Dossier zur Nutzenbewertung gemäß § 35a SGB V

Selumetinib (Koselugo®)

Alexion Pharma Germany GmbH

Anhang 4-G5

Studie SPRINKLE
1. Datenschnitt vom 08. April 2024 –
weitere Auswertungen

Stand: 14.11.2025

Inhaltsverzeichnis

Anhang 4-G5 Studie SPRINKLE – weitere Auswertungen

1 Endpunktkategorie Sicherheit

1.1 Endpunkt Unerwünschte Ereignisse

1.1.1 Gesamtraten unerwünschter Ereignisse (UE) und nach Schweregrad inkl. Subgruppenanalysen

Study Code: D1346C00004 Phase I/II Page1 of 1
DCO1 PSC Data Cut-Off 2024-04-08
Table 1: Overall summary of adverse events - by age category and sex (Safety analysis set)

	Age Category		Sex		Study Total
	>=1 to <3 years (N=13) n (%)	>=3 to <7 years (N=23) n (%)	Female (N=14) n (%)	Male (N=22) n (%)	Total (N=36) n (%)
Any adverse event (AE)	13 (100)	23 (100)	14 (100)	22 (100)	36 (100)
Any AE of CTCAE Grade 3 or higher	2 (15.4)	2 (8.7)	1 (7.1)	3 (13.6)	4 (11.1)
Any AE of CTCAE Grade 3	2 (15.4)	2 (8.7)	1 (7.1)	3 (13.6)	4 (11.1)
Any AE of CTCAE Grade 4	0	0	0	0	0
Any AE of CTCAE Grade 5	0	0	0	0	0
Any serious adverse event (SAE)	1 (7.7)	1 (4.3)	0	2 (9.1)	2 (5.6)
Any AE leading to discontinuation of selumetinib	0	0	0	0	0
Any AE leading to interruption of selumetinib	5 (38.5)	6 (26.1)	6 (42.9)	5 (22.7)	11 (30.6)
Any AE leading to dose reduction of selumetinib	0	0	0	0	0

Includes AEs with an onset or worsening date on or after the date of first selumetinib dose up to and including 30 days after the date of last selumetinib dose.
Subjects with multiple occurrences in the same category are counted once per category regardless of the number of occurrences.
CTCAE Common Terminology Criteria for Adverse Events version 5.0.
N=Number of subjects per subgroup factor; n=Number of subjects per category.
Program: t_overall_ae.sas Date of output generation: 24OCT2025:16:59:02

1.1.2 Unerwünschte Ereignisse nach System Organ Class (SOC) und Preferred Terms (PT) bei ≥ 10 % der Patienten inkl. Subgruppenanalysen

Study Code: D1346C00004 Phase I/II Page 1 of 3
DCO1 PSC Data Cut-Off 2024-04-08
Table 2: Adverse Events by System Organ Class and Preferred Term occurring at least 10% in a study arm (Safety Analysis Set)

	Age Category		Sex		Study Total
System Organ Class Preferred Term	>=1 to < 3 years (N=13) n (%)	>=3 to < 7 years (N=23) n (%)	Female (N=14) n (%)	Male (N=22) n (%)	Total (N=36) n (%)
Subjects with any AE	13 (100.0)	23 (100.0)	14 (100.0)	22 (100.0)	36 (100.0)
INFECTIONS AND INFESTATIONS	11 (84.6)	20 (87.0)	12 (85.7)	19 (86.4)	31 (86.1)
Folliculitis	3 (23.1)	6 (26.1)	4 (28.6)	5 (22.7)	9 (25.0)
Gastroenteritis	2 (15.4)	3 (13.0)	1 (7.1)	4 (18.2)	5 (13.9)
Nasopharyngitis	2 (15.4)	4 (17.4)	5 (35.7)	1 (4.5)	6 (16.7)
Paronychia	6 (46.2)	10 (43.5)	6 (42.9)	10 (45.5)	16 (44.4)
Rhinitis	3 (23.1)	3 (13.0)	2 (14.3)	4 (18.2)	6 (16.7)
Upper respiratory tract infection	5 (38.5)	9 (39.1)	7 (50.0)	7 (31.8)	14 (38.9)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	4 (30.8)	5 (21.7)	1 (7.1)	8 (36.4)	9 (25.0)
Anaemia	3 (23.1)	5 (21.7)	1 (7.1)	7 (31.8)	8 (22.2)
METABOLISM AND NUTRITION DISORDERS	5 (38.5)	5 (21.7)	5 (35.7)	5 (22.7)	10 (27.8)
PSYCHIATRIC DISORDERS	1 (7.7)	3 (13.0)	2 (14.3)	2 (9.1)	4 (11.1)
NERVOUS SYSTEM DISORDERS	2 (15.4)	2 (8.7)	1 (7.1)	3 (13.6)	4 (11.1)

