SOC: Injury, poisoning and procedural complications	3 (12.0)	(2.5, 31.2)
	SOC: Renal and urinary disorders	1 (4.0)	(0.1, 20.4)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Renal impairment at baseline	SOC: Vascular disorders	1 (4.0)	(0.1, 20.4)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

Subgroup	SOC/Preferred Term	Overall 5.4 mg/kg (N = 184) n (%)	95% CI [a]
Hepatic impairment at baseline	SOC: Gastrointestinal disorders	101 (96.2)	(90.5, 99.0)
Within Normal Range (N = 105)	Nausea	83 (79.0)	(70.0, 86.4)
	Vomiting	57 (54.3)	(44.3, 64.0)
	Diarrhoea	37 (35.2)	(26.2, 45.2)
	Constipation	32 (30.5)	(21.9, 40.2)
	Abdominal pain	18 (17.1)	(10.5, 25.7)
	Stomatitis	18 (17.1)	(10.5, 25.7)
	Dyspepsia	17 (16.2)	(9.7, 24.7)
	Abdominal pain upper	12 (11.4)	(6.0, 19.1)
	Gastrooesophageal reflux disease	10 (9.5)	(4.7, 16.8)
	Haemorrhoids	6 (5.7)	(2.1, 12.0)
	SOC: General disorders and administration site conditions	79 (75.2)	(65.9, 83.1)
	Fatigue	54 (51.4)	(41.5, 61.3)
	Asthenia	16 (15.2)	(9.0, 23.6)
	Pyrexia	10 (9.5)	(4.7, 16.8)
	Influenza like illness	8 (7.6)	(3.3, 14.5)
	Oedema peripheral	8 (7.6)	(3.3, 14.5)
	Mucosal inflammation	7 (6.7)	(2.7, 13.3)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Hepatic impairment at baseline	SOC: Respiratory, thoracic and mediastinal disorders	67 (63.8)	(53.9, 73.0)
Within Normal Range (N = 105)	Cough	30 (28.6)	(20.2, 38.2)
	Dyspnoea	20 (19.0)	(12.0, 27.9)
	Epistaxis	14 (13.3)	(7.5, 21.4)
	Pneumonitis	11 (10.5)	(5.3, 18.0)
	Interstitial lung disease	9 (8.6)	(4.0, 15.6)
	SOC: Skin and subcutaneous tissue disorders	66 (62.9)	(52.9, 72.1)
	Alopecia	52 (49.5)	(39.6, 59.5)
	Rash	10 (9.5)	(4.7, 16.8)
	Nail disorder	6 (5.7)	(2.1, 12.0)
	Dry skin	3 (2.9)	(0.6, 8.1)
	SOC: Infections and infestations	60 (57.1)	(47.1, 66.8)
	Nasopharyngitis	16 (15.2)	(9.0, 23.6)
	Urinary tract infection	16 (15.2)	(9.0, 23.6)
	Upper respiratory tract infection	14 (13.3)	(7.5, 21.4)
	Pneumonia	8 (7.6)	(3.3, 14.5)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Hepatic impairment at baseline	SOC: Investigations	60 (57.1)	(47.1, 66.8)
Within Normal Range (N = 105)	Neutrophil count decreased	24 (22.9)	(15.2, 32.1)
	White blood cell count decreased	22 (21.0)	(13.6, 30.0)
	Aspartate aminotransferase increased	20 (19.0)	(12.0, 27.9)
	Platelet count decreased	15 (14.3)	(8.2, 22.5)
	Alanine aminotransferase increased	13 (12.4)	(6.8, 20.2)
	Lymphocyte count decreased	11 (10.5)	(5.3, 18.0)
	Electrocardiogram QT prolonged	8 (7.6)	(3.3, 14.5)
	Blood bilirubin increased	7 (6.7)	(2.7, 13.3)
	Weight decreased	7 (6.7)	(2.7, 13.3)
	Blood alkaline phosphatase increased	6 (5.7)	(2.1, 12.0)
	SOC: Nervous system disorders	50 (47.6)	(37.8, 57.6)
	Headache	25 (23.8)	(16.0, 33.1)
	Dizziness	12 (11.4)	(6.0, 19.1)
	Neuropathy peripheral	10 (9.5)	(4.7, 16.8)
	Dysgeusia	8 (7.6)	(3.3, 14.5)
	Peripheral sensory neuropathy	5 (4.8)	(1.6, 10.8)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

Subgroup	SOC/Preferred Term	Overall 5.4 mg/kg (N = 184) n (%)	95% CI [a]
Hepatic impairment at baseline	SOC: Blood and lymphatic system disorders	49 (46.7)	(36.9, 56.7)
Within Normal Range (N = 105)	Anaemia	35 (33.3)	(24.4, 43.2)
	Neutropenia	16 (15.2)	(9.0, 23.6)
	Thrombocytopenia	8 (7.6)	(3.3, 14.5)
	Lymphopenia	7 (6.7)	(2.7, 13.3)
	SOC: Metabolism and nutrition disorders	44 (41.9)	(32.3, 51.9)
	Decreased appetite	29 (27.6)	(19.3, 37.2)
	Hypokalaemia	12 (11.4)	(6.0, 19.1)
	SOC: Musculoskeletal and connective tissue disorders	39 (37.1)	(27.9, 47.1)
	Arthralgia	14 (13.3)	(7.5, 21.4)
	Muscle spasms	13 (12.4)	(6.8, 20.2)
	Back pain	10 (9.5)	(4.7, 16.8)
	Myalgia	8 (7.6)	(3.3, 14.5)
	Pain in extremity	7 (6.7)	(2.7, 13.3)
	SOC: Eye disorders	33 (31.4)	(22.7, 41.2)
	Dry eye	9 (8.6)	(4.0, 15.6)
	SOC: Vascular disorders	20 (19.0)	(12.0, 27.9)
	SOC: Injury, poisoning and procedural complications	17 (16.2)	(9.7, 24.7)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Hepatic impairment at baseline	SOC: Ear and labyrinth disorders	14 (13.3)	(7.5, 21.4)
Within Normal Range (N = 105)	SOC: Psychiatric disorders	13 (12.4)	(6.8, 20.2)
	Insomnia	6 (5.7)	(2.1, 12.0)
	Anxiety	3 (2.9)	(0.6, 8.1)
	SOC: Cardiac disorders	12 (11.4)	(6.0, 19.1)
	SOC: Renal and urinary disorders	11 (10.5)	(5.3, 18.0)
	SOC: Reproductive system and breast disorders	9 (8.6)	(4.0, 15.6)
	SOC: Hepatobiliary disorders	4 (3.8)	(1.0, 9.5)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

Subgroup	SOC/Preferred Term	Overall 5.4 mg/kg (N = 184) n (%)	95% CI [a]
Hepatic impairment at baseline	SOC: Gastrointestinal disorders	69 (90.8)	(81.9, 96.2)
Mild Impairment (N = 76)	Nausea	58 (76.3)	(65.2, 85.3)
	Vomiting	31 (40.8)	(29.6, 52.7)
	Constipation	30 (39.5)	(28.4, 51.4)
	Diarrhoea	21 (27.6)	(18.0, 39.1)
	Dyspepsia	13 (17.1)	(9.4, 27.5)
	Stomatitis	11 (14.5)	(7.5, 24.4)
	Gastrooesophageal reflux disease	8 (10.5)	(4.7, 19.7)
	Abdominal pain	7 (9.2)	(3.8, 18.1)
	Abdominal pain upper	4 (5.3)	(1.5, 12.9)
	Haemorrhoids	4 (5.3)	(1.5, 12.9)
	SOC: General disorders and administration site conditions	56 (73.7)	(62.3, 83.1)
	Fatigue	38 (50.0)	(38.3, 61.7)
	Mucosal inflammation	9 (11.8)	(5.6, 21.3)
	Oedema peripheral	9 (11.8)	(5.6, 21.3)
	Asthenia	8 (10.5)	(4.7, 19.7)
	Pyrexia	7 (9.2)	(3.8, 18.1)
	Influenza like illness	4 (5.3)	(1.5, 12.9)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Hepatic impairment at baseline	SOC: Skin and subcutaneous tissue disorders	49 (64.5)	(52.7, 75.1)
Mild Impairment (N = 76)	Alopecia	36 (47.4)	(35.8, 59.2)
	Rash	9 (11.8)	(5.6, 21.3)
	Dry skin	8 (10.5)	(4.7, 19.7)
	Nail disorder	4 (5.3)	(1.5, 12.9)
	SOC: Investigations	44 (57.9)	(46.0, 69.1)
	Neutrophil count decreased	17 (22.4)	(13.6, 33.4)
	Platelet count decreased	15 (19.7)	(11.5, 30.5)
	White blood cell count decreased	14 (18.4)	(10.5, 29.0)
	Aspartate aminotransferase increased	13 (17.1)	(9.4, 27.5)
	Alanine aminotransferase increased	8 (10.5)	(4.7, 19.7)
	Lymphocyte count decreased	8 (10.5)	(4.7, 19.7)
	Blood bilirubin increased	7 (9.2)	(3.8, 18.1)
	Weight decreased	7 (9.2)	(3.8, 18.1)
	Blood alkaline phosphatase increased	5 (6.6)	(2.2, 14.7)
	Electrocardiogram QT prolonged	2 (2.6)	(0.3, 9.2)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Hepatic impairment at baseline	SOC: Nervous system disorders	40 (52.6)	(40.8, 64.2)
Mild Impairment (N = 76)	Headache	14 (18.4)	(10.5, 29.0)
	Peripheral sensory neuropathy	10 (13.2)	(6.5, 22.9)
	Dizziness	7 (9.2)	(3.8, 18.1)
	Dysgeusia	5 (6.6)	(2.2, 14.7)
	Neuropathy peripheral	2 (2.6)	(0.3, 9.2)
	SOC: Infections and infestations	39 (51.3)	(39.6, 63.0)
	Upper respiratory tract infection	10 (13.2)	(6.5, 22.9)
	Urinary tract infection	6 (7.9)	(3.0, 16.4)
	Nasopharyngitis	4 (5.3)	(1.5, 12.9)
	Pneumonia	2 (2.6)	(0.3, 9.2)
	SOC: Metabolism and nutrition disorders	39 (51.3)	(39.6, 63.0)
	Decreased appetite	30 (39.5)	(28.4, 51.4)
	Hypokalaemia	9 (11.8)	(5.6, 21.3)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Hepatic impairment at baseline	SOC: Respiratory, thoracic and mediastinal disorders	37 (48.7)	(37.0, 60.4)
Mild Impairment (N = 76)	Cough	15 (19.7)	(11.5, 30.5)
	Dyspnoea	11 (14.5)	(7.5, 24.4)
	Epistaxis	11 (14.5)	(7.5, 24.4)
	Pneumonitis	5 (6.6)	(2.2, 14.7)
	Interstitial lung disease	2 (2.6)	(0.3, 9.2)
	SOC: Blood and lymphatic system disorders	30 (39.5)	(28.4, 51.4)
	Anaemia	22 (28.9)	(19.1, 40.5)
	Neutropenia	11 (14.5)	(7.5, 24.4)
	Thrombocytopenia	5 (6.6)	(2.2, 14.7)
	Lymphopenia	3 (3.9)	(0.8, 11.1)
	SOC: Musculoskeletal and connective tissue disorders	30 (39.5)	(28.4, 51.4)
	Arthralgia	10 (13.2)	(6.5, 22.9)
	Back pain	10 (13.2)	(6.5, 22.9)
	Myalgia	10 (13.2)	(6.5, 22.9)
	Pain in extremity	5 (6.6)	(2.2, 14.7)
	Muscle spasms	2 (2.6)	(0.3, 9.2)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Hepatic impairment at baseline	SOC: Eye disorders	27 (35.5)	(24.9, 47.3)
Mild Impairment (N = 76)	Dry eye	12 (15.8)	(8.4, 26.0)
	SOC: Psychiatric disorders	14 (18.4)	(10.5, 29.0)
	Anxiety	9 (11.8)	(5.6, 21.3)
	Insomnia	6 (7.9)	(3.0, 16.4)
	SOC: Cardiac disorders	10 (13.2)	(6.5, 22.9)
	SOC: Injury, poisoning and procedural complications	8 (10.5)	(4.7, 19.7)
	SOC: Renal and urinary disorders	7 (9.2)	(3.8, 18.1)
	SOC: Vascular disorders	7 (9.2)	(3.8, 18.1)
	SOC: Ear and labyrinth disorders	5 (6.6)	(2.2, 14.7)
	SOC: Hepatobiliary disorders	5 (6.6)	(2.2, 14.7)
	SOC: Reproductive system and breast disorders	3 (3.9)	(0.8, 11.1)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Best response to T-DM1 therapy	SOC: Gastrointestinal disorders	71 (89.9)	(81.0, 95.5)
CR/PR/SD (N = 79)	Nausea	62 (78.5)	(67.8, 86.9)
	Constipation	32 (40.5)	(29.6, 52.1)
	Vomiting	29 (36.7)	(26.1, 48.3)
	Diarrhoea	18 (22.8)	(14.1, 33.6)
	Dyspepsia	14 (17.7)	(10.0, 27.9)
	Stomatitis	14 (17.7)	(10.0, 27.9)
	Abdominal pain	8 (10.1)	(4.5, 19.0)
	Gastrooesophageal reflux disease	7 (8.9)	(3.6, 17.4)
	Abdominal pain upper	6 (7.6)	(2.8, 15.8)
	Haemorrhoids	4 (5.1)	(1.4, 12.5)
	SOC: General disorders and administration site conditions	56 (70.9)	(59.6, 80.6)
	Fatigue	40 (50.6)	(39.1, 62.1)
	Mucosal inflammation	9 (11.4)	(5.3, 20.5)
	Asthenia	8 (10.1)	(4.5, 19.0)
	Oedema peripheral	8 (10.1)	(4.5, 19.0)
	Pyrexia	8 (10.1)	(4.5, 19.0)
	Influenza like illness	4 (5.1)	(1.4, 12.5)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Best response to T-DM1 therapy	SOC: Skin and subcutaneous tissue disorders	54 (68.4)	(56.9, 78.4)
CR/PR/SD (N = 79)	Alopecia	38 (48.1)	(36.7, 59.6)
	Dry skin	7 (8.9)	(3.6, 17.4)
	Rash	6 (7.6)	(2.8, 15.8)
	Nail disorder	3 (3.8)	(0.8, 10.7)
	SOC: Infections and infestations	46 (58.2)	(46.6, 69.2)
	Upper respiratory tract infection	10 (12.7)	(6.2, 22.0)
	Urinary tract infection	9 (11.4)	(5.3, 20.5)
	Nasopharyngitis	8 (10.1)	(4.5, 19.0)
	Pneumonia	7 (8.9)	(3.6, 17.4)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Best response to T-DM1 therapy	SOC: Investigations	46 (58.2)	(46.6, 69.2)
CR/PR/SD (N = 79)	Neutrophil count decreased	20 (25.3)	(16.2, 36.4)
	Platelet count decreased	19 (24.1)	(15.1, 35.0)
	White blood cell count decreased	17 (21.5)	(13.1, 32.2)
	Aspartate aminotransferase increased	16 (20.3)	(12.0, 30.8)
	Lymphocyte count decreased	11 (13.9)	(7.2, 23.5)
	Alanine aminotransferase increased	10 (12.7)	(6.2, 22.0)
	Blood bilirubin increased	6 (7.6)	(2.8, 15.8)
	Blood alkaline phosphatase increased	5 (6.3)	(2.1, 14.2)
	Weight decreased	5 (6.3)	(2.1, 14.2)
	Electrocardiogram QT prolonged	3 (3.8)	(0.8, 10.7)
	SOC: Respiratory, thoracic and mediastinal disorders	46 (58.2)	(46.6, 69.2)
	Cough	16 (20.3)	(12.0, 30.8)
	Dyspnoea	13 (16.5)	(9.1, 26.5)
	Epistaxis	12 (15.2)	(8.1, 25.0)
	Pneumonitis	8 (10.1)	(4.5, 19.0)
	Interstitial lung disease	3 (3.8)	(0.8, 10.7)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Best response to T-DM1 therapy CR/PR/SD (N = 79)	SOC: Nervous system disorders	42 (53.2)	(41.6, 64.5)
	Headache	19 (24.1)	(15.1, 35.0)
	Peripheral sensory neuropathy	13 (16.5)	(9.1, 26.5)
	Dizziness	6 (7.6)	(2.8, 15.8)
	Neuropathy peripheral	6 (7.6)	(2.8, 15.8)
	Dysgeusia	5 (6.3)	(2.1, 14.2)
	SOC: Blood and lymphatic system disorders	37 (46.8)	(35.5, 58.4)
	Anaemia	26 (32.9)	(22.7, 44.4)
	Neutropenia	13 (16.5)	(9.1, 26.5)
	Thrombocytopenia	6 (7.6)	(2.8, 15.8)
	Lymphopenia	4 (5.1)	(1.4, 12.5)
