Dossier zur Nutzenbewertung gemäß § 35a SGB V

Difelikefalin (Kapruvia[®])

Fresenius Medical Care Nephrologica Deutschland GmbH

Separater Anhang 4-I

Erwachsene Hämodialysepatienten mit moderatem bis schwerem Pruritus im Zusammenhang mit einer CKD

> Medizinischer Nutzen und medizinischer Zusatznutzen, Patientengruppen mit therapeutisch bedeutsamem Zusatznutzen

> > Stand: 29.09.2022

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Table CT3DDO_LMHO: Change from OL-baseline in 5-D degree score SAF-L

		Treatment	N	n (%)	Mean (SD)	Min	Q50	Max
5-D degree score	OL Baseline	Pre: CR845	151	151 (100.0)	2.5 (0.8)	1	2.0	5
J-D degree score	OL DASEIINE	Pre: Placebo	162	162 (100.0)	2.8 (0.9)	1	3.0	5
	OL Week 4	Pre: CR845	151	146 (96.7)	2.4 (0.8)	1	2.0	5
	OD WEEK T	Pre: Placebo	162	152 (93.8)	2.5 (0.8)	1	2.0	5
	OL Week 8	Pre: CR845	151	141 (93.4)	2.3 (0.8)	1	2.0	5
	OH WEEK O	Pre: Placebo	162	150 (92.6)	2.4 (0.9)	1	2.0	5
	OL Week 12	Pre: CR845	151	134 (88.7)	2.3 (0.8)	1	2.0	5
	OH WEEK IN	Pre: Placebo	162	142 (87.7)	2.3 (0.8)	1	2.0	5
	OL Week 24	Pre: CR845	151	126 (83.4)	2.2 (0.8)	1	2.0	5
	OH WEEK L4	Pre: Placebo	162	130 (80.2)	2.3 (0.9)	1	2.0	5
	OL Week 36	Pre: CR845	151	121 (80.1)	2.2 (0.8)	1	2.0	5
		Pre: Placebo	162	123 (75.9)	2.3 (0.8)	1	2.0	5
	OL Week 52	Pre: CR845	151	92 (60.9)	2.1 (0.9)	1	2.0	4
		Pre: Placebo	162	94 (58.0)	2.3 (0.9)	1	2.0	5
Change from OL-baseline in 5-D degree score	OL Week 4	Pre: CR845	151	146 (96.7)	-0.1 (0.8)	-3	0.0	2
		Pre: Placebo	162	152 (93.8)	-0.3 (1.0)	-3	0.0	2
	OL Week 8	Pre: CR845	151	141 (93.4)	-0.2 (0.8)	-3	0.0	2
		Pre: Placebo	162	150 (92.6)	-0.5(1.0)	-3	0.0	3
	OL Week 12	Pre: CR845	151	134 (88.7)	-0.3 (0.9)	-3	0.0	2
		Pre: Placebo	162	142 (87.7)	-0.5(1.0)	-3	-1.0	2
	OL Week 24	Pre: CR845	151	126 (83.4)	-0.3 (0.9)	-4	0.0	2
		Pre: Placebo	162	130 (80.2)	-0.6 (1.2)	-3	0.0	3
	OL Week 36	Pre: CR845	151	121 (80.1)	-0.3 (0.8)	-3	0.0	2
		Pre: Placebo	162	123 (75.9)	-0.6 (1.1)	-3	-1.0	3
	OL Week 52	Pre: CR845	151	92 (60.9)	-0.4 (1.0)	-4	0.0	2
		Pre: Placebo	162	94 (58.0)	-0.6 (1.2)	-3	-1.0	3

Note: SAF-L = Week 52 Safety set.

Table CT3DDO_LMD0:	Change from	OL-baseline	in 5-D degree	score - 2	LSMEANS	confidence	intervals
			SAF-L				