Includes AEs with an onset or worsening date on or after the date of first selumetinib dose up to and including 30 days after the date of last selumetinib dose.
A subject can have one or more preferred terms reported under a given system organ class.
N= Number of subjects per subgroup factor; n=Number of subjects with AE; Percentages are based on total number of subjects in the subgroup factor(N).
Sorted by international order for the system organ class and alphabetically for preferred term.
Program: t_ae_soc_pt.sas Date of output generation: 03NOV2025:16:53:47

Study Code: D1346C00004 Phase I/II
DCO1 PSC Data Cut-Off 2024-04-08
Table 2: Adverse Events by System Organ Class and Preferred Term occurring at least 10% in a study arm (Safety Analysis Set)

	Age Category		Sex		Study Total
System Organ Class Preferred Term	>=1 to < 3 years (N=13) n (%)	>=3 to < 7 years (N=23) n (%)	Female (N=14) n (%)	Male (N=22) n (%)	Total (N=36) n (%)
EYE DISORDERS	1 (7.7)	3 (13.0)	2 (14.3)	2 (9.1)	4 (11.1)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	6 (46.2)	6 (26.1)	4 (28.6)	8 (36.4)	12 (33.3)
Rhinorrhoea	2 (15.4)	2 (8.7)	2 (14.3)	2 (9.1)	4 (11.1)
GASTROINTESTINAL DISORDERS	11 (84.6)	18 (78.3)	9 (64.3)	20 (90.9)	29 (80.6)
Abdominal pain	1 (7.7)	4 (17.4)	2 (14.3)	3 (13.6)	5 (13.9)
Diarrhoea	6 (46.2)	8 (34.8)	3 (21.4)	11 (50.0)	14 (38.9)
Stomatitis	1 (7.7)	4 (17.4)	2 (14.3)	3 (13.6)	5 (13.9)
Vomiting	6 (46.2)	8 (34.8)	6 (42.9)	8 (36.4)	14 (38.9)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	12 (92.3)	21 (91.3)	14 (100.0)	19 (86.4)	33 (91.7)
Alopecia	3 (23.1)	5 (21.7)	4 (28.6)	4 (18.2)	8 (22.2)
Dry skin	4 (30.8)	13 (56.5)	6 (42.9)	11 (50.0)	17 (47.2)
Eczema	5 (38.5)	9 (39.1)	7 (50.0)	7 (31.8)	14 (38.9)
Hair colour changes	1 (7.7)	5 (21.7)	1 (7.1)	5 (22.7)	6 (16.7)

Includes AEs with an onset or worsening date on or after the date of first selumetinib dose up to and including 30 days after the date of last selumetinib dose.
A subject can have one or more preferred terms reported under a given system organ class.
N= Number of subjects per subgroup factor; n=Number of subjects with AE; Percentages are based on total number of subjects in the subgroup factor(N).
Sorted by international order for the system organ class and alphabetically for preferred term.
Program: t_ae_soc_pt.sas Date of output generation: 03NOV2025:16:53:47