	SOC: Metabolism and nutrition disorders	37 (46.8)	(35.5, 58.4)
	Decreased appetite	24 (30.4)	(20.5, 41.8)
	Hypokalaemia	9 (11.4)	(5.3, 20.5)
	SOC: Eye disorders	28 (35.4)	(25.0, 47.0)
	Dry eye	8 (10.1)	(4.5, 19.0)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Best response to T-DM1 therapy	SOC: Musculoskeletal and connective tissue disorders	27 (34.2)	(23.9, 45.7)
CR/PR/SD (N = 79)	Myalgia	10 (12.7)	(6.2, 22.0)
	Arthralgia	8 (10.1)	(4.5, 19.0)
	Back pain	5 (6.3)	(2.1, 14.2)
	Muscle spasms	5 (6.3)	(2.1, 14.2)
	Pain in extremity	5 (6.3)	(2.1, 14.2)
	SOC: Injury, poisoning and procedural complications	13 (16.5)	(9.1, 26.5)
	SOC: Cardiac disorders	11 (13.9)	(7.2, 23.5)
	SOC: Psychiatric disorders	11 (13.9)	(7.2, 23.5)
	Insomnia	8 (10.1)	(4.5, 19.0)
	Anxiety	4 (5.1)	(1.4, 12.5)
	SOC: Ear and labyrinth disorders	10 (12.7)	(6.2, 22.0)
	SOC: Vascular disorders	9 (11.4)	(5.3, 20.5)
	SOC: Renal and urinary disorders	8 (10.1)	(4.5, 19.0)
	SOC: Hepatobiliary disorders	3 (3.8)	(0.8, 10.7)
	SOC: Reproductive system and breast disorders	1 (1.3)	(0.0, 6.9)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

Subgroup	SOC/Preferred Term	Overall 5.4 mg/kg (N = 184) n (%)	95% CI [a]
Best response to T-DM1 therapy	SOC: Gastrointestinal disorders	63 (95.5)	(87.3, 99.1)
PD (N = 66)	Nausea	48 (72.7)	(60.4, 83.0)
	Vomiting	39 (59.1)	(46.3, 71.0)
	Diarrhoea	27 (40.9)	(29.0, 53.7)
	Constipation	19 (28.8)	(18.3, 41.3)
	Abdominal pain	14 (21.2)	(12.1, 33.0)
	Stomatitis	11 (16.7)	(8.6, 27.9)
	Dyspepsia	9 (13.6)	(6.4, 24.3)
	Gastrooesophageal reflux disease	8 (12.1)	(5.4, 22.5)
	Abdominal pain upper	6 (9.1)	(3.4, 18.7)
	Haemorrhoids	4 (6.1)	(1.7, 14.8)
	SOC: General disorders and administration site conditions	51 (77.3)	(65.3, 86.7)
	Fatigue	30 (45.5)	(33.1, 58.2)
	Asthenia	14 (21.2)	(12.1, 33.0)
	Pyrexia	8 (12.1)	(5.4, 22.5)
	Influenza like illness	7 (10.6)	(4.4, 20.6)
	Oedema peripheral	6 (9.1)	(3.4, 18.7)
	Mucosal inflammation	4 (6.1)	(1.7, 14.8)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Best response to T-DM1 therapy	SOC: Skin and subcutaneous tissue disorders	46 (69.7)	(57.1, 80.4)
PD (N = 66)	Alopecia	38 (57.6)	(44.8, 69.7)
	Rash	10 (15.2)	(7.5, 26.1)
	Nail disorder	7 (10.6)	(4.4, 20.6)
	Dry skin	3 (4.5)	(0.9, 12.7)
	SOC: Investigations	39 (59.1)	(46.3, 71.0)
	White blood cell count decreased	17 (25.8)	(15.8, 38.0)
	Neutrophil count decreased	16 (24.2)	(14.5, 36.4)
	Aspartate aminotransferase increased	11 (16.7)	(8.6, 27.9)
	Platelet count decreased	8 (12.1)	(5.4, 22.5)
	Alanine aminotransferase increased	7 (10.6)	(4.4, 20.6)
	Weight decreased	7 (10.6)	(4.4, 20.6)
	Blood bilirubin increased	6 (9.1)	(3.4, 18.7)
	Lymphocyte count decreased	6 (9.1)	(3.4, 18.7)
	Electrocardiogram QT prolonged	5 (7.6)	(2.5, 16.8)
	Blood alkaline phosphatase increased	4 (6.1)	(1.7, 14.8)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Best response to T-DM1 therapy	SOC: Respiratory, thoracic and mediastinal disorders	38 (57.6)	(44.8, 69.7)
PD (N = 66)	Cough	18 (27.3)	(17.0, 39.6)
	Epistaxis	12 (18.2)	(9.8, 29.6)
	Dyspnoea	11 (16.7)	(8.6, 27.9)
	Interstitial lung disease	8 (12.1)	(5.4, 22.5)
	Pneumonitis	4 (6.1)	(1.7, 14.8)
	SOC: Nervous system disorders	35 (53.0)	(40.3, 65.4)
	Headache	14 (21.2)	(12.1, 33.0)
	Dizziness	9 (13.6)	(6.4, 24.3)
	Dysgeusia	6 (9.1)	(3.4, 18.7)
	Neuropathy peripheral	5 (7.6)	(2.5, 16.8)
	Peripheral sensory neuropathy	1 (1.5)	(0.0, 8.2)
	SOC: Infections and infestations	32 (48.5)	(36.0, 61.1)
	Urinary tract infection	10 (15.2)	(7.5, 26.1)
	Nasopharyngitis	9 (13.6)	(6.4, 24.3)
	Upper respiratory tract infection	8 (12.1)	(5.4, 22.5)
	Pneumonia	3 (4.5)	(0.9, 12.7)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Best response to T-DM1 therapy	SOC: Metabolism and nutrition disorders	31 (47.0)	(34.6, 59.7)
PD (N = 66)	Decreased appetite	22 (33.3)	(22.2, 46.0)
	Hypokalaemia	10 (15.2)	(7.5, 26.1)
	SOC: Blood and lymphatic system disorders	28 (42.4)	(30.3, 55.2)
	Anaemia	21 (31.8)	(20.9, 44.4)
	Neutropenia	9 (13.6)	(6.4, 24.3)
	Lymphopenia	6 (9.1)	(3.4, 18.7)
	Thrombocytopenia	4 (6.1)	(1.7, 14.8)
	SOC: Musculoskeletal and connective tissue disorders	24 (36.4)	(24.9, 49.1)
	Back pain	9 (13.6)	(6.4, 24.3)
	Arthralgia	8 (12.1)	(5.4, 22.5)
	Muscle spasms	7 (10.6)	(4.4, 20.6)
	Myalgia	4 (6.1)	(1.7, 14.8)
	Pain in extremity	3 (4.5)	(0.9, 12.7)
	SOC: Eye disorders	22 (33.3)	(22.2, 46.0)
	Dry eye	7 (10.6)	(4.4, 20.6)
	SOC: Vascular disorders	13 (19.7)	(10.9, 31.3)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Best response to T-DM1 therapy	SOC: Psychiatric disorders	12 (18.2)	(9.8, 29.6)
PD (N = 66)	Anxiety	5 (7.6)	(2.5, 16.8)
	Insomnia	4 (6.1)	(1.7, 14.8)
	SOC: Injury, poisoning and procedural complications	11 (16.7)	(8.6, 27.9)
	SOC: Renal and urinary disorders	9 (13.6)	(6.4, 24.3)
	SOC: Cardiac disorders	7 (10.6)	(4.4, 20.6)
	SOC: Reproductive system and breast disorders	7 (10.6)	(4.4, 20.6)
	SOC: Ear and labyrinth disorders	5 (7.6)	(2.5, 16.8)
	SOC: Hepatobiliary disorders	5 (7.6)	(2.5, 16.8)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Brain metastases	SOC: Gastrointestinal disorders	22 (91.7)	(73.0, 99.0)
Yes (N = 24)	Nausea	16 (66.7)	(44.7, 84.4)
	Vomiting	11 (45.8)	(25.6, 67.2)
	Diarrhoea	10 (41.7)	(22.1, 63.4)
	Stomatitis	8 (33.3)	(15.6, 55.3)
	Constipation	7 (29.2)	(12.6, 51.1)
	Dyspepsia	4 (16.7)	(4.7, 37.4)
	Abdominal pain	3 (12.5)	(2.7, 32.4)
	Gastrooesophageal reflux disease	2 (8.3)	(1.0, 27.0)
	SOC: General disorders and administration site conditions	18 (75.0)	(53.3, 90.2)
	Fatigue	14 (58.3)	(36.6, 77.9)
	Mucosal inflammation	4 (16.7)	(4.7, 37.4)
	Pyrexia	4 (16.7)	(4.7, 37.4)
	Asthenia	1 (4.2)	(0.1, 21.1)
	Influenza like illness	1 (4.2)	(0.1, 21.1)
	Oedema peripheral	1 (4.2)	(0.1, 21.1)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Brain metastases	SOC: Investigations	17 (70.8)	(48.9, 87.4)
Yes (N = 24)	Aspartate aminotransferase increased	6 (25.0)	(9.8, 46.7)
	Neutrophil count decreased	6 (25.0)	(9.8, 46.7)
	White blood cell count decreased	6 (25.0)	(9.8, 46.7)
	Electrocardiogram QT prolonged	4 (16.7)	(4.7, 37.4)
	Platelet count decreased	4 (16.7)	(4.7, 37.4)
	Weight decreased	4 (16.7)	(4.7, 37.4)
	Blood bilirubin increased	3 (12.5)	(2.7, 32.4)
	Alanine aminotransferase increased	2 (8.3)	(1.0, 27.0)
	Blood alkaline phosphatase increased	2 (8.3)	(1.0, 27.0)
	Lymphocyte count decreased	2 (8.3)	(1.0, 27.0)
	SOC: Infections and infestations	15 (62.5)	(40.6, 81.2)
	Urinary tract infection	6 (25.0)	(9.8, 46.7)
	Upper respiratory tract infection	4 (16.7)	(4.7, 37.4)
	Nasopharyngitis	2 (8.3)	(1.0, 27.0)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Brain metastases	SOC: Skin and subcutaneous tissue disorders	15 (62.5)	(40.6, 81.2)
Yes (N = 24)	Alopecia	13 (54.2)	(32.8, 74.4)
	Nail disorder	2 (8.3)	(1.0, 27.0)
	Rash	2 (8.3)	(1.0, 27.0)
	Dry skin	1 (4.2)	(0.1, 21.1)
	SOC: Nervous system disorders	14 (58.3)	(36.6, 77.9)
	Headache	6 (25.0)	(9.8, 46.7)
	Dizziness	5 (20.8)	(7.1, 42.2)
	Peripheral sensory neuropathy	3 (12.5)	(2.7, 32.4)
	Neuropathy peripheral	2 (8.3)	(1.0, 27.0)
	SOC: Blood and lymphatic system disorders	13 (54.2)	(32.8, 74.4)
	Anaemia	8 (33.3)	(15.6, 55.3)
	Neutropenia	5 (20.8)	(7.1, 42.2)
	Lymphopenia	4 (16.7)	(4.7, 37.4)
	Thrombocytopenia	3 (12.5)	(2.7, 32.4)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

Subgroup	SOC/Preferred Term	Overall 5.4 mg/kg (N = 184) n (%)	95% CI [a]
Brain metastases	SOC: Respiratory, thoracic and mediastinal disorders	13 (54.2)	(32.8, 74.4)
Yes (N = 24)	Cough	6 (25.0)	(9.8, 46.7)
	Epistaxis	4 (16.7)	(4.7, 37.4)
	Interstitial lung disease	3 (12.5)	(2.7, 32.4)
	Pneumonitis	3 (12.5)	(2.7, 32.4)
	Dyspnoea	2 (8.3)	(1.0, 27.0)
	SOC: Metabolism and nutrition disorders	11 (45.8)	(25.6, 67.2)
	Decreased appetite	9 (37.5)	(18.8, 59.4)
	Hypokalaemia	4 (16.7)	(4.7, 37.4)
	SOC: Musculoskeletal and connective tissue disorders	9 (37.5)	(18.8, 59.4)
	Arthralgia	3 (12.5)	(2.7, 32.4)
	Back pain	3 (12.5)	(2.7, 32.4)
	Muscle spasms	3 (12.5)	(2.7, 32.4)
	Myalgia	1 (4.2)	(0.1, 21.1)
	SOC: Eye disorders	6 (25.0)	(9.8, 46.7)
	Dry eye	2 (8.3)	(1.0, 27.0)
	SOC: Injury, poisoning and procedural complications	5 (20.8)	(7.1, 42.2)
	SOC: Vascular disorders	4 (16.7)	(4.7, 37.4)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Brain metastases	SOC: Reproductive system and breast disorders	3 (12.5)	(2.7, 32.4)
Yes (N = 24)	SOC: Cardiac disorders	2 (8.3)	(1.0, 27.0)
	SOC: Ear and labyrinth disorders	2 (8.3)	(1.0, 27.0)
	SOC: Hepatobiliary disorders	2 (8.3)	(1.0, 27.0)
	SOC: Psychiatric disorders	2 (8.3)	(1.0, 27.0)
	Insomnia	1 (4.2)	(0.1, 21.1)
	SOC: Renal and urinary disorders	2 (8.3)	(1.0, 27.0)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Brain metastases	SOC: Gastrointestinal disorders	151 (94.4)	(89.6, 97.4)
No (N = 160)	Nausea	128 (80.0)	(73.0, 85.9)
	Vomiting	77 (48.1)	(40.2, 56.2)
	Constipation	58 (36.3)	(28.8, 44.2)
	Diarrhoea	48 (30.0)	(23.0, 37.7)
	Dyspepsia	27 (16.9)	(11.4, 23.6)
	Abdominal pain	22 (13.8)	(8.8, 20.1)
	Stomatitis	21 (13.1)	(8.3, 19.4)
	Abdominal pain upper	16 (10.0)	(5.8, 15.7)
	Gastrooesophageal reflux disease	16 (10.0)	(5.8, 15.7)
	Haemorrhoids	11 (6.9)	(3.5, 12.0)
	SOC: General disorders and administration site conditions	119 (74.4)	(66.9, 80.9)
	Fatigue	78 (48.8)	(40.8, 56.8)
	Asthenia	25 (15.6)	(10.4, 22.2)
	Oedema peripheral	16 (10.0)	(5.8, 15.7)
	Pyrexia	13 (8.1)	(4.4, 13.5)
	Mucosal inflammation	12 (7.5)	(3.9, 12.7)
	Influenza like illness	11 (6.9)	(3.5, 12.0)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Brain metastases	SOC: Skin and subcutaneous tissue disorders	101 (63.1)	(55.1, 70.6)
No (N = 160)	Alopecia	76 (47.5)	(39.6, 55.5)
	Rash	17 (10.6)	(6.3, 16.5)
	Dry skin	10 (6.3)	(3.0, 11.2)
	Nail disorder	8 (5.0)	(2.2, 9.6)
	SOC: Respiratory, thoracic and mediastinal disorders	92 (57.5)	(49.4, 65.3)
	Cough	39 (24.4)	(17.9, 31.8)
	Dyspnoea	29 (18.1)	(12.5, 25.0)
	Epistaxis	22 (13.8)	(8.8, 20.1)
	Pneumonitis	13 (8.1)	(4.4, 13.5)
	Interstitial lung disease	8 (5.0)	(2.2, 9.6)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Brain metastases	SOC: Investigations	89 (55.6)	(47.6, 63.5)
No (N = 160)	Neutrophil count decreased	35 (21.9)	(15.7, 29.1)
	White blood cell count decreased	30 (18.8)	(13.0, 25.7)
	Aspartate aminotransferase increased	27 (16.9)	(11.4, 23.6)
	Platelet count decreased	26 (16.3)	(10.9, 22.9)
	Alanine aminotransferase increased	19 (11.9)	(7.3, 17.9)
	Lymphocyte count decreased	17 (10.6)	(6.3, 16.5)
	Blood bilirubin increased	12 (7.5)	(3.9, 12.7)
	Weight decreased	11 (6.9)	(3.5, 12.0)
	Blood alkaline phosphatase increased	9 (5.6)	(2.6, 10.4)
	Electrocardiogram QT prolonged	6 (3.8)	(1.4, 8.0)
	SOC: Infections and infestations	84 (52.5)	(44.5, 60.4)
	Upper respiratory tract infection	20 (12.5)	(7.8, 18.6)
	Nasopharyngitis	18 (11.3)	(6.8, 17.2)
	Urinary tract infection	16 (10.0)	(5.8, 15.7)
	Pneumonia	10 (6.3)	(3.0, 11.2)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Brain metastases	SOC: Nervous system disorders	77 (48.1)	(40.2, 56.2)
No (N = 160)	Headache	34 (21.3)	(15.2, 28.4)
	Dizziness	14 (8.8)	(4.9, 14.2)
	Dysgeusia	13 (8.1)	(4.4, 13.5)
	Peripheral sensory neuropathy	13 (8.1)	(4.4, 13.5)
	Neuropathy peripheral	10 (6.3)	(3.0, 11.2)