Study Code: D1346C00004 Phase I/II
DCO1 PSC Data Cut-Off 2024-04-08
Table 2: Adverse Events by System Organ Class and Preferred Term occurring at least 10% in a study arm (Safety Analysis Set)

	Age Category		Sex		Study Total
System Organ Class Preferred Term	>=1 to < 3 years (N=13) n (%)	>=3 to < 7 years (N=23) n (%)	Female (N=14) n (%)	Male (N=22) n (%)	Total (N=36) n (%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	9 (69.2)	12 (52.2)	6 (42.9)	15 (68.2)	21 (58.3)
Fatigue	1 (7.7)	5 (21.7)	1 (7.1)	5 (22.7)	6 (16.7)
Pyrexia	8 (61.5)	9 (39.1)	5 (35.7)	12 (54.5)	17 (47.2)
INVESTIGATIONS	2 (15.4)	10 (43.5)	3 (21.4)	9 (40.9)	12 (33.3)
Aspartate aminotransferase increased	1 (7.7)	3 (13.0)	0	4 (18.2)	4 (11.1)
Blood creatine phosphokinase increased	2 (15.4)	9 (39.1)	3 (21.4)	8 (36.4)	11 (30.6)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	4 (17.4)	1 (7.1)	3 (13.6)	4 (11.1)

Includes AEs with an onset or worsening date on or after the date of first selumetinib dose up to and including 30 days after the date of last selumetinib dose.
A subject can have one or more preferred terms reported under a given system organ class.
N= Number of subjects per subgroup factor; n=Number of subjects with AE; Percentages are based on total number of subjects in the subgroup factor(N).
Sorted by international order for the system organ class and alphabetically for preferred term.
Program: t_ae_soc_pt.sas Date of output generation: 03NOV2025:16:53:47

1.1.3 Schwere unerwünschte Ereignisse (CTCAE Grad ≥ 3) nach System Organ Class (SOC) und Preferred Terms (PT) bei ≥ 5 % der Patienten inkl. Subgruppenanalysen

Study Code: D1346C00004 Phase I/II
DCO1 PSC Data Cut-Off 2024-04-08
Table 3: Adverse Events CTCAE Grade 3 or higher by System Organ Class and Preferred Term occurring at least 5% in a study arm (Safety Analysis Set)

	Age Category		Sex		Study Total
System Organ Class Preferred Term	>=1 to < 3 years (N=13) n (%)	>=3 to < 7 years (N=23) n (%)	Female (N=14) n (%)	Male (N=22) n (%)	Total (N=36) n (%)
Subjects with any AE of CTCAE Grade 3 or higher	2 (15.4)	2 (8.7)	1 (7.1)	3 (13.6)	4 (11.1)
INFECTIONS AND INFESTATIONS	1 (7.7)	1 (4.3)	0	2 (9.1)	2 (5.6)

Includes AEs with an onset or worsening date on or after the date of first selumetinib dose up to and including 30 days after the date of last selumetinib dose.
A subject can have one or more preferred terms reported under a given system organ class.
N= Number of subjects per subgroup factor; n=Number of subjects with AE; Percentages are based on total number of subjects in the subgroup factor(N).
Sorted by international order for the system organ class and alphabetically for preferred term.
Program: t_ae_soc_pt.sas Date of output generation: 03NOV2025:16:53:49

1.1.4 Schwerwiegende unerwünschte Ereignisse nach System Organ Class (SOC) und Preferred Terms (PT) bei ≥ 5 % der Patienten

Study Code: D1346C00004 Phase I/II Page 1 of 1
DCO1 PSC Data Cut-Off 2024-04-08
Table 4: Serious Adverse Events by System Organ Class and Preferred Term occurring at least 5% in a study arm (Safety Analysis Set)

No data to report as there are no SOC or PT for serious adverse events with at least 5% frequency in study arm.

Program: t_ae_soc_pt.sas Date of output generation: 03NOV2025:16:53:49

1.1.5 Abbruch der Studienmedikation aufgrund von unerwünschten Ereignissen nach System Organ Class (SOC) und Preferred Terms (PT)

Study Code: D1346C00004 Phase I/II Page 1 of 1
DCO1 PSC Data Cut-Off 2024-04-08
Table 5: Adverse Events leading to discontinuation of selumetinib by System Organ Class and Preferred Term

No data to report as there are no adverse events leading to discontinuation of selumetinib.

Program: t_ae_soc_pt_disc.sas Date of output generation: 24OCT2025:17:01:30

1.1.6 Adverse Events of Special Interest (AESI)

1.1.6.1 Operationalisierung Adverse Events of Special Interest (AESI) in der Studie SPRINKLE

Tabelle 6: Operationalisierung Adverse Events of Special Interest (AESI) in der Studie **SPRINKLE**

AESI	**MedDRA Preferred Terms Defining the AESIs**
Ocular toxicity	Chorioretinopathy (central serous retinopathy); Retinal detachment; Retinal tear; Vision blurred; Visual impairment; Vitreous floaters; Photopsia; Eye disorder; Photophobia; Retinal vein occlusion; Detachment of retinal pigment epithelium (Retinal pigment epithelial detachment).
Hepatotoxicity	DILI; ALT increased; AST increased.
Muscular toxicity	Blood creatine phosphokinase increased; Musculoskeletal pain; Muscular weakness; Myalgia; Rhabdomyolysis; Myoglobin blood increased; Myoglobin urine present; Acute kidney injury; Myopathy.
Cardiac toxicity	Ejection fraction decreased; Oedema peripheral; Peripheral swelling; Oedema; Left ventricular dysfunction; Ventricular dysfunction.
Physeal dysplasia	Metaphyseal dysplasia; Multiple epiphyseal dysplasia; Arthralgia; Joint stiffness; Joint hyperextension; Gait disturbance; Short stature.
Choking	Choking; Retching.

AESI: adverse event of special interest; ALT: alanine transaminase; AST: aspartate transaminase; DILI: drug-induced liver injury; MedDRA: Medical Dictionary for Regulatory Activities.

Quelle: AstraZeneca. Clinical Study Report – D1346C00004: A Phase I/II, Single-Arm, Open-label Study to Evaluate the Pharmacokinetics, Safety/Tolerability and Efficacy of the Selumetinib Granule Formulation in Children Aged ≥ 1 to < 7 Years with Neurofibromatosis Type 1 (NF1) Related Symptomatic, Inoperable Plexiform Neurofibromas (PN) (SPRINKLE). Clinical Study Report (Primary Analysis). Data on File. Stand: 05.08.2024. 2024.

1.1.6.2 Gesamtraten Adverse Events of Special Interest (AESI)

Tabelle 7: Ergebnisse für den Endpunkt „Gesamtraten unerwünschter Ereignisse von besonderem Interesse“ aus der Studie **SPRINKLE**

Studie	**Selumetinib 25 mg/m² BID**
SPRINKLE **Datenschnitt: 08. April 2024**	***Safety*-Population** **N = 36**
Gesamtraten AESI	**Anzahl Patienten, n/N (%)**
Jegliches AESI	13/36 (36,1)
AESI – Okulotoxizität	2/36 (5,6)
AESI – Lebertoxizität	4/36 (11,1)
AESI – Muskeltoxizität	11/36 (30,6)
AESI – Kardiotoxizität	1/36 (2,8)
AESI: Unerwünschte Ereignisse von besonderem Interesse (engl. Adverse Events of Special Interest); BID: Zweimal täglich. Quelle: AstraZeneca. Clinical Study Report – D1346C00004: A Phase I/II, Single-Arm, Open-label Study to Evaluate the Pharmacokinetics, Safety/Tolerability and Efficacy of the Selumetinib Granule Formulation in Children Aged ≥ 1 to < 7 Years with Neurofibromatosis Type 1 (NF1) Related Symptomatic, Inoperable Plexiform Neurofibromas (PN) (SPRINKLE). Clinical Study Report (Primary Analysis). Data on File. Stand: 05.08.2024. 2024.	