	SOC: Metabolism and nutrition disorders	73 (45.6)	(37.7, 53.7)
	Decreased appetite	50 (31.3)	(24.2, 39.0)
	Hypokalaemia	18 (11.3)	(6.8, 17.2)
	SOC: Blood and lymphatic system disorders	67 (41.9)	(34.1, 49.9)
	Anaemia	50 (31.3)	(24.2, 39.0)
	Neutropenia	22 (13.8)	(8.8, 20.1)
	Thrombocytopenia	11 (6.9)	(3.5, 12.0)
	Lymphopenia	7 (4.4)	(1.8, 8.8)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Brain metastases	SOC: Musculoskeletal and connective tissue disorders	61 (38.1)	(30.6, 46.1)
No (N = 160)	Arthralgia	21 (13.1)	(8.3, 19.4)
	Back pain	17 (10.6)	(6.3, 16.5)
	Myalgia	17 (10.6)	(6.3, 16.5)
	Muscle spasms	12 (7.5)	(3.9, 12.7)
	Pain in extremity	12 (7.5)	(3.9, 12.7)
	SOC: Eye disorders	55 (34.4)	(27.1, 42.3)
	Dry eye	19 (11.9)	(7.3, 17.9)
	SOC: Psychiatric disorders	26 (16.3)	(10.9, 22.9)
	Anxiety	12 (7.5)	(3.9, 12.7)
	Insomnia	12 (7.5)	(3.9, 12.7)
	SOC: Vascular disorders	23 (14.4)	(9.3, 20.8)
	SOC: Injury, poisoning and procedural complications	21 (13.1)	(8.3, 19.4)
	SOC: Cardiac disorders	20 (12.5)	(7.8, 18.6)
	SOC: Ear and labyrinth disorders	17 (10.6)	(6.3, 16.5)
	SOC: Renal and urinary disorders	17 (10.6)	(6.3, 16.5)
	SOC: Reproductive system and breast disorders	9 (5.6)	(2.6, 10.4)
	SOC: Hepatobiliary disorders	8 (5.0)	(2.2, 9.6)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Bone metastases	SOC: Gastrointestinal disorders	53 (100.0)	(93.3, 100.0)
Yes (N = 53)	Nausea	49 (92.5)	(81.8, 97.9)
	Vomiting	31 (58.5)	(44.1, 71.9)
	Constipation	21 (39.6)	(26.5, 54.0)
	Diarrhoea	20 (37.7)	(24.8, 52.1)
	Abdominal pain	10 (18.9)	(9.4, 32.0)
	Stomatitis	9 (17.0)	(8.1, 29.8)
	Dyspepsia	8 (15.1)	(6.7, 27.6)
	Abdominal pain upper	5 (9.4)	(3.1, 20.7)
	Haemorrhoids	5 (9.4)	(3.1, 20.7)
	Gastrooesophageal reflux disease	4 (7.5)	(2.1, 18.2)
	SOC: General disorders and administration site conditions	41 (77.4)	(63.8, 87.7)
	Fatigue	28 (52.8)	(38.6, 66.7)
	Asthenia	10 (18.9)	(9.4, 32.0)
	Oedema peripheral	9 (17.0)	(8.1, 29.8)
	Mucosal inflammation	7 (13.2)	(5.5, 25.3)
	Pyrexia	5 (9.4)	(3.1, 20.7)
	Influenza like illness	3 (5.7)	(1.2, 15.7)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Bone metastases	SOC: Respiratory, thoracic and mediastinal disorders	36 (67.9)	(53.7, 80.1)
Yes (N = 53)	Cough	13 (24.5)	(13.8, 38.3)
	Dyspnoea	12 (22.6)	(12.3, 36.2)
	Epistaxis	8 (15.1)	(6.7, 27.6)
	Pneumonitis	7 (13.2)	(5.5, 25.3)
	Interstitial lung disease	3 (5.7)	(1.2, 15.7)
	SOC: Skin and subcutaneous tissue disorders	33 (62.3)	(47.9, 75.2)
	Alopecia	27 (50.9)	(36.8, 64.9)
	Nail disorder	7 (13.2)	(5.5, 25.3)
	Dry skin	5 (9.4)	(3.1, 20.7)
	Rash	4 (7.5)	(2.1, 18.2)
	SOC: Nervous system disorders	32 (60.4)	(46.0, 73.5)
	Headache	12 (22.6)	(12.3, 36.2)
	Dizziness	7 (13.2)	(5.5, 25.3)
	Dysgeusia	5 (9.4)	(3.1, 20.7)
	Neuropathy peripheral	5 (9.4)	(3.1, 20.7)
	Peripheral sensory neuropathy	4 (7.5)	(2.1, 18.2)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Bone metastases	SOC: Metabolism and nutrition disorders	31 (58.5)	(44.1, 71.9)
Yes (N = 53)	Decreased appetite	23 (43.4)	(29.8, 57.7)
	Hypokalaemia	7 (13.2)	(5.5, 25.3)
	SOC: Investigations	30 (56.6)	(42.3, 70.2)
	Neutrophil count decreased	15 (28.3)	(16.8, 42.3)
	White blood cell count decreased	12 (22.6)	(12.3, 36.2)
	Aspartate aminotransferase increased	11 (20.8)	(10.8, 34.1)
	Platelet count decreased	10 (18.9)	(9.4, 32.0)
	Electrocardiogram QT prolonged	7 (13.2)	(5.5, 25.3)
	Lymphocyte count decreased	7 (13.2)	(5.5, 25.3)
	Weight decreased	6 (11.3)	(4.3, 23.0)
	Alanine aminotransferase increased	4 (7.5)	(2.1, 18.2)
	Blood alkaline phosphatase increased	4 (7.5)	(2.1, 18.2)
	Blood bilirubin increased	3 (5.7)	(1.2, 15.7)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Bone metastases	SOC: Infections and infestations	29 (54.7)	(40.4, 68.4)
Yes (N = 53)	Urinary tract infection	7 (13.2)	(5.5, 25.3)
	Nasopharyngitis	6 (11.3)	(4.3, 23.0)
	Pneumonia	5 (9.4)	(3.1, 20.7)
	Upper respiratory tract infection	3 (5.7)	(1.2, 15.7)
	SOC: Musculoskeletal and connective tissue disorders	23 (43.4)	(29.8, 57.7)
	Back pain	9 (17.0)	(8.1, 29.8)
	Arthralgia	6 (11.3)	(4.3, 23.0)
	Muscle spasms	5 (9.4)	(3.1, 20.7)
	Pain in extremity	4 (7.5)	(2.1, 18.2)
	Myalgia	3 (5.7)	(1.2, 15.7)
	SOC: Blood and lymphatic system disorders	22 (41.5)	(28.1, 55.9)
	Anaemia	18 (34.0)	(21.5, 48.3)
	Neutropenia	6 (11.3)	(4.3, 23.0)
	Lymphopenia	3 (5.7)	(1.2, 15.7)
	Thrombocytopenia	3 (5.7)	(1.2, 15.7)
	SOC: Eye disorders	17 (32.1)	(19.9, 46.3)
	Dry eye	6 (11.3)	(4.3, 23.0)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Bone metastases	SOC: Cardiac disorders	10 (18.9)	(9.4, 32.0)
Yes (N = 53)	SOC: Injury, poisoning and procedural complications	9 (17.0)	(8.1, 29.8)
	SOC: Ear and labyrinth disorders	8 (15.1)	(6.7, 27.6)
	SOC: Psychiatric disorders	8 (15.1)	(6.7, 27.6)
	Anxiety	5 (9.4)	(3.1, 20.7)
	Insomnia	4 (7.5)	(2.1, 18.2)
	SOC: Vascular disorders	8 (15.1)	(6.7, 27.6)
	SOC: Renal and urinary disorders	5 (9.4)	(3.1, 20.7)
	SOC: Hepatobiliary disorders	4 (7.5)	(2.1, 18.2)
	SOC: Reproductive system and breast disorders	4 (7.5)	(2.1, 18.2)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Bone metastases	SOC: Gastrointestinal disorders	120 (91.6)	(85.5, 95.7)
No (N = 131)	Nausea	95 (72.5)	(64.0, 80.0)
	Vomiting	57 (43.5)	(34.9, 52.4)
	Constipation	44 (33.6)	(25.6, 42.4)
	Diarrhoea	38 (29.0)	(21.4, 37.6)
	Dyspepsia	23 (17.6)	(11.5, 25.2)
	Stomatitis	20 (15.3)	(9.6, 22.6)
	Abdominal pain	15 (11.5)	(6.6, 18.2)
	Gastrooesophageal reflux disease	14 (10.7)	(6.0, 17.3)
	Abdominal pain upper	11 (8.4)	(4.3, 14.5)
	Haemorrhoids	6 (4.6)	(1.7, 9.7)
	SOC: General disorders and administration site conditions	96 (73.3)	(64.8, 80.6)
	Fatigue	64 (48.9)	(40.0, 57.7)
	Asthenia	16 (12.2)	(7.1, 19.1)
	Pyrexia	12 (9.2)	(4.8, 15.5)
	Influenza like illness	9 (6.9)	(3.2, 12.6)
	Mucosal inflammation	9 (6.9)	(3.2, 12.6)
	Oedema peripheral	8 (6.1)	(2.7, 11.7)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Bone metastases	SOC: Skin and subcutaneous tissue disorders	83 (63.4)	(54.5, 71.6)
No (N = 131)	Alopecia	62 (47.3)	(38.5, 56.2)
	Rash	15 (11.5)	(6.6, 18.2)
	Dry skin	6 (4.6)	(1.7, 9.7)
	Nail disorder	3 (2.3)	(0.5, 6.5)
	SOC: Investigations	76 (58.0)	(49.1, 66.6)
	Neutrophil count decreased	26 (19.8)	(13.4, 27.7)
	White blood cell count decreased	24 (18.3)	(12.1, 26.0)
	Aspartate aminotransferase increased	22 (16.8)	(10.8, 24.3)
	Platelet count decreased	20 (15.3)	(9.6, 22.6)
	Alanine aminotransferase increased	17 (13.0)	(7.7, 20.0)
	Blood bilirubin increased	12 (9.2)	(4.8, 15.5)
	Lymphocyte count decreased	12 (9.2)	(4.8, 15.5)
	Weight decreased	9 (6.9)	(3.2, 12.6)
	Blood alkaline phosphatase increased	7 (5.3)	(2.2, 10.7)
	Electrocardiogram QT prolonged	3 (2.3)	(0.5, 6.5)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Bone metastases	SOC: Infections and infestations	70 (53.4)	(44.5, 62.2)
No (N = 131)	Upper respiratory tract infection	21 (16.0)	(10.2, 23.5)
	Urinary tract infection	15 (11.5)	(6.6, 18.2)
	Nasopharyngitis	14 (10.7)	(6.0, 17.3)
	Pneumonia	5 (3.8)	(1.3, 8.7)
	SOC: Respiratory, thoracic and mediastinal disorders	69 (52.7)	(43.8, 61.5)
	Cough	32 (24.4)	(17.3, 32.7)
	Dyspnoea	19 (14.5)	(9.0, 21.7)
	Epistaxis	18 (13.7)	(8.4, 20.8)
	Pneumonitis	9 (6.9)	(3.2, 12.6)
	Interstitial lung disease	8 (6.1)	(2.7, 11.7)
	SOC: Nervous system disorders	59 (45.0)	(36.3, 54.0)
	Headache	28 (21.4)	(14.7, 29.4)
	Dizziness	12 (9.2)	(4.8, 15.5)
	Peripheral sensory neuropathy	12 (9.2)	(4.8, 15.5)
	Dysgeusia	8 (6.1)	(2.7, 11.7)
	Neuropathy peripheral	7 (5.3)	(2.2, 10.7)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Bone metastases	SOC: Blood and lymphatic system disorders	58 (44.3)	(35.6, 53.2)
No (N = 131)	Anaemia	40 (30.5)	(22.8, 39.2)
	Neutropenia	21 (16.0)	(10.2, 23.5)
	Thrombocytopenia	11 (8.4)	(4.3, 14.5)
	Lymphopenia	8 (6.1)	(2.7, 11.7)
	SOC: Metabolism and nutrition disorders	53 (40.5)	(32.0, 49.4)
	Decreased appetite	36 (27.5)	(20.0, 36.0)
	Hypokalaemia	15 (11.5)	(6.6, 18.2)
	SOC: Musculoskeletal and connective tissue disorders	47 (35.9)	(27.7, 44.7)
	Arthralgia	18 (13.7)	(8.4, 20.8)
	Myalgia	15 (11.5)	(6.6, 18.2)
	Back pain	11 (8.4)	(4.3, 14.5)
	Muscle spasms	10 (7.6)	(3.7, 13.6)
	Pain in extremity	8 (6.1)	(2.7, 11.7)
	SOC: Eye disorders	44 (33.6)	(25.6, 42.4)
	Dry eye	15 (11.5)	(6.6, 18.2)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Bone metastases	SOC: Psychiatric disorders	20 (15.3)	(9.6, 22.6)
No (N = 131)	Insomnia	9 (6.9)	(3.2, 12.6)
	Anxiety	7 (5.3)	(2.2, 10.7)
	SOC: Vascular disorders	19 (14.5)	(9.0, 21.7)
	SOC: Injury, poisoning and procedural complications	17 (13.0)	(7.7, 20.0)
	SOC: Renal and urinary disorders	14 (10.7)	(6.0, 17.3)
	SOC: Cardiac disorders	12 (9.2)	(4.8, 15.5)
	SOC: Ear and labyrinth disorders	11 (8.4)	(4.3, 14.5)
	SOC: Reproductive system and breast disorders	8 (6.1)	(2.7, 11.7)
	SOC: Hepatobiliary disorders	6 (4.6)	(1.7, 9.7)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
History of visceral disease	SOC: Gastrointestinal disorders	158 (93.5)	(88.7, 96.7)
Yes (N = 169)	Nausea	133 (78.7)	(71.7, 84.6)
	Vomiting	80 (47.3)	(39.6, 55.1)
	Constipation	60 (35.5)	(28.3, 43.2)
	Diarrhoea	53 (31.4)	(24.5, 38.9)
	Dyspepsia	31 (18.3)	(12.8, 25.0)
	Stomatitis	26 (15.4)	(10.3, 21.7)
	Abdominal pain	24 (14.2)	(9.3, 20.4)
	Abdominal pain upper	16 (9.5)	(5.5, 14.9)
	Gastrooesophageal reflux disease	15 (8.9)	(5.1, 14.2)
	Haemorrhoids	9 (5.3)	(2.5, 9.9)
	SOC: General disorders and administration site conditions	128 (75.7)	(68.6, 82.0)
	Fatigue	86 (50.9)	(43.1, 58.6)
	Asthenia	24 (14.2)	(9.3, 20.4)
	Pyrexia	17 (10.1)	(6.0, 15.6)
	Oedema peripheral	16 (9.5)	(5.5, 14.9)
	Mucosal inflammation	14 (8.3)	(4.6, 13.5)
	Influenza like illness	10 (5.9)	(2.9, 10.6)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
History of visceral disease	SOC: Skin and subcutaneous tissue disorders	106 (62.7)	(55.0, 70.0)
Yes (N = 169)	Alopecia	80 (47.3)	(39.6, 55.1)
	Rash	19 (11.2)	(6.9, 17.0)
	Dry skin	9 (5.3)	(2.5, 9.9)
	Nail disorder	9 (5.3)	(2.5, 9.9)
	SOC: Investigations	94 (55.6)	(47.8, 63.2)
	Neutrophil count decreased	35 (20.7)	(14.9, 27.6)
	Aspartate aminotransferase increased	30 (17.8)	(12.3, 24.4)
	White blood cell count decreased	29 (17.2)	(11.8, 23.7)
	Platelet count decreased	24 (14.2)	(9.3, 20.4)
	Alanine aminotransferase increased	19 (11.2)	(6.9, 17.0)
	Lymphocyte count decreased	16 (9.5)	(5.5, 14.9)
	Blood bilirubin increased	12 (7.1)	(3.7, 12.1)
	Weight decreased	12 (7.1)	(3.7, 12.1)
	Electrocardiogram QT prolonged	9 (5.3)	(2.5, 9.9)
	Blood alkaline phosphatase increased	8 (4.7)	(2.1, 9.1)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
History of visceral disease	SOC: Infections and infestations	93 (55.0)	(47.2, 62.7)
Yes (N = 169)	Upper respiratory tract infection	22 (13.0)	(8.3, 19.0)
	Urinary tract infection	21 (12.4)	(7.9, 18.4)
	Nasopharyngitis	19 (11.2)	(6.9, 17.0)
	Pneumonia	10 (5.9)	(2.9, 10.6)
	SOC: Respiratory, thoracic and mediastinal disorders	93 (55.0)	(47.2, 62.7)
	Cough	38 (22.5)	(16.4, 29.5)
	Dyspnoea	30 (17.8)	(12.3, 24.4)
	Epistaxis	23 (13.6)	(8.8, 19.7)
	Pneumonitis	14 (8.3)	(4.6, 13.5)
	Interstitial lung disease	10 (5.9)	(2.9, 10.6)
	SOC: Nervous system disorders	84 (49.7)	(41.9, 57.5)
	Headache	35 (20.7)	(14.9, 27.6)
	Dizziness	18 (10.7)	(6.4, 16.3)
	Peripheral sensory neuropathy	15 (8.9)	(5.1, 14.2)
	Dysgeusia	12 (7.1)	(3.7, 12.1)
	Neuropathy peripheral	12 (7.1)	(3.7, 12.1)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
History of visceral disease	SOC: Metabolism and nutrition disorders	76 (45.0)	(37.3, 52.8)
Yes (N = 169)	Decreased appetite	56 (33.1)	(26.1, 40.8)
	Hypokalaemia	19 (11.2)	(6.9, 17.0)
	SOC: Blood and lymphatic system disorders	69 (40.8)	(33.3, 48.6)
	Anaemia	48 (28.4)	(21.7, 35.8)
	Neutropenia	23 (13.6)	(8.8, 19.7)
	Thrombocytopenia	13 (7.7)	(4.2, 12.8)
	Lymphopenia	10 (5.9)	(2.9, 10.6)
	SOC: Musculoskeletal and connective tissue disorders	64 (37.9)	(30.5, 45.6)
	Arthralgia	23 (13.6)	(8.8, 19.7)
	Back pain	17 (10.1)	(6.0, 15.6)
	Myalgia	16 (9.5)	(5.5, 14.9)
	Muscle spasms	15 (8.9)	(5.1, 14.2)
	Pain in extremity	12 (7.1)	(3.7, 12.1)
	SOC: Eye disorders	56 (33.1)	(26.1, 40.8)
	Dry eye	20 (11.8)	(7.4, 17.7)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
History of visceral disease	SOC: Psychiatric disorders	25 (14.8)	(9.8, 21.1)
Yes (N = 169)	Insomnia	12 (7.1)	(3.7, 12.1)
	Anxiety	11 (6.5)	(3.3, 11.3)
	SOC: Vascular disorders	24 (14.2)	(9.3, 20.4)
	SOC: Injury, poisoning and procedural complications	23 (13.6)	(8.8, 19.7)
	SOC: Cardiac disorders	21 (12.4)	(7.9, 18.4)
	SOC: Renal and urinary disorders	18 (10.7)	(6.4, 16.3)
	SOC: Ear and labyrinth disorders	17 (10.1)	(6.0, 15.6)
	SOC: Hepatobiliary disorders	10 (5.9)	(2.9, 10.6)
	SOC: Reproductive system and breast disorders	10 (5.9)	(2.9, 10.6)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
History of visceral disease	SOC: Gastrointestinal disorders	15 (100.0)	(78.2, 100.0)
No (N = 15)	Nausea	11 (73.3)	(44.9, 92.2)
	Vomiting	8 (53.3)	(26.6, 78.7)
	Constipation	5 (33.3)	(11.8, 61.6)
	Diarrhoea	5 (33.3)	(11.8, 61.6)
	Gastrooesophageal reflux disease	3 (20.0)	(4.3, 48.1)
	Stomatitis	3 (20.0)	(4.3, 48.1)
	Haemorrhoids	2 (13.3)	(1.7, 40.5)
	Abdominal pain	1 (6.7)	(0.2, 31.9)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
History of visceral disease	SOC: Investigations	12 (80.0)	(51.9, 95.7)
No (N = 15)	White blood cell count decreased	7 (46.7)	(21.3, 73.4)
	Neutrophil count decreased	6 (40.0)	(16.3, 67.7)
	Platelet count decreased	6 (40.0)	(16.3, 67.7)
	Aspartate aminotransferase increased	3 (20.0)	(4.3, 48.1)
	Blood alkaline phosphatase increased	3 (20.0)	(4.3, 48.1)
	Blood bilirubin increased	3 (20.0)	(4.3, 48.1)
	Lymphocyte count decreased	3 (20.0)	(4.3, 48.1)
	Weight decreased	3 (20.0)	(4.3, 48.1)
	Alanine aminotransferase increased	2 (13.3)	(1.7, 40.5)
	Electrocardiogram QT prolonged	1 (6.7)	(0.2, 31.9)
	SOC: Respiratory, thoracic and mediastinal disorders	12 (80.0)	(51.9, 95.7)
	Cough	7 (46.7)	(21.3, 73.4)
	Epistaxis	3 (20.0)	(4.3, 48.1)
	Pneumonitis	2 (13.3)	(1.7, 40.5)
	Dyspnoea	1 (6.7)	(0.2, 31.9)
	Interstitial lung disease	1 (6.7)	(0.2, 31.9)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
History of visceral disease	SOC: Blood and lymphatic system disorders	11 (73.3)	(44.9, 92.2)
No (N = 15)	Anaemia	10 (66.7)	(38.4, 88.2)
	Neutropenia	4 (26.7)	(7.8, 55.1)
	Lymphopenia	1 (6.7)	(0.2, 31.9)
	Thrombocytopenia	1 (6.7)	(0.2, 31.9)
	SOC: Skin and subcutaneous tissue disorders	10 (66.7)	(38.4, 88.2)
	Alopecia	9 (60.0)	(32.3, 83.7)
	Dry skin	2 (13.3)	(1.7, 40.5)
	Nail disorder	1 (6.7)	(0.2, 31.9)
	SOC: General disorders and administration site conditions	9 (60.0)	(32.3, 83.7)
	Fatigue	6 (40.0)	(16.3, 67.7)
	Asthenia	2 (13.3)	(1.7, 40.5)
	Influenza like illness	2 (13.3)	(1.7, 40.5)
	Mucosal inflammation	2 (13.3)	(1.7, 40.5)
	Oedema peripheral	1 (6.7)	(0.2, 31.9)
	SOC: Metabolism and nutrition disorders	8 (53.3)	(26.6, 78.7)
	Decreased appetite	3 (20.0)	(4.3, 48.1)
	Hypokalaemia	3 (20.0)	(4.3, 48.1)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
History of visceral disease	SOC: Nervous system disorders	7 (46.7)	(21.3, 73.4)
No (N = 15)	Headache	5 (33.3)	(11.8, 61.6)
	Dizziness	1 (6.7)	(0.2, 31.9)
	Dysgeusia	1 (6.7)	(0.2, 31.9)
	Peripheral sensory neuropathy	1 (6.7)	(0.2, 31.9)
	SOC: Infections and infestations	6 (40.0)	(16.3, 67.7)
	Upper respiratory tract infection	2 (13.3)	(1.7, 40.5)
	Nasopharyngitis	1 (6.7)	(0.2, 31.9)
	Urinary tract infection	1 (6.7)	(0.2, 31.9)
	SOC: Musculoskeletal and connective tissue disorders	6 (40.0)	(16.3, 67.7)
	Back pain	3 (20.0)	(4.3, 48.1)
	Myalgia	2 (13.3)	(1.7, 40.5)
	Arthralgia	1 (6.7)	(0.2, 31.9)
	SOC: Eye disorders	5 (33.3)	(11.8, 61.6)
	Dry eye	1 (6.7)	(0.2, 31.9)
	SOC: Injury, poisoning and procedural complications	3 (20.0)	(4.3, 48.1)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
History of visceral disease	SOC: Psychiatric disorders	3 (20.0)	(4.3, 48.1)
No (N = 15)	Anxiety	1 (6.7)	(0.2, 31.9)
	Insomnia	1 (6.7)	(0.2, 31.9)
	SOC: Vascular disorders	3 (20.0)	(4.3, 48.1)
	SOC: Ear and labyrinth disorders	2 (13.3)	(1.7, 40.5)
	SOC: Reproductive system and breast disorders	2 (13.3)	(1.7, 40.5)
	SOC: Cardiac disorders	1 (6.7)	(0.2, 31.9)
	SOC: Renal and urinary disorders	1 (6.7)	(0.2, 31.9)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Age	SOC: Gastrointestinal disorders	131 (93.6)	(88.1, 97.0)
<65 years (N = 140)	Nausea	114 (81.4)	(74.0, 87.5)
	Vomiting	68 (48.6)	(40.0, 57.2)
	Constipation	47 (33.6)	(25.8, 42.0)
	Diarrhoea	37 (26.4)	(19.3, 34.5)
	Dyspepsia	28 (20.0)	(13.7, 27.6)
	Abdominal pain	20 (14.3)	(8.9, 21.2)
	Stomatitis	20 (14.3)	(8.9, 21.2)
	Abdominal pain upper	13 (9.3)	(5.0, 15.4)
	Gastrooesophageal reflux disease	10 (7.1)	(3.5, 12.7)
	Haemorrhoids	9 (6.4)	(3.0, 11.9)
	SOC: General disorders and administration site conditions	100 (71.4)	(63.2, 78.7)
	Fatigue	65 (46.4)	(38.0, 55.0)
	Asthenia	19 (13.6)	(8.4, 20.4)
	Mucosal inflammation	11 (7.9)	(4.0, 13.6)
	Pyrexia	10 (7.1)	(3.5, 12.7)
	Influenza like illness	9 (6.4)	(3.0, 11.9)
	Oedema peripheral	7 (5.0)	(2.0, 10.0)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Age	SOC: Skin and subcutaneous tissue disorders	89 (63.6)	(55.0, 71.5)
<65 years (N = 140)	Alopecia	69 (49.3)	(40.7, 57.9)
	Rash	16 (11.4)	(6.7, 17.9)
	Dry skin	6 (4.3)	(1.6, 9.1)
	Nail disorder	5 (3.6)	(1.2, 8.1)
	SOC: Investigations	76 (54.3)	(45.7, 62.7)
	Neutrophil count decreased	27 (19.3)	(13.1, 26.8)
	White blood cell count decreased	23 (16.4)	(10.7, 23.6)
	Aspartate aminotransferase increased	21 (15.0)	(9.5, 22.0)
	Platelet count decreased	19 (13.6)	(8.4, 20.4)
	Alanine aminotransferase increased	15 (10.7)	(6.1, 17.1)
	Lymphocyte count decreased	12 (8.6)	(4.5, 14.5)
	Weight decreased	10 (7.1)	(3.5, 12.7)
	Blood bilirubin increased	9 (6.4)	(3.0, 11.9)
	Blood alkaline phosphatase increased	8 (5.7)	(2.5, 10.9)
	Electrocardiogram QT prolonged	6 (4.3)	(1.6, 9.1)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Age	SOC: Infections and infestations	75 (53.6)	(45.0, 62.0)
<65 years (N = 140)	Upper respiratory tract infection	19 (13.6)	(8.4, 20.4)
	Nasopharyngitis	15 (10.7)	(6.1, 17.1)
	Urinary tract infection	15 (10.7)	(6.1, 17.1)
	Pneumonia	5 (3.6)	(1.2, 8.1)
	SOC: Nervous system disorders	72 (51.4)	(42.8, 60.0)
	Headache	31 (22.1)	(15.6, 29.9)
	Dizziness	13 (9.3)	(5.0, 15.4)
	Dysgeusia	11 (7.9)	(4.0, 13.6)
	Neuropathy peripheral	11 (7.9)	(4.0, 13.6)
	Peripheral sensory neuropathy	11 (7.9)	(4.0, 13.6)
	SOC: Respiratory, thoracic and mediastinal disorders	72 (51.4)	(42.8, 60.0)
	Cough	33 (23.6)	(16.8, 31.5)
	Dyspnoea	22 (15.7)	(10.1, 22.8)
	Epistaxis	13 (9.3)	(5.0, 15.4)
	Pneumonitis	13 (9.3)	(5.0, 15.4)
	Interstitial lung disease	5 (3.6)	(1.2, 8.1)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Age	SOC: Metabolism and nutrition disorders	59 (42.1)	(33.9, 50.8)
<65 years (N = 140)	Decreased appetite	40 (28.6)	(21.3, 36.8)
	Hypokalaemia	10 (7.1)	(3.5, 12.7)
	SOC: Musculoskeletal and connective tissue disorders	55 (39.3)	(31.1, 47.9)
	Arthralgia	17 (12.1)	(7.2, 18.7)
	Myalgia	17 (12.1)	(7.2, 18.7)
	Back pain	14 (10.0)	(5.6, 16.2)
	Muscle spasms	14 (10.0)	(5.6, 16.2)
	Pain in extremity	10 (7.1)	(3.5, 12.7)
	SOC: Blood and lymphatic system disorders	53 (37.9)	(29.8, 46.4)
	Anaemia	38 (27.1)	(20.0, 35.3)
	Neutropenia	21 (15.0)	(9.5, 22.0)
	Thrombocytopenia	10 (7.1)	(3.5, 12.7)
	Lymphopenia	7 (5.0)	(2.0, 10.0)
	SOC: Eye disorders	42 (30.0)	(22.6, 38.3)
	Dry eye	19 (13.6)	(8.4, 20.4)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Age	SOC: Psychiatric disorders	23 (16.4)	(10.7, 23.6)
<65 years (N = 140)	Anxiety	11 (7.9)	(4.0, 13.6)
	Insomnia	10 (7.1)	(3.5, 12.7)
	SOC: Injury, poisoning and procedural complications	19 (13.6)	(8.4, 20.4)
	SOC: Vascular disorders	18 (12.9)	(7.8, 19.6)
	SOC: Renal and urinary disorders	15 (10.7)	(6.1, 17.1)
	SOC: Ear and labyrinth disorders	14 (10.0)	(5.6, 16.2)
	SOC: Cardiac disorders	12 (8.6)	(4.5, 14.5)
	SOC: Reproductive system and breast disorders	9 (6.4)	(3.0, 11.9)
	SOC: Hepatobiliary disorders	7 (5.0)	(2.0, 10.0)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Age	SOC: Gastrointestinal disorders	42 (95.5)	(84.5, 99.4)
>=65 years (N = 44)	Nausea	30 (68.2)	(52.4, 81.4)
	Diarrhoea	21 (47.7)	(32.5, 63.3)
	Vomiting	20 (45.5)	(30.4, 61.2)
	Constipation	18 (40.9)	(26.3, 56.8)
	Stomatitis	9 (20.5)	(9.8, 35.3)
	Gastrooesophageal reflux disease	8 (18.2)	(8.2, 32.7)
	Abdominal pain	5 (11.4)	(3.8, 24.6)
	Abdominal pain upper	3 (6.8)	(1.4, 18.7)
	Dyspepsia	3 (6.8)	(1.4, 18.7)
	Haemorrhoids	2 (4.5)	(0.6, 15.5)
	SOC: General disorders and administration site conditions	37 (84.1)	(69.9, 93.4)
	Fatigue	27 (61.4)	(45.5, 75.6)
	Oedema peripheral	10 (22.7)	(11.5, 37.8)
	Asthenia	7 (15.9)	(6.6, 30.1)
	Pyrexia	7 (15.9)	(6.6, 30.1)
	Mucosal inflammation	5 (11.4)	(3.8, 24.6)
	Influenza like illness	3 (6.8)	(1.4, 18.7)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Age	SOC: Respiratory, thoracic and mediastinal disorders	33 (75.0)	(59.7, 86.8)
>=65 years (N = 44)	Epistaxis	13 (29.5)	(16.8, 45.2)
	Cough	12 (27.3)	(15.0, 42.8)
	Dyspnoea	9 (20.5)	(9.8, 35.3)
	Interstitial lung disease	6 (13.6)	(5.2, 27.4)
	Pneumonitis	3 (6.8)	(1.4, 18.7)
	SOC: Investigations	30 (68.2)	(52.4, 81.4)
	Neutrophil count decreased	14 (31.8)	(18.6, 47.6)
	White blood cell count decreased	13 (29.5)	(16.8, 45.2)
	Aspartate aminotransferase increased	12 (27.3)	(15.0, 42.8)
	Platelet count decreased	11 (25.0)	(13.2, 40.3)
	Lymphocyte count decreased	7 (15.9)	(6.6, 30.1)
	Alanine aminotransferase increased	6 (13.6)	(5.2, 27.4)
	Blood bilirubin increased	6 (13.6)	(5.2, 27.4)
	Weight decreased	5 (11.4)	(3.8, 24.6)
	Electrocardiogram QT prolonged	4 (9.1)	(2.5, 21.7)
	Blood alkaline phosphatase increased	3 (6.8)	(1.4, 18.7)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Age	SOC: Blood and lymphatic system disorders	27 (61.4)	(45.5, 75.6)
>=65 years (N = 44)	Anaemia	20 (45.5)	(30.4, 61.2)
	Neutropenia	6 (13.6)	(5.2, 27.4)
	Lymphopenia	4 (9.1)	(2.5, 21.7)
	Thrombocytopenia	4 (9.1)	(2.5, 21.7)
	SOC: Skin and subcutaneous tissue disorders	27 (61.4)	(45.5, 75.6)
	Alopecia	20 (45.5)	(30.4, 61.2)
	Dry skin	5 (11.4)	(3.8, 24.6)
	Nail disorder	5 (11.4)	(3.8, 24.6)
	Rash	3 (6.8)	(1.4, 18.7)
	SOC: Metabolism and nutrition disorders	25 (56.8)	(41.0, 71.7)
	Decreased appetite	19 (43.2)	(28.3, 59.0)
	Hypokalaemia	12 (27.3)	(15.0, 42.8)
	SOC: Infections and infestations	24 (54.5)	(38.8, 69.6)
	Urinary tract infection	7 (15.9)	(6.6, 30.1)
	Nasopharyngitis	5 (11.4)	(3.8, 24.6)
	Pneumonia	5 (11.4)	(3.8, 24.6)
	Upper respiratory tract infection	5 (11.4)	(3.8, 24.6)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Age	SOC: Eye disorders	19 (43.2)	(28.3, 59.0)
>=65 years (N = 44)	Dry eye	2 (4.5)	(0.6, 15.5)
	SOC: Nervous system disorders	19 (43.2)	(28.3, 59.0)
	Headache	9 (20.5)	(9.8, 35.3)
	Dizziness	6 (13.6)	(5.2, 27.4)
	Peripheral sensory neuropathy	5 (11.4)	(3.8, 24.6)
	Dysgeusia	2 (4.5)	(0.6, 15.5)
	Neuropathy peripheral	1 (2.3)	(0.1, 12.0)
	SOC: Musculoskeletal and connective tissue disorders	15 (34.1)	(20.5, 49.9)
	Arthralgia	7 (15.9)	(6.6, 30.1)
	Back pain	6 (13.6)	(5.2, 27.4)
	Pain in extremity	2 (4.5)	(0.6, 15.5)
	Muscle spasms	1 (2.3)	(0.1, 12.0)
	Myalgia	1 (2.3)	(0.1, 12.0)
	SOC: Cardiac disorders	10 (22.7)	(11.5, 37.8)
	SOC: Vascular disorders	9 (20.5)	(9.8, 35.3)
	SOC: Injury, poisoning and procedural complications	7 (15.9)	(6.6, 30.1)
	SOC: Ear and labyrinth disorders	5 (11.4)	(3.8, 24.6)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Age	SOC: Psychiatric disorders	5 (11.4)	(3.8, 24.6)
>=65 years (N = 44)	Insomnia	3 (6.8)	(1.4, 18.7)
	Anxiety	1 (2.3)	(0.1, 12.0)
	SOC: Renal and urinary disorders	4 (9.1)	(2.5, 21.7)
	SOC: Hepatobiliary disorders	3 (6.8)	(1.4, 18.7)
	SOC: Reproductive system and breast disorders	3 (6.8)	(1.4, 18.7)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Region	SOC: Gastrointestinal disorders	57 (90.5)	(80.4, 96.4)
Asia (N = 63)	Nausea	46 (73.0)	(60.3, 83.4)
	Constipation	21 (33.3)	(22.0, 46.3)
	Vomiting	21 (33.3)	(22.0, 46.3)
	Dyspepsia	12 (19.0)	(10.2, 30.9)
	Stomatitis	11 (17.5)	(9.1, 29.1)
	Diarrhoea	10 (15.9)	(7.9, 27.3)
	Abdominal pain upper	4 (6.3)	(1.8, 15.5)
	Abdominal pain	2 (3.2)	(0.4, 11.0)
	Haemorrhoids	2 (3.2)	(0.4, 11.0)
	Gastrooesophageal reflux disease	1 (1.6)	(0.0, 8.5)
	SOC: Skin and subcutaneous tissue disorders	43 (68.3)	(55.3, 79.4)
	Alopecia	32 (50.8)	(37.9, 63.6)
	Dry skin	8 (12.7)	(5.6, 23.5)
	Rash	6 (9.5)	(3.6, 19.6)
	Nail disorder	2 (3.2)	(0.4, 11.0)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Region	SOC: Investigations	37 (58.7)	(45.6, 71.0)
Asia (N = 63)	Neutrophil count decreased	24 (38.1)	(26.1, 51.2)
	White blood cell count decreased	24 (38.1)	(26.1, 51.2)
	Platelet count decreased	16 (25.4)	(15.3, 37.9)
	Aspartate aminotransferase increased	12 (19.0)	(10.2, 30.9)
	Lymphocyte count decreased	11 (17.5)	(9.1, 29.1)
	Alanine aminotransferase increased	8 (12.7)	(5.6, 23.5)
	Electrocardiogram QT prolonged	5 (7.9)	(2.6, 17.6)
	Blood bilirubin increased	3 (4.8)	(1.0, 13.3)
	Weight decreased	2 (3.2)	(0.4, 11.0)
	Blood alkaline phosphatase increased	1 (1.6)	(0.0, 8.5)
	SOC: General disorders and administration site conditions	34 (54.0)	(40.9, 66.6)
	Fatigue	22 (34.9)	(23.3, 48.0)
	Mucosal inflammation	4 (6.3)	(1.8, 15.5)
	Influenza like illness	3 (4.8)	(1.0, 13.3)
	Oedema peripheral	2 (3.2)	(0.4, 11.0)
	Pyrexia	2 (3.2)	(0.4, 11.0)
	Asthenia	1 (1.6)	(0.0, 8.5)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Region	SOC: Respiratory, thoracic and mediastinal disorders	34 (54.0)	(40.9, 66.6)
Asia (N = 63)	Epistaxis	11 (17.5)	(9.1, 29.1)
	Cough	9 (14.3)	(6.7, 25.4)
	Interstitial lung disease	7 (11.1)	(4.6, 21.6)
	Pneumonitis	7 (11.1)	(4.6, 21.6)
	Dyspnoea	4 (6.3)	(1.8, 15.5)
	SOC: Nervous system disorders	30 (47.6)	(34.9, 60.6)
	Headache	14 (22.2)	(12.7, 34.5)
	Peripheral sensory neuropathy	9 (14.3)	(6.7, 25.4)
	Dizziness	4 (6.3)	(1.8, 15.5)
	Dysgeusia	3 (4.8)	(1.0, 13.3)
	Neuropathy peripheral	2 (3.2)	(0.4, 11.0)
	SOC: Infections and infestations	29 (46.0)	(33.4, 59.1)
	Upper respiratory tract infection	8 (12.7)	(5.6, 23.5)
	Nasopharyngitis	7 (11.1)	(4.6, 21.6)
	Pneumonia	4 (6.3)	(1.8, 15.5)
	Urinary tract infection	3 (4.8)	(1.0, 13.3)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Region	SOC: Metabolism and nutrition disorders	29 (46.0)	(33.4, 59.1)
Asia (N = 63)	Decreased appetite	23 (36.5)	(24.7, 49.6)
	Hypokalaemia	1 (1.6)	(0.0, 8.5)
	SOC: Blood and lymphatic system disorders	28 (44.4)	(31.9, 57.5)
	Anaemia	20 (31.7)	(20.6, 44.7)
	Neutropenia	9 (14.3)	(6.7, 25.4)
	Lymphopenia	1 (1.6)	(0.0, 8.5)
	Thrombocytopenia	1 (1.6)	(0.0, 8.5)
	SOC: Musculoskeletal and connective tissue disorders	19 (30.2)	(19.2, 43.0)
	Myalgia	11 (17.5)	(9.1, 29.1)
	Arthralgia	4 (6.3)	(1.8, 15.5)
	Pain in extremity	3 (4.8)	(1.0, 13.3)
	Back pain	2 (3.2)	(0.4, 11.0)
	Muscle spasms	2 (3.2)	(0.4, 11.0)
	SOC: Eye disorders	14 (22.2)	(12.7, 34.5)
	Dry eye	6 (9.5)	(3.6, 19.6)
	SOC: Injury, poisoning and procedural complications	10 (15.9)	(7.9, 27.3)
	SOC: Ear and labyrinth disorders	6 (9.5)	(3.6, 19.6)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Region	SOC: Psychiatric disorders	6 (9.5)	(3.6, 19.6)
Asia (N = 63)	Insomnia	5 (7.9)	(2.6, 17.6)
	Anxiety	2 (3.2)	(0.4, 11.0)
	SOC: Cardiac disorders	4 (6.3)	(1.8, 15.5)
	SOC: Renal and urinary disorders	3 (4.8)	(1.0, 13.3)
	SOC: Reproductive system and breast disorders	1 (1.6)	(0.0, 8.5)
	SOC: Vascular disorders	1 (1.6)	(0.0, 8.5)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

Subgroup	SOC/Preferred Term	Overall 5.4 mg/kg (N = 184) n (%)	95% CI [a]
Region	SOC: Gastrointestinal disorders	53 (100.0)	(93.3, 100.0)
North America (N = 53)	Nausea	43 (81.1)	(68.0, 90.6)
	Vomiting	31 (58.5)	(44.1, 71.9)
	Diarrhoea	23 (43.4)	(29.8, 57.7)
	Constipation	18 (34.0)	(21.5, 48.3)
	Abdominal pain	11 (20.8)	(10.8, 34.1)
	Gastrooesophageal reflux disease	11 (20.8)	(10.8, 34.1)
	Stomatitis	10 (18.9)	(9.4, 32.0)
	Dyspepsia	7 (13.2)	(5.5, 25.3)
	Abdominal pain upper	3 (5.7)	(1.2, 15.7)
	Haemorrhoids	3 (5.7)	(1.2, 15.7)
	SOC: General disorders and administration site conditions	46 (86.8)	(74.7, 94.5)
	Fatigue	41 (77.4)	(63.8, 87.7)
	Oedema peripheral	6 (11.3)	(4.3, 23.0)
	Pyrexia	4 (7.5)	(2.1, 18.2)
	Mucosal inflammation	3 (5.7)	(1.2, 15.7)
	Asthenia	2 (3.8)	(0.5, 13.0)
	Influenza like illness	1 (1.9)	(0.0, 10.1)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Region	SOC: Skin and subcutaneous tissue disorders	36 (67.9)	(53.7, 80.1)
North America (N = 53)	Alopecia	30 (56.6)	(42.3, 70.2)
	Rash	7 (13.2)	(5.5, 25.3)
	Nail disorder	3 (5.7)	(1.2, 15.7)
	Dry skin	1 (1.9)	(0.0, 10.1)
	SOC: Investigations	32 (60.4)	(46.0, 73.5)
	Neutrophil count decreased	11 (20.8)	(10.8, 34.1)
	Platelet count decreased	10 (18.9)	(9.4, 32.0)
	Weight decreased	10 (18.9)	(9.4, 32.0)
	White blood cell count decreased	10 (18.9)	(9.4, 32.0)
	Aspartate aminotransferase increased	9 (17.0)	(8.1, 29.8)
	Blood bilirubin increased	6 (11.3)	(4.3, 23.0)
	Blood alkaline phosphatase increased	5 (9.4)	(3.1, 20.7)
	Lymphocyte count decreased	4 (7.5)	(2.1, 18.2)
	Alanine aminotransferase increased	3 (5.7)	(1.2, 15.7)
	Electrocardiogram QT prolonged	2 (3.8)	(0.5, 13.0)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Region	SOC: Respiratory, thoracic and mediastinal disorders	32 (60.4)	(46.0, 73.5)
North America (N = 53)	Cough	21 (39.6)	(26.5, 54.0)
	Dyspnoea	7 (13.2)	(5.5, 25.3)
	Epistaxis	6 (11.3)	(4.3, 23.0)
	Pneumonitis	4 (7.5)	(2.1, 18.2)
	SOC: Infections and infestations	31 (58.5)	(44.1, 71.9)
	Upper respiratory tract infection	11 (20.8)	(10.8, 34.1)
	Urinary tract infection	7 (13.2)	(5.5, 25.3)
	Nasopharyngitis	5 (9.4)	(3.1, 20.7)
	Pneumonia	2 (3.8)	(0.5, 13.0)
	SOC: Nervous system disorders	30 (56.6)	(42.3, 70.2)
	Headache	14 (26.4)	(15.3, 40.3)
	Dizziness	10 (18.9)	(9.4, 32.0)
	Dysgeusia	6 (11.3)	(4.3, 23.0)
	Neuropathy peripheral	5 (9.4)	(3.1, 20.7)
	Peripheral sensory neuropathy	4 (7.5)	(2.1, 18.2)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Region	SOC: Metabolism and nutrition disorders	28 (52.8)	(38.6, 66.7)
North America (N = 53)	Decreased appetite	17 (32.1)	(19.9, 46.3)
	Hypokalaemia	12 (22.6)	(12.3, 36.2)
	SOC: Eye disorders	23 (43.4)	(29.8, 57.7)
	Dry eye	8 (15.1)	(6.7, 27.6)
	SOC: Musculoskeletal and connective tissue disorders	21 (39.6)	(26.5, 54.0)
	Arthralgia	13 (24.5)	(13.8, 38.3)
	Back pain	8 (15.1)	(6.7, 27.6)
	Muscle spasms	5 (9.4)	(3.1, 20.7)
	Myalgia	3 (5.7)	(1.2, 15.7)
	Pain in extremity	1 (1.9)	(0.0, 10.1)
	SOC: Blood and lymphatic system disorders	20 (37.7)	(24.8, 52.1)
	Anaemia	17 (32.1)	(19.9, 46.3)
	Neutropenia	6 (11.3)	(4.3, 23.0)
	Thrombocytopenia	3 (5.7)	(1.2, 15.7)
	Lymphopenia	1 (1.9)	(0.0, 10.1)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Region	SOC: Psychiatric disorders	13 (24.5)	(13.8, 38.3)
North America (N = 53)	Anxiety	6 (11.3)	(4.3, 23.0)
	Insomnia	4 (7.5)	(2.1, 18.2)
	SOC: Vascular disorders	12 (22.6)	(12.3, 36.2)
	SOC: Injury, poisoning and procedural complications	9 (17.0)	(8.1, 29.8)
	SOC: Ear and labyrinth disorders	8 (15.1)	(6.7, 27.6)
	SOC: Renal and urinary disorders	8 (15.1)	(6.7, 27.6)
	SOC: Reproductive system and breast disorders	7 (13.2)	(5.5, 25.3)
	SOC: Cardiac disorders	6 (11.3)	(4.3, 23.0)
	SOC: Hepatobiliary disorders	3 (5.7)	(1.2, 15.7)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Region	SOC: Gastrointestinal disorders	63 (92.6)	(83.7, 97.6)
EU (N = 68)	Nausea	55 (80.9)	(69.5, 89.4)
	Vomiting	36 (52.9)	(40.4, 65.2)
	Constipation	26 (38.2)	(26.7, 50.8)
	Diarrhoea	25 (36.8)	(25.4, 49.3)
	Abdominal pain	12 (17.6)	(9.5, 28.8)
	Dyspepsia	12 (17.6)	(9.5, 28.8)
	Abdominal pain upper	9 (13.2)	(6.2, 23.6)
	Stomatitis	8 (11.8)	(5.2, 21.9)
	Gastrooesophageal reflux disease	6 (8.8)	(3.3, 18.2)
	Haemorrhoids	6 (8.8)	(3.3, 18.2)
	SOC: General disorders and administration site conditions	57 (83.8)	(72.9, 91.6)
	Fatigue	29 (42.6)	(30.7, 55.2)
	Asthenia	23 (33.8)	(22.8, 46.3)
	Pyrexia	11 (16.2)	(8.4, 27.1)
	Mucosal inflammation	9 (13.2)	(6.2, 23.6)
	Oedema peripheral	9 (13.2)	(6.2, 23.6)
	Influenza like illness	8 (11.8)	(5.2, 21.9)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Region	SOC: Infections and infestations	39 (57.4)	(44.8, 69.3)
EU (N = 68)	Urinary tract infection	12 (17.6)	(9.5, 28.8)
	Nasopharyngitis	8 (11.8)	(5.2, 21.9)
	Upper respiratory tract infection	5 (7.4)	(2.4, 16.3)
	Pneumonia	4 (5.9)	(1.6, 14.4)
	SOC: Respiratory, thoracic and mediastinal disorders	39 (57.4)	(44.8, 69.3)
	Dyspnoea	20 (29.4)	(19.0, 41.7)
	Cough	15 (22.1)	(12.9, 33.8)
	Epistaxis	9 (13.2)	(6.2, 23.6)
	Pneumonitis	5 (7.4)	(2.4, 16.3)
	Interstitial lung disease	4 (5.9)	(1.6, 14.4)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Region	SOC: Investigations	37 (54.4)	(41.9, 66.5)
EU (N = 68)	Aspartate aminotransferase increased	12 (17.6)	(9.5, 28.8)
	Alanine aminotransferase increased	10 (14.7)	(7.3, 25.4)
	Blood bilirubin increased	6 (8.8)	(3.3, 18.2)
	Neutrophil count decreased	6 (8.8)	(3.3, 18.2)
	Blood alkaline phosphatase increased	5 (7.4)	(2.4, 16.3)
	Lymphocyte count decreased	4 (5.9)	(1.6, 14.4)
	Platelet count decreased	4 (5.9)	(1.6, 14.4)
	Electrocardiogram QT prolonged	3 (4.4)	(0.9, 12.4)
	Weight decreased	3 (4.4)	(0.9, 12.4)
	White blood cell count decreased	2 (2.9)	(0.4, 10.2)
	SOC: Skin and subcutaneous tissue disorders	37 (54.4)	(41.9, 66.5)
	Alopecia	27 (39.7)	(28.0, 52.3)
	Rash	6 (8.8)	(3.3, 18.2)
	Nail disorder	5 (7.4)	(2.4, 16.3)
	Dry skin	2 (2.9)	(0.4, 10.2)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Region	SOC: Blood and lymphatic system disorders	32 (47.1)	(34.8, 59.6)
EU (N = 68)	Anaemia	21 (30.9)	(20.2, 43.3)
	Neutropenia	12 (17.6)	(9.5, 28.8)
	Thrombocytopenia	10 (14.7)	(7.3, 25.4)
	Lymphopenia	9 (13.2)	(6.2, 23.6)
	SOC: Nervous system disorders	31 (45.6)	(33.5, 58.1)
	Headache	12 (17.6)	(9.5, 28.8)
	Dizziness	5 (7.4)	(2.4, 16.3)
	Neuropathy peripheral	5 (7.4)	(2.4, 16.3)
	Dysgeusia	4 (5.9)	(1.6, 14.4)
	Peripheral sensory neuropathy	3 (4.4)	(0.9, 12.4)
	SOC: Musculoskeletal and connective tissue disorders	30 (44.1)	(32.1, 56.7)
	Back pain	10 (14.7)	(7.3, 25.4)
	Muscle spasms	8 (11.8)	(5.2, 21.9)
	Pain in extremity	8 (11.8)	(5.2, 21.9)
	Arthralgia	7 (10.3)	(4.2, 20.1)
	Myalgia	4 (5.9)	(1.6, 14.4)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Region	SOC: Metabolism and nutrition disorders	27 (39.7)	(28.0, 52.3)
EU (N = 68)	Decreased appetite	19 (27.9)	(17.7, 40.1)
	Hypokalaemia	9 (13.2)	(6.2, 23.6)
	SOC: Eye disorders	24 (35.3)	(24.1, 47.8)
	Dry eye	7 (10.3)	(4.2, 20.1)
	SOC: Vascular disorders	14 (20.6)	(11.7, 32.1)
	SOC: Cardiac disorders	12 (17.6)	(9.5, 28.8)
	SOC: Psychiatric disorders	9 (13.2)	(6.2, 23.6)
	Anxiety	4 (5.9)	(1.6, 14.4)
	Insomnia	4 (5.9)	(1.6, 14.4)
	SOC: Renal and urinary disorders	8 (11.8)	(5.2, 21.9)
	SOC: Hepatobiliary disorders	7 (10.3)	(4.2, 20.1)
	SOC: Injury, poisoning and procedural complications	7 (10.3)	(4.2, 20.1)
	SOC: Ear and labyrinth disorders	5 (7.4)	(2.4, 16.3)
	SOC: Reproductive system and breast disorders	4 (5.9)	(1.6, 14.4)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
ECOG performance status	SOC: Gastrointestinal disorders	97 (95.1)	(88.9, 98.4)
0 (N = 102)	Nausea	79 (77.5)	(68.1, 85.1)
	Vomiting	52 (51.0)	(40.9, 61.0)
	Constipation	43 (42.2)	(32.4, 52.3)
	Diarrhoea	32 (31.4)	(22.5, 41.3)
	Dyspepsia	22 (21.6)	(14.0, 30.8)
	Abdominal pain	19 (18.6)	(11.6, 27.6)
	Stomatitis	19 (18.6)	(11.6, 27.6)
	Gastrooesophageal reflux disease	13 (12.7)	(7.0, 20.8)
	Abdominal pain upper	9 (8.8)	(4.1, 16.1)
	Haemorrhoids	9 (8.8)	(4.1, 16.1)
	SOC: General disorders and administration site conditions	80 (78.4)	(69.2, 86.0)
	Fatigue	53 (52.0)	(41.8, 62.0)
	Asthenia	15 (14.7)	(8.5, 23.1)
	Mucosal inflammation	9 (8.8)	(4.1, 16.1)
	Pyrexia	9 (8.8)	(4.1, 16.1)
	Oedema peripheral	8 (7.8)	(3.4, 14.9)
	Influenza like illness	5 (4.9)	(1.6, 11.1)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
ECOG performance status	SOC: Skin and subcutaneous tissue disorders	65 (63.7)	(53.6, 73.0)
0 (N = 102)	Alopecia	51 (50.0)	(39.9, 60.1)
	Rash	9 (8.8)	(4.1, 16.1)
	Dry skin	7 (6.9)	(2.8, 13.6)
	Nail disorder	5 (4.9)	(1.6, 11.1)
	SOC: Respiratory, thoracic and mediastinal disorders	64 (62.7)	(52.6, 72.1)
	Cough	30 (29.4)	(20.8, 39.3)
	Dyspnoea	15 (14.7)	(8.5, 23.1)
	Epistaxis	14 (13.7)	(7.7, 22.0)
	Pneumonitis	11 (10.8)	(5.5, 18.5)
	Interstitial lung disease	9 (8.8)	(4.1, 16.1)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
ECOG performance status	SOC: Investigations	63 (61.8)	(51.6, 71.2)
0 (N = 102)	Neutrophil count decreased	24 (23.5)	(15.7, 33.0)
	Aspartate aminotransferase increased	22 (21.6)	(14.0, 30.8)
	White blood cell count decreased	22 (21.6)	(14.0, 30.8)
	Platelet count decreased	17 (16.7)	(10.0, 25.3)
	Alanine aminotransferase increased	14 (13.7)	(7.7, 22.0)
	Lymphocyte count decreased	14 (13.7)	(7.7, 22.0)
	Blood bilirubin increased	7 (6.9)	(2.8, 13.6)
	Electrocardiogram QT prolonged	6 (5.9)	(2.2, 12.4)
	Blood alkaline phosphatase increased	5 (4.9)	(1.6, 11.1)
	Weight decreased	5 (4.9)	(1.6, 11.1)
	SOC: Infections and infestations	57 (55.9)	(45.7, 65.7)
	Upper respiratory tract infection	15 (14.7)	(8.5, 23.1)
	Urinary tract infection	12 (11.8)	(6.2, 19.6)
	Nasopharyngitis	11 (10.8)	(5.5, 18.5)
	Pneumonia	6 (5.9)	(2.2, 12.4)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
ECOG performance status	SOC: Metabolism and nutrition disorders	48 (47.1)	(37.1, 57.2)
0 (N = 102)	Decreased appetite	34 (33.3)	(24.3, 43.4)
	Hypokalaemia	7 (6.9)	(2.8, 13.6)
	SOC: Nervous system disorders	48 (47.1)	(37.1, 57.2)
	Headache	22 (21.6)	(14.0, 30.8)
	Dizziness	12 (11.8)	(6.2, 19.6)
	Dysgeusia	10 (9.8)	(4.8, 17.3)
	Neuropathy peripheral	7 (6.9)	(2.8, 13.6)
	Peripheral sensory neuropathy	7 (6.9)	(2.8, 13.6)
	SOC: Blood and lymphatic system disorders	47 (46.1)	(36.2, 56.2)
	Anaemia	39 (38.2)	(28.8, 48.4)
	Neutropenia	14 (13.7)	(7.7, 22.0)
	Thrombocytopenia	6 (5.9)	(2.2, 12.4)
	Lymphopenia	5 (4.9)	(1.6, 11.1)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
ECOG performance status	SOC: Musculoskeletal and connective tissue disorders	39 (38.2)	(28.8, 48.4)
0 (N = 102)	Arthralgia	14 (13.7)	(7.7, 22.0)
	Back pain	12 (11.8)	(6.2, 19.6)
	Muscle spasms	11 (10.8)	(5.5, 18.5)
	Myalgia	9 (8.8)	(4.1, 16.1)
	Pain in extremity	7 (6.9)	(2.8, 13.6)
	SOC: Eye disorders	38 (37.3)	(27.9, 47.4)
	Dry eye	14 (13.7)	(7.7, 22.0)
	SOC: Psychiatric disorders	19 (18.6)	(11.6, 27.6)
	Anxiety	9 (8.8)	(4.1, 16.1)
	Insomnia	7 (6.9)	(2.8, 13.6)
	SOC: Vascular disorders	18 (17.6)	(10.8, 26.4)
	SOC: Injury, poisoning and procedural complications	15 (14.7)	(8.5, 23.1)
	SOC: Ear and labyrinth disorders	13 (12.7)	(7.0, 20.8)
	SOC: Cardiac disorders	10 (9.8)	(4.8, 17.3)
	SOC: Renal and urinary disorders	9 (8.8)	(4.1, 16.1)
	SOC: Hepatobiliary disorders	6 (5.9)	(2.2, 12.4)
	SOC: Reproductive system and breast disorders	5 (4.9)	(1.6, 11.1)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
ECOG performance status	SOC: Gastrointestinal disorders	76 (93.8)	(86.2, 98.0)
1 (N = 81)	Nausea	65 (80.2)	(69.9, 88.3)
	Vomiting	36 (44.4)	(33.4, 55.9)
	Diarrhoea	26 (32.1)	(22.2, 43.4)
	Constipation	22 (27.2)	(17.9, 38.2)
	Stomatitis	10 (12.3)	(6.1, 21.5)
	Dyspepsia	9 (11.1)	(5.2, 20.0)
	Abdominal pain upper	7 (8.6)	(3.5, 17.0)
	Abdominal pain	6 (7.4)	(2.8, 15.4)
	Gastrooesophageal reflux disease	5 (6.2)	(2.0, 13.8)
	Haemorrhoids	2 (2.5)	(0.3, 8.6)
	SOC: General disorders and administration site conditions	56 (69.1)	(57.9, 78.9)
	Fatigue	39 (48.1)	(36.9, 59.5)
	Asthenia	11 (13.6)	(7.0, 23.0)
	Oedema peripheral	9 (11.1)	(5.2, 20.0)
	Influenza like illness	7 (8.6)	(3.5, 17.0)
	Mucosal inflammation	7 (8.6)	(3.5, 17.0)
	Pyrexia	7 (8.6)	(3.5, 17.0)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
ECOG performance status	SOC: Skin and subcutaneous tissue disorders	50 (61.7)	(50.3, 72.3)
1 (N = 81)	Alopecia	37 (45.7)	(34.6, 57.1)
	Rash	10 (12.3)	(6.1, 21.5)
	Nail disorder	5 (6.2)	(2.0, 13.8)
	Dry skin	4 (4.9)	(1.4, 12.2)
	SOC: Investigations	43 (53.1)	(41.7, 64.3)
	Neutrophil count decreased	17 (21.0)	(12.7, 31.5)
	White blood cell count decreased	14 (17.3)	(9.8, 27.3)
	Platelet count decreased	13 (16.0)	(8.8, 25.9)
	Aspartate aminotransferase increased	11 (13.6)	(7.0, 23.0)
	Weight decreased	10 (12.3)	(6.1, 21.5)
	Blood bilirubin increased	8 (9.9)	(4.4, 18.5)
	Alanine aminotransferase increased	7 (8.6)	(3.5, 17.0)
	Blood alkaline phosphatase increased	6 (7.4)	(2.8, 15.4)
	Lymphocyte count decreased	5 (6.2)	(2.0, 13.8)
	Electrocardiogram QT prolonged	4 (4.9)	(1.4, 12.2)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
ECOG performance status	SOC: Nervous system disorders	43 (53.1)	(41.7, 64.3)
1 (N = 81)	Headache	18 (22.2)	(13.7, 32.8)
	Peripheral sensory neuropathy	9 (11.1)	(5.2, 20.0)
	Dizziness	7 (8.6)	(3.5, 17.0)
	Neuropathy peripheral	5 (6.2)	(2.0, 13.8)
	Dysgeusia	3 (3.7)	(0.8, 10.4)
	SOC: Infections and infestations	41 (50.6)	(39.3, 61.9)
	Nasopharyngitis	9 (11.1)	(5.2, 20.0)
	Upper respiratory tract infection	9 (11.1)	(5.2, 20.0)
	Urinary tract infection	9 (11.1)	(5.2, 20.0)
	Pneumonia	4 (4.9)	(1.4, 12.2)
	SOC: Respiratory, thoracic and mediastinal disorders	40 (49.4)	(38.1, 60.7)
	Dyspnoea	15 (18.5)	(10.8, 28.7)
	Cough	14 (17.3)	(9.8, 27.3)
	Epistaxis	12 (14.8)	(7.9, 24.4)
	Pneumonitis	5 (6.2)	(2.0, 13.8)
	Interstitial lung disease	2 (2.5)	(0.3, 8.6)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
ECOG performance status	SOC: Metabolism and nutrition disorders	36 (44.4)	(33.4, 55.9)
1 (N = 81)	Decreased appetite	25 (30.9)	(21.1, 42.1)
	Hypokalaemia	15 (18.5)	(10.8, 28.7)
	SOC: Blood and lymphatic system disorders	33 (40.7)	(29.9, 52.2)
	Anaemia	19 (23.5)	(14.8, 34.2)
	Neutropenia	13 (16.0)	(8.8, 25.9)
	Thrombocytopenia	8 (9.9)	(4.4, 18.5)
	Lymphopenia	6 (7.4)	(2.8, 15.4)
	SOC: Musculoskeletal and connective tissue disorders	31 (38.3)	(27.7, 49.7)
	Arthralgia	10 (12.3)	(6.1, 21.5)
	Myalgia	9 (11.1)	(5.2, 20.0)
	Back pain	8 (9.9)	(4.4, 18.5)
	Pain in extremity	5 (6.2)	(2.0, 13.8)
	Muscle spasms	4 (4.9)	(1.4, 12.2)
	SOC: Eye disorders	23 (28.4)	(18.9, 39.5)
	Dry eye	7 (8.6)	(3.5, 17.0)
	SOC: Cardiac disorders	12 (14.8)	(7.9, 24.4)
	SOC: Injury, poisoning and procedural complications	11 (13.6)	(7.0, 23.0)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
ECOG performance status	SOC: Renal and urinary disorders	10 (12.3)	(6.1, 21.5)
1 (N = 81)	SOC: Psychiatric disorders	9 (11.1)	(5.2, 20.0)
	Insomnia	6 (7.4)	(2.8, 15.4)
	Anxiety	3 (3.7)	(0.8, 10.4)
	SOC: Vascular disorders	9 (11.1)	(5.2, 20.0)
	SOC: Reproductive system and breast disorders	7 (8.6)	(3.5, 17.0)
	SOC: Ear and labyrinth disorders	6 (7.4)	(2.8, 15.4)
	SOC: Hepatobiliary disorders	4 (4.9)	(1.4, 12.2)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

Subgroup	SOC/Preferred Term	Overall 5.4 mg/kg (N = 184) n (%)	95% CI [a]
Baseline sum of diameters of target lesions	SOC: Gastrointestinal disorders	71 (95.9)	(88.6, 99.2)
<5 cm (N = 74)	Nausea	57 (77.0)	(65.8, 86.0)
	Vomiting	34 (45.9)	(34.3, 57.9)
	Diarrhoea	26 (35.1)	(24.4, 47.1)
	Constipation	24 (32.4)	(22.0, 44.3)
	Dyspepsia	13 (17.6)	(9.7, 28.2)
	Stomatitis	13 (17.6)	(9.7, 28.2)
	Abdominal pain upper	9 (12.2)	(5.7, 21.8)
	Gastrooesophageal reflux disease	8 (10.8)	(4.8, 20.2)
	Abdominal pain	7 (9.5)	(3.9, 18.5)
	Haemorrhoids	4 (5.4)	(1.5, 13.3)
	SOC: General disorders and administration site conditions	60 (81.1)	(70.3, 89.3)
	Fatigue	37 (50.0)	(38.1, 61.9)
	Asthenia	14 (18.9)	(10.7, 29.7)
	Pyrexia	10 (13.5)	(6.7, 23.5)
	Influenza like illness	7 (9.5)	(3.9, 18.5)
	Mucosal inflammation	6 (8.1)	(3.0, 16.8)
	Oedema peripheral	4 (5.4)	(1.5, 13.3)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Baseline sum of diameters of target lesions	SOC: Skin and subcutaneous tissue disorders	49 (66.2)	(54.3, 76.8)
<5 cm (N = 74)	Alopecia	43 (58.1)	(46.1, 69.5)
	Rash	6 (8.1)	(3.0, 16.8)
	Dry skin	3 (4.1)	(0.8, 11.4)
	Nail disorder	2 (2.7)	(0.3, 9.4)
	SOC: Respiratory, thoracic and mediastinal disorders	48 (64.9)	(52.9, 75.6)
	Cough	20 (27.0)	(17.4, 38.6)
	Dyspnoea	12 (16.2)	(8.7, 26.6)
	Epistaxis	12 (16.2)	(8.7, 26.6)
	Pneumonitis	12 (16.2)	(8.7, 26.6)
	Interstitial lung disease	3 (4.1)	(0.8, 11.4)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Baseline sum of diameters of target lesions	SOC: Investigations	42 (56.8)	(44.7, 68.2)
<5 cm (N = 74)	White blood cell count decreased	15 (20.3)	(11.8, 31.2)
	Neutrophil count decreased	14 (18.9)	(10.7, 29.7)
	Platelet count decreased	12 (16.2)	(8.7, 26.6)
	Aspartate aminotransferase increased	10 (13.5)	(6.7, 23.5)
	Alanine aminotransferase increased	8 (10.8)	(4.8, 20.2)
	Lymphocyte count decreased	7 (9.5)	(3.9, 18.5)
	Blood bilirubin increased	5 (6.8)	(2.2, 15.1)
	Electrocardiogram QT prolonged	5 (6.8)	(2.2, 15.1)
	Blood alkaline phosphatase increased	4 (5.4)	(1.5, 13.3)
	Weight decreased	4 (5.4)	(1.5, 13.3)
	SOC: Infections and infestations	41 (55.4)	(43.4, 67.0)
	Nasopharyngitis	9 (12.2)	(5.7, 21.8)
	Upper respiratory tract infection	8 (10.8)	(4.8, 20.2)
	Urinary tract infection	8 (10.8)	(4.8, 20.2)
	Pneumonia	5 (6.8)	(2.2, 15.1)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Baseline sum of diameters of target lesions	SOC: Nervous system disorders	36 (48.6)	(36.9, 60.6)
<5 cm (N = 74)	Headache	13 (17.6)	(9.7, 28.2)
	Peripheral sensory neuropathy	7 (9.5)	(3.9, 18.5)
	Dizziness	6 (8.1)	(3.0, 16.8)
	Neuropathy peripheral	6 (8.1)	(3.0, 16.8)
	Dysgeusia	5 (6.8)	(2.2, 15.1)
	SOC: Blood and lymphatic system disorders	33 (44.6)	(33.0, 56.6)
	Anaemia	25 (33.8)	(23.2, 45.7)
	Neutropenia	11 (14.9)	(7.7, 25.0)
	Thrombocytopenia	5 (6.8)	(2.2, 15.1)
	Lymphopenia	3 (4.1)	(0.8, 11.4)
	SOC: Metabolism and nutrition disorders	32 (43.2)	(31.8, 55.3)
	Decreased appetite	21 (28.4)	(18.5, 40.1)
	Hypokalaemia	8 (10.8)	(4.8, 20.2)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Baseline sum of diameters of target lesions	SOC: Musculoskeletal and connective tissue disorders	29 (39.2)	(28.0, 51.2)
<5 cm (N = 74)	Arthralgia	11 (14.9)	(7.7, 25.0)
	Back pain	9 (12.2)	(5.7, 21.8)
	Myalgia	8 (10.8)	(4.8, 20.2)
	Pain in extremity	5 (6.8)	(2.2, 15.1)
	Muscle spasms	3 (4.1)	(0.8, 11.4)
	SOC: Eye disorders	26 (35.1)	(24.4, 47.1)
	Dry eye	7 (9.5)	(3.9, 18.5)
	SOC: Ear and labyrinth disorders	10 (13.5)	(6.7, 23.5)
	SOC: Injury, poisoning and procedural complications	10 (13.5)	(6.7, 23.5)
	SOC: Psychiatric disorders	10 (13.5)	(6.7, 23.5)
	Insomnia	4 (5.4)	(1.5, 13.3)
	Anxiety	2 (2.7)	(0.3, 9.4)
	SOC: Vascular disorders	10 (13.5)	(6.7, 23.5)
	SOC: Cardiac disorders	8 (10.8)	(4.8, 20.2)
	SOC: Renal and urinary disorders	8 (10.8)	(4.8, 20.2)
	SOC: Reproductive system and breast disorders	5 (6.8)	(2.2, 15.1)
	SOC: Hepatobiliary disorders	2 (2.7)	(0.3, 9.4)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Baseline sum of diameters of target lesions >=5 cm (N = 96)	SOC: Gastrointestinal disorders	89 (92.7)	(85.6, 97.0)
	Nausea	77 (80.2)	(70.8, 87.6)
	Vomiting	49 (51.0)	(40.6, 61.4)
	Constipation	34 (35.4)	(25.9, 45.8)
	Diarrhoea	30 (31.3)	(22.2, 41.5)
	Dyspepsia	16 (16.7)	(9.8, 25.6)
	Abdominal pain	15 (15.6)	(9.0, 24.5)
	Stomatitis	11 (11.5)	(5.9, 19.6)
	Gastrooesophageal reflux disease	9 (9.4)	(4.4, 17.1)
	Abdominal pain upper	6 (6.3)	(2.3, 13.1)
	Haemorrhoids	5 (5.2)	(1.7, 11.7)
	SOC: General disorders and administration site conditions	68 (70.8)	(60.7, 79.7)
	Fatigue	48 (50.0)	(39.6, 60.4)
	Oedema peripheral	12 (12.5)	(6.6, 20.8)
	Asthenia	9 (9.4)	(4.4, 17.1)
	Mucosal inflammation	8 (8.3)	(3.7, 15.8)
	Pyrexia	6 (6.3)	(2.3, 13.1)
	Influenza like illness	4 (4.2)	(1.1, 10.3)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Baseline sum of diameters of target lesions >=5 cm (N = 96)	SOC: Skin and subcutaneous tissue disorders	57 (59.4)	(48.9, 69.3)
	Alopecia	40 (41.7)	(31.7, 52.2)
	Rash	12 (12.5)	(6.6, 20.8)
	Dry skin	8 (8.3)	(3.7, 15.8)
	Nail disorder	7 (7.3)	(3.0, 14.4)
	SOC: Investigations	56 (58.3)	(47.8, 68.3)
	Neutrophil count decreased	24 (25.0)	(16.7, 34.9)
	Aspartate aminotransferase increased	18 (18.8)	(11.5, 28.0)
	White blood cell count decreased	18 (18.8)	(11.5, 28.0)
	Platelet count decreased	15 (15.6)	(9.0, 24.5)
	Lymphocyte count decreased	10 (10.4)	(5.1, 18.3)
	Weight decreased	10 (10.4)	(5.1, 18.3)
	Alanine aminotransferase increased	9 (9.4)	(4.4, 17.1)
	Blood bilirubin increased	9 (9.4)	(4.4, 17.1)
	Blood alkaline phosphatase increased	6 (6.3)	(2.3, 13.1)
	Electrocardiogram QT prolonged	4 (4.2)	(1.1, 10.3)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Baseline sum of diameters of target lesions >=5 cm (N = 96)	SOC: Infections and infestations	48 (50.0)	(39.6, 60.4)
	Upper respiratory tract infection	15 (15.6)	(9.0, 24.5)
	Urinary tract infection	13 (13.5)	(7.4, 22.0)
	Nasopharyngitis	8 (8.3)	(3.7, 15.8)
	Pneumonia	3 (3.1)	(0.6, 8.9)
	SOC: Respiratory, thoracic and mediastinal disorders	48 (50.0)	(39.6, 60.4)
	Cough	20 (20.8)	(13.2, 30.3)
	Dyspnoea	15 (15.6)	(9.0, 24.5)
	Epistaxis	14 (14.6)	(8.2, 23.3)
	Interstitial lung disease	6 (6.3)	(2.3, 13.1)
	Pneumonitis	2 (2.1)	(0.3, 7.3)
	SOC: Metabolism and nutrition disorders	47 (49.0)	(38.6, 59.4)
	Decreased appetite	35 (36.5)	(26.9, 46.9)
	Hypokalaemia	14 (14.6)	(8.2, 23.3)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Baseline sum of diameters of target lesions >=5 cm (N = 96)	SOC: Nervous system disorders	47 (49.0)	(38.6, 59.4)
	Headache	24 (25.0)	(16.7, 34.9)
	Dizziness	12 (12.5)	(6.6, 20.8)
	Peripheral sensory neuropathy	7 (7.3)	(3.0, 14.4)
	Dysgeusia	6 (6.3)	(2.3, 13.1)
	Neuropathy peripheral	4 (4.2)	(1.1, 10.3)
	SOC: Blood and lymphatic system disorders	41 (42.7)	(32.7, 53.2)
	Anaemia	29 (30.2)	(21.3, 40.4)
	Neutropenia	14 (14.6)	(8.2, 23.3)
	Lymphopenia	7 (7.3)	(3.0, 14.4)
	Thrombocytopenia	6 (6.3)	(2.3, 13.1)
	SOC: Musculoskeletal and connective tissue disorders	34 (35.4)	(25.9, 45.8)
	Arthralgia	12 (12.5)	(6.6, 20.8)
	Back pain	8 (8.3)	(3.7, 15.8)
	Muscle spasms	8 (8.3)	(3.7, 15.8)
	Myalgia	8 (8.3)	(3.7, 15.8)
	Pain in extremity	5 (5.2)	(1.7, 11.7)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
Baseline sum of diameters of target lesions >=5 cm (N = 96)	SOC: Eye disorders	31 (32.3)	(23.1, 42.6)
	Dry eye	13 (13.5)	(7.4, 22.0)
	SOC: Vascular disorders	16 (16.7)	(9.8, 25.6)
	SOC: Injury, poisoning and procedural complications	15 (15.6)	(9.0, 24.5)
	SOC: Psychiatric disorders	15 (15.6)	(9.0, 24.5)
	Anxiety	7 (7.3)	(3.0, 14.4)
	Insomnia	7 (7.3)	(3.0, 14.4)
	SOC: Cardiac disorders	11 (11.5)	(5.9, 19.6)
	SOC: Hepatobiliary disorders	7 (7.3)	(3.0, 14.4)
	SOC: Renal and urinary disorders	7 (7.3)	(3.0, 14.4)
	SOC: Ear and labyrinth disorders	5 (5.2)	(1.7, 11.7)
	SOC: Reproductive system and breast disorders	5 (5.2)	(1.7, 11.7)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
DS-8201a immediately following initial T-DM1	SOC: Gastrointestinal disorders	51 (91.1)	(80.4, 97.0)
Yes (N = 56)	Nausea	39 (69.6)	(55.9, 81.2)
	Vomiting	24 (42.9)	(29.7, 56.8)
	Constipation	19 (33.9)	(21.8, 47.8)
	Diarrhoea	12 (21.4)	(11.6, 34.4)
	Dyspepsia	11 (19.6)	(10.2, 32.4)
	Stomatitis	7 (12.5)	(5.2, 24.1)
	Abdominal pain upper	6 (10.7)	(4.0, 21.9)
	Abdominal pain	5 (8.9)	(3.0, 19.6)
	Gastrooesophageal reflux disease	3 (5.4)	(1.1, 14.9)
	Haemorrhoids	2 (3.6)	(0.4, 12.3)
	SOC: General disorders and administration site conditions	41 (73.2)	(59.7, 84.2)
	Fatigue	28 (50.0)	(36.3, 63.7)
	Influenza like illness	4 (7.1)	(2.0, 17.3)
	Pyrexia	4 (7.1)	(2.0, 17.3)
	Asthenia	3 (5.4)	(1.1, 14.9)
	Mucosal inflammation	3 (5.4)	(1.1, 14.9)
	Oedema peripheral	3 (5.4)	(1.1, 14.9)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
DS-8201a immediately following initial T-DM1	SOC: Skin and subcutaneous tissue disorders	39 (69.6)	(55.9, 81.2)
Yes (N = 56)	Alopecia	30 (53.6)	(39.7, 67.0)
	Rash	5 (8.9)	(3.0, 19.6)
	Dry skin	4 (7.1)	(2.0, 17.3)
	Nail disorder	2 (3.6)	(0.4, 12.3)
	SOC: Investigations	37 (66.1)	(52.2, 78.2)
	Neutrophil count decreased	15 (26.8)	(15.8, 40.3)
	White blood cell count decreased	14 (25.0)	(14.4, 38.4)
	Aspartate aminotransferase increased	13 (23.2)	(13.0, 36.4)
	Platelet count decreased	12 (21.4)	(11.6, 34.4)
	Alanine aminotransferase increased	9 (16.1)	(7.6, 28.3)
	Lymphocyte count decreased	8 (14.3)	(6.4, 26.2)
	Blood bilirubin increased	5 (8.9)	(3.0, 19.6)
	Weight decreased	4 (7.1)	(2.0, 17.3)
	Blood alkaline phosphatase increased	3 (5.4)	(1.1, 14.9)
	Electrocardiogram QT prolonged	2 (3.6)	(0.4, 12.3)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
DS-8201a immediately following initial T-DM1	SOC: Infections and infestations	33 (58.9)	(45.0, 71.9)
Yes (N = 56)	Upper respiratory tract infection	10 (17.9)	(8.9, 30.4)
	Nasopharyngitis	7 (12.5)	(5.2, 24.1)
	Pneumonia	5 (8.9)	(3.0, 19.6)
	Urinary tract infection	2 (3.6)	(0.4, 12.3)
	SOC: Respiratory, thoracic and mediastinal disorders	32 (57.1)	(43.2, 70.3)
	Cough	10 (17.9)	(8.9, 30.4)
	Epistaxis	9 (16.1)	(7.6, 28.3)
	Dyspnoea	5 (8.9)	(3.0, 19.6)
	Interstitial lung disease	3 (5.4)	(1.1, 14.9)
	Pneumonitis	3 (5.4)	(1.1, 14.9)
	SOC: Nervous system disorders	28 (50.0)	(36.3, 63.7)
	Headache	14 (25.0)	(14.4, 38.4)
	Peripheral sensory neuropathy	6 (10.7)	(4.0, 21.9)
	Neuropathy peripheral	3 (5.4)	(1.1, 14.9)
	Dizziness	2 (3.6)	(0.4, 12.3)
	Dysgeusia	2 (3.6)	(0.4, 12.3)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
DS-8201a immediately following initial T-DM1	SOC: Blood and lymphatic system disorders	24 (42.9)	(29.7, 56.8)
Yes (N = 56)	Anaemia	21 (37.5)	(24.9, 51.5)
	Neutropenia	4 (7.1)	(2.0, 17.3)
	Lymphopenia	2 (3.6)	(0.4, 12.3)
	Thrombocytopenia	2 (3.6)	(0.4, 12.3)
	SOC: Metabolism and nutrition disorders	22 (39.3)	(26.5, 53.2)
	Decreased appetite	12 (21.4)	(11.6, 34.4)
	Hypokalaemia	4 (7.1)	(2.0, 17.3)
	SOC: Musculoskeletal and connective tissue disorders	22 (39.3)	(26.5, 53.2)
	Myalgia	8 (14.3)	(6.4, 26.2)
	Arthralgia	6 (10.7)	(4.0, 21.9)
	Back pain	5 (8.9)	(3.0, 19.6)
	Pain in extremity	4 (7.1)	(2.0, 17.3)
	Muscle spasms	1 (1.8)	(0.0, 9.6)
	SOC: Eye disorders	18 (32.1)	(20.3, 46.0)
	Dry eye	6 (10.7)	(4.0, 21.9)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
DS-8201a immediately following initial T-DM1	SOC: Psychiatric disorders	11 (19.6)	(10.2, 32.4)
Yes (N = 56)	Anxiety	6 (10.7)	(4.0, 21.9)
	Insomnia	5 (8.9)	(3.0, 19.6)
	SOC: Injury, poisoning and procedural complications	10 (17.9)	(8.9, 30.4)
	SOC: Renal and urinary disorders	7 (12.5)	(5.2, 24.1)
	SOC: Reproductive system and breast disorders	4 (7.1)	(2.0, 17.3)
	SOC: Cardiac disorders	3 (5.4)	(1.1, 14.9)
	SOC: Vascular disorders	3 (5.4)	(1.1, 14.9)
	SOC: Ear and labyrinth disorders	2 (3.6)	(0.4, 12.3)
	SOC: Hepatobiliary disorders	2 (3.6)	(0.4, 12.3)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
DS-8201a immediately following initial T-DM1	SOC: Gastrointestinal disorders	122 (95.3)	(90.1, 98.3)
No (N = 128)	Nausea	105 (82.0)	(74.3, 88.3)
	Vomiting	64 (50.0)	(41.0, 59.0)
	Constipation	46 (35.9)	(27.7, 44.9)
	Diarrhoea	46 (35.9)	(27.7, 44.9)
	Stomatitis	22 (17.2)	(11.1, 24.9)
	Abdominal pain	20 (15.6)	(9.8, 23.1)
	Dyspepsia	20 (15.6)	(9.8, 23.1)
	Gastrooesophageal reflux disease	15 (11.7)	(6.7, 18.6)
	Abdominal pain upper	10 (7.8)	(3.8, 13.9)
	Haemorrhoids	9 (7.0)	(3.3, 12.9)
	SOC: General disorders and administration site conditions	96 (75.0)	(66.6, 82.2)
	Fatigue	64 (50.0)	(41.0, 59.0)
	Asthenia	23 (18.0)	(11.7, 25.7)
	Oedema peripheral	14 (10.9)	(6.1, 17.7)
	Mucosal inflammation	13 (10.2)	(5.5, 16.7)
	Pyrexia	13 (10.2)	(5.5, 16.7)
	Influenza like illness	8 (6.3)	(2.7, 11.9)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
DS-8201a immediately following initial T-DM1	SOC: Skin and subcutaneous tissue disorders	77 (60.2)	(51.1, 68.7)
No (N = 128)	Alopecia	59 (46.1)	(37.2, 55.1)
	Rash	14 (10.9)	(6.1, 17.7)
	Nail disorder	8 (6.3)	(2.7, 11.9)
	Dry skin	7 (5.5)	(2.2, 10.9)
	SOC: Respiratory, thoracic and mediastinal disorders	73 (57.0)	(48.0, 65.7)
	Cough	35 (27.3)	(19.8, 35.9)
	Dyspnoea	26 (20.3)	(13.7, 28.3)
	Epistaxis	17 (13.3)	(7.9, 20.4)
	Pneumonitis	13 (10.2)	(5.5, 16.7)
	Interstitial lung disease	8 (6.3)	(2.7, 11.9)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
DS-8201a immediately following initial T-DM1	SOC: Investigations	69 (53.9)	(44.9, 62.8)
No (N = 128)	Neutrophil count decreased	26 (20.3)	(13.7, 28.3)
	White blood cell count decreased	22 (17.2)	(11.1, 24.9)
	Aspartate aminotransferase increased	20 (15.6)	(9.8, 23.1)
	Platelet count decreased	18 (14.1)	(8.6, 21.3)
	Alanine aminotransferase increased	12 (9.4)	(4.9, 15.8)
	Lymphocyte count decreased	11 (8.6)	(4.4, 14.9)
	Weight decreased	11 (8.6)	(4.4, 14.9)
	Blood bilirubin increased	10 (7.8)	(3.8, 13.9)
	Blood alkaline phosphatase increased	8 (6.3)	(2.7, 11.9)
	Electrocardiogram QT prolonged	8 (6.3)	(2.7, 11.9)
	SOC: Infections and infestations	66 (51.6)	(42.6, 60.5)
	Urinary tract infection	20 (15.6)	(9.8, 23.1)
	Upper respiratory tract infection	14 (10.9)	(6.1, 17.7)
	Nasopharyngitis	13 (10.2)	(5.5, 16.7)
	Pneumonia	5 (3.9)	(1.3, 8.9)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
DS-8201a immediately following initial T-DM1	SOC: Nervous system disorders	63 (49.2)	(40.3, 58.2)
No (N = 128)	Headache	26 (20.3)	(13.7, 28.3)
	Dizziness	17 (13.3)	(7.9, 20.4)
	Dysgeusia	11 (8.6)	(4.4, 14.9)
	Peripheral sensory neuropathy	10 (7.8)	(3.8, 13.9)
	Neuropathy peripheral	9 (7.0)	(3.3, 12.9)
	SOC: Metabolism and nutrition disorders	62 (48.4)	(39.5, 57.4)
	Decreased appetite	47 (36.7)	(28.4, 45.7)
	Hypokalaemia	18 (14.1)	(8.6, 21.3)
	SOC: Blood and lymphatic system disorders	56 (43.8)	(35.0, 52.8)
	Anaemia	37 (28.9)	(21.2, 37.6)
	Neutropenia	23 (18.0)	(11.7, 25.7)
	Thrombocytopenia	12 (9.4)	(4.9, 15.8)
	Lymphopenia	9 (7.0)	(3.3, 12.9)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
DS-8201a immediately following initial T-DM1	SOC: Musculoskeletal and connective tissue disorders	48 (37.5)	(29.1, 46.5)
No (N = 128)	Arthralgia	18 (14.1)	(8.6, 21.3)
	Back pain	15 (11.7)	(6.7, 18.6)
	Muscle spasms	14 (10.9)	(6.1, 17.7)
	Myalgia	10 (7.8)	(3.8, 13.9)
	Pain in extremity	8 (6.3)	(2.7, 11.9)
	SOC: Eye disorders	43 (33.6)	(25.5, 42.5)
	Dry eye	15 (11.7)	(6.7, 18.6)
	SOC: Vascular disorders	24 (18.8)	(12.4, 26.6)
	SOC: Cardiac disorders	19 (14.8)	(9.2, 22.2)
	SOC: Ear and labyrinth disorders	17 (13.3)	(7.9, 20.4)
	SOC: Psychiatric disorders	17 (13.3)	(7.9, 20.4)
	Insomnia	8 (6.3)	(2.7, 11.9)
	Anxiety	6 (4.7)	(1.7, 9.9)
	SOC: Injury, poisoning and procedural complications	16 (12.5)	(7.3, 19.5)
	SOC: Renal and urinary disorders	12 (9.4)	(4.9, 15.8)
	SOC: Hepatobiliary disorders	8 (6.3)	(2.7, 11.9)
	SOC: Reproductive system and breast disorders	8 (6.3)	(2.7, 11.9)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
HER2 status	SOC: Gastrointestinal disorders	144 (93.5)	(88.4, 96.8)
IHC3+ (N = 154)	Nausea	122 (79.2)	(72.0, 85.3)
	Vomiting	72 (46.8)	(38.7, 55.0)
	Constipation	53 (34.4)	(27.0, 42.5)
	Diarrhoea	48 (31.2)	(24.0, 39.1)
	Dyspepsia	28 (18.2)	(12.4, 25.2)
	Stomatitis	26 (16.9)	(11.3, 23.8)
	Abdominal pain	21 (13.6)	(8.6, 20.1)
	Gastrooesophageal reflux disease	14 (9.1)	(5.1, 14.8)
	Abdominal pain upper	13 (8.4)	(4.6, 14.0)
	Haemorrhoids	10 (6.5)	(3.2, 11.6)
	SOC: General disorders and administration site conditions	113 (73.4)	(65.7, 80.2)
	Fatigue	76 (49.4)	(41.2, 57.5)
	Asthenia	24 (15.6)	(10.2, 22.3)
	Mucosal inflammation	14 (9.1)	(5.1, 14.8)
	Oedema peripheral	14 (9.1)	(5.1, 14.8)
	Pyrexia	14 (9.1)	(5.1, 14.8)
	Influenza like illness	11 (7.1)	(3.6, 12.4)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
HER2 status	SOC: Skin and subcutaneous tissue disorders	101 (65.6)	(57.5, 73.0)
IHC3+ (N = 154)	Alopecia	76 (49.4)	(41.2, 57.5)
	Rash	19 (12.3)	(7.6, 18.6)
	Dry skin	9 (5.8)	(2.7, 10.8)
	Nail disorder	9 (5.8)	(2.7, 10.8)
	SOC: Investigations	93 (60.4)	(52.2, 68.2)
	Neutrophil count decreased	38 (24.7)	(18.1, 32.3)
	White blood cell count decreased	31 (20.1)	(14.1, 27.3)
	Aspartate aminotransferase increased	29 (18.8)	(13.0, 25.9)
	Platelet count decreased	27 (17.5)	(11.9, 24.5)
	Alanine aminotransferase increased	18 (11.7)	(7.1, 17.8)
	Lymphocyte count decreased	16 (10.4)	(6.1, 16.3)
	Weight decreased	13 (8.4)	(4.6, 14.0)
	Blood bilirubin increased	12 (7.8)	(4.1, 13.2)
	Electrocardiogram QT prolonged	9 (5.8)	(2.7, 10.8)
	Blood alkaline phosphatase increased	8 (5.2)	(2.3, 10.0)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
HER2 status	SOC: Respiratory, thoracic and mediastinal disorders	89 (57.8)	(49.6, 65.7)
IHC3+ (N = 154)	Cough	38 (24.7)	(18.1, 32.3)
	Dyspnoea	24 (15.6)	(10.2, 22.3)
	Epistaxis	24 (15.6)	(10.2, 22.3)
	Pneumonitis	13 (8.4)	(4.6, 14.0)
	Interstitial lung disease	11 (7.1)	(3.6, 12.4)
	SOC: Infections and infestations	83 (53.9)	(45.7, 61.9)
	Upper respiratory tract infection	21 (13.6)	(8.6, 20.1)
	Urinary tract infection	20 (13.0)	(8.1, 19.3)
	Nasopharyngitis	17 (11.0)	(6.6, 17.1)
	Pneumonia	9 (5.8)	(2.7, 10.8)
	SOC: Nervous system disorders	77 (50.0)	(41.8, 58.2)
	Headache	31 (20.1)	(14.1, 27.3)
	Dizziness	16 (10.4)	(6.1, 16.3)
	Peripheral sensory neuropathy	14 (9.1)	(5.1, 14.8)
	Dysgeusia	12 (7.8)	(4.1, 13.2)
	Neuropathy peripheral	11 (7.1)	(3.6, 12.4)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
HER2 status	SOC: Metabolism and nutrition disorders	71 (46.1)	(38.1, 54.3)
IHC3+ (N = 154)	Decreased appetite	53 (34.4)	(27.0, 42.5)
	Hypokalaemia	17 (11.0)	(6.6, 17.1)
	SOC: Blood and lymphatic system disorders	70 (45.5)	(37.4, 53.7)
	Anaemia	52 (33.8)	(26.4, 41.8)
	Neutropenia	25 (16.2)	(10.8, 23.0)
	Thrombocytopenia	13 (8.4)	(4.6, 14.0)
	Lymphopenia	9 (5.8)	(2.7, 10.8)
	SOC: Musculoskeletal and connective tissue disorders	55 (35.7)	(28.2, 43.8)
	Arthralgia	22 (14.3)	(9.2, 20.8)
	Myalgia	16 (10.4)	(6.1, 16.3)
	Back pain	14 (9.1)	(5.1, 14.8)
	Muscle spasms	11 (7.1)	(3.6, 12.4)
	Pain in extremity	10 (6.5)	(3.2, 11.6)
	SOC: Eye disorders	51 (33.1)	(25.8, 41.1)
	Dry eye	17 (11.0)	(6.6, 17.1)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
HER2 status	SOC: Psychiatric disorders	22 (14.3)	(9.2, 20.8)
IHC3+ (N = 154)	Insomnia	12 (7.8)	(4.1, 13.2)
	Anxiety	8 (5.2)	(2.3, 10.0)
	SOC: Injury, poisoning and procedural complications	21 (13.6)	(8.6, 20.1)
	SOC: Vascular disorders	20 (13.0)	(8.1, 19.3)
	SOC: Renal and urinary disorders	18 (11.7)	(7.1, 17.8)
	SOC: Cardiac disorders	17 (11.0)	(6.6, 17.1)
	SOC: Ear and labyrinth disorders	15 (9.7)	(5.6, 15.6)
	SOC: Reproductive system and breast disorders	10 (6.5)	(3.2, 11.6)
	SOC: Hepatobiliary disorders	9 (5.8)	(2.7, 10.8)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

[a] The two-sided 95% confidence intervals (CI) are based on the exact (Clopper-Pearson) binomial distribution.

Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
HER2 status	SOC: Gastrointestinal disorders	27 (96.4)	(81.7, 99.9)
ISH+ except IHC3+ (N = 28)	Nausea	20 (71.4)	(51.3, 86.8)
	Vomiting	14 (50.0)	(30.6, 69.4)
	Constipation	11 (39.3)	(21.5, 59.4)
	Diarrhoea	10 (35.7)	(18.6, 55.9)
	Abdominal pain	4 (14.3)	(4.0, 32.7)
	Gastrooesophageal reflux disease	4 (14.3)	(4.0, 32.7)
	Abdominal pain upper	3 (10.7)	(2.3, 28.2)
	Stomatitis	3 (10.7)	(2.3, 28.2)
	Dyspepsia	2 (7.1)	(0.9, 23.5)
	Haemorrhoids	1 (3.6)	(0.1, 18.3)
	SOC: General disorders and administration site conditions	22 (78.6)	(59.0, 91.7)
	Fatigue	14 (50.0)	(30.6, 69.4)
	Oedema peripheral	3 (10.7)	(2.3, 28.2)
	Pyrexia	3 (10.7)	(2.3, 28.2)
	Asthenia	2 (7.1)	(0.9, 23.5)
	Mucosal inflammation	2 (7.1)	(0.9, 23.5)
	Influenza like illness	1 (3.6)	(0.1, 18.3)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
HER2 status	SOC: Respiratory, thoracic and mediastinal disorders	15 (53.6)	(33.9, 72.5)
ISH+ except IHC3+ (N = 28)	Cough	7 (25.0)	(10.7, 44.9)
	Dyspnoea	7 (25.0)	(10.7, 44.9)
	Pneumonitis	3 (10.7)	(2.3, 28.2)
	Epistaxis	1 (3.6)	(0.1, 18.3)
	SOC: Skin and subcutaneous tissue disorders	15 (53.6)	(33.9, 72.5)
	Alopecia	13 (46.4)	(27.5, 66.1)
	Dry skin	2 (7.1)	(0.9, 23.5)
	Nail disorder	1 (3.6)	(0.1, 18.3)
	SOC: Infections and infestations	14 (50.0)	(30.6, 69.4)
	Nasopharyngitis	3 (10.7)	(2.3, 28.2)
	Upper respiratory tract infection	2 (7.1)	(0.9, 23.5)
	Urinary tract infection	2 (7.1)	(0.9, 23.5)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
HER2 status	SOC: Musculoskeletal and connective tissue disorders	14 (50.0)	(30.6, 69.4)
ISH+ except IHC3+ (N = 28)	Back pain	6 (21.4)	(8.3, 41.0)
	Muscle spasms	4 (14.3)	(4.0, 32.7)
	Myalgia	2 (7.1)	(0.9, 23.5)
	Pain in extremity	2 (7.1)	(0.9, 23.5)
	Arthralgia	1 (3.6)	(0.1, 18.3)
	SOC: Metabolism and nutrition disorders	13 (46.4)	(27.5, 66.1)
	Decreased appetite	6 (21.4)	(8.3, 41.0)
	Hypokalaemia	5 (17.9)	(6.1, 36.9)
	SOC: Nervous system disorders	13 (46.4)	(27.5, 66.1)
	Headache	8 (28.6)	(13.2, 48.7)
	Dizziness	3 (10.7)	(2.3, 28.2)
	Peripheral sensory neuropathy	2 (7.1)	(0.9, 23.5)
	Dysgeusia	1 (3.6)	(0.1, 18.3)
	Neuropathy peripheral	1 (3.6)	(0.1, 18.3)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
HER2 status	SOC: Investigations	12 (42.9)	(24.5, 62.8)
ISH+ except IHC3+ (N = 28)	White blood cell count decreased	5 (17.9)	(6.1, 36.9)
	Aspartate aminotransferase increased	4 (14.3)	(4.0, 32.7)
	Alanine aminotransferase increased	3 (10.7)	(2.3, 28.2)
	Blood alkaline phosphatase increased	3 (10.7)	(2.3, 28.2)
	Blood bilirubin increased	3 (10.7)	(2.3, 28.2)
	Lymphocyte count decreased	3 (10.7)	(2.3, 28.2)
	Platelet count decreased	3 (10.7)	(2.3, 28.2)
	Neutrophil count decreased	2 (7.1)	(0.9, 23.5)
	Weight decreased	2 (7.1)	(0.9, 23.5)
	Electrocardiogram QT prolonged	1 (3.6)	(0.1, 18.3)
	SOC: Blood and lymphatic system disorders	10 (35.7)	(18.6, 55.9)
	Anaemia	6 (21.4)	(8.3, 41.0)
	Lymphopenia	2 (7.1)	(0.9, 23.5)
	Neutropenia	2 (7.1)	(0.9, 23.5)
	Thrombocytopenia	1 (3.6)	(0.1, 18.3)
	SOC: Eye disorders	9 (32.1)	(15.9, 52.4)
	Dry eye	3 (10.7)	(2.3, 28.2)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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Table 24 Treatment-emergent adverse events by system organ class, preferred term with incidence >= 1% and observed for >= 10 patients per subgroup, overall and by subgroup - Safety Analysis Set

		Overall 5.4 mg/kg (N = 184)	
Subgroup	SOC/Preferred Term	n (%)	95% CI [a]
HER2 status	SOC: Vascular disorders	7 (25.0)	(10.7, 44.9)
ISH+ except IHC3+ (N = 28)	SOC: Cardiac disorders	5 (17.9)	(6.1, 36.9)
	SOC: Injury, poisoning and procedural complications	5 (17.9)	(6.1, 36.9)
	SOC: Psychiatric disorders	5 (17.9)	(6.1, 36.9)
	Anxiety	3 (10.7)	(2.3, 28.2)
	Insomnia	1 (3.6)	(0.1, 18.3)
	SOC: Ear and labyrinth disorders	4 (14.3)	(4.0, 32.7)
	SOC: Reproductive system and breast disorders	2 (7.1)	(0.9, 23.5)
	SOC: Hepatobiliary disorders	1 (3.6)	(0.1, 18.3)
	SOC: Renal and urinary disorders	1 (3.6)	(0.1, 18.3)

Notes: SOC: System organ class; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Percentages are based on the number of subjects in the Safety Analysis Set within the specified subgroup. Adverse events were coded using the MedDRA dictionary, Version 20.1. If a subject has more than one event per cycle, the subject is counted once at each level. Due to missing and/or invalid baseline data it was not possible to classify all subjects in the analysis set into a level for all the subgroups. Data cut-off date: 26 March 2021.

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