a) c a				Repeated mea	sures analysis
Change from C degree score	L-baseline in 5-D	_		Change fr	om Baseline
Time	Treatment	Ν	n (%)	LS-Mean (SE)	95% CI
OL Week 4	Pre: CR845	151	146 (96.7)	-0.1(0.1)	(-0.2, -0.0)
	Pre: Placebo	162	152 (93.8)	-0.3 (0.1)	(-0.5, -0.2)
OL Week 8	Pre: CR845	151	141 (93.4)	-0.2 (0.1)	(-0.3, -0.1)
	Pre: Placebo	162	150 (92.6)	-0.4 (0.1)	(-0.6, -0.3)
OL Week 12	Pre: CR845	151	134 (88.7)	-0.2 (0.1)	(-0.4, -0.1)
	Pre: Placebo	162	142 (87.7)	-0.5 (0.1)	(-0.7, -0.4)
OL Week 24	Pre: CR845	151	126 (83.4)	-0.3 (0.1)	(-0.4, -0.1)
	Pre: Placebo	162	130 (80.2)	-0.5 (0.1)	(-0.7, -0.4)
OL Week 36	Pre: CR845	151	121 (80.1)	-0.3 (0.1)	(-0.4, -0.2)
	Pre: Placebo	162	123 (75.9)	-0.6 (0.1)	(-0.7, -0.4)
OL Week 52	Pre: CR845	151	92 (60.9)	-0.4 (0.1)	(-0.6, -0.3)
	Pre: Placebo	162	94 (58.0)	-0.6 (0.1)	(-0.8, -0.4)

Note: SAF-L = Week 52 Safety set.

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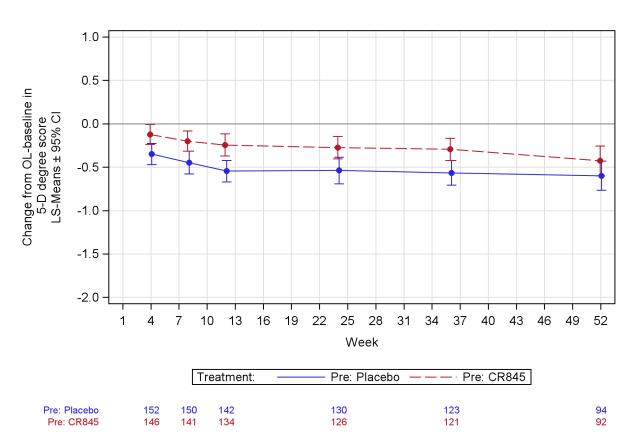


Figure CF3DDO_LMG0: Change from OL-baseline in 5-D degree score - Course of LSMEANS SAF-L

Note: SAF-L = Week 52 Safety set.

Symbols present least square mean (LS-Mean), bars present 95% confidence intervals (CI).

CR845 = Difelikefalin, OL - baseline = Baseline of open label period.

Source Table: CT3DDO LMD0

Table CT3DLO_LMHO: Change from OL-baseline in 5-D duration score SAF-L

		Treatment	Ν	n (%)	Mean (SD)	Min	Q50	Max
5-D duration score	OL Baseline	Pre: CR845	1 5 1	151 (100 0)	1 7 (1 0)	1	1 0	F
5-D duration score	OL Baseline	Pre: CR845 Pre: Placebo	151 162	151 (100.0) 162 (100.0)	1.7 (1.0) 2.2 (1.3)	1 1	1.0 2.0	5 5
	OL Week 4	Pre: CR845	162	146 (96.7)	1.5(0.9)	1	2.0	5
	OL Week 4	Pre: Placebo	162	146 (98.7) 152 (93.8)	1.3 (0.9) 1.8 (1.2)	1	1.0	5
	OL Week 8	Pre: CR845	162	141 (93.4)	1.8 (1.2) 1.4 (0.9)	1	1.0	5
	OL WEEK 0	Pre: Placebo	162	150 (92.6)	1.4 (0.9) 1.7 (1.1)	1	1.0	5
	OL Week 12	Pre: CR845	162	134 (88.7)	1.7 (1.1) 1.4 (0.8)	1	1.0	5
	OL Week 12	Pre: Placebo	162			1	1.0	5
	OL Week 24	Pre: CR845		142 (87.7) 125 (82.8)	1.7(1.1)		1.0	
	OL Week 24	Pre: CR845 Pre: Placebo	151	· · ·	1.5 (0.9)	1		5
	OT Usels 20		162	130 (80.2)	1.7(1.1)	1	1.0	5
	OL Week 36	Pre: CR845 Pre: Placebo	151	120 (79.5)	1.4 (0.8)	1	1.0	5
			162	123 (75.9)	1.7(1.1)	1	1.0	5
	OL Week 52	Pre: CR845	151	92 (60.9)	1.3 (0.8)	1	1.0	5
		Pre: Placebo	162	94 (58.0)	1.5 (1.0)	1	1.0	5
Change from OL-baseline in 5-D duration score	OL Week 4	Pre: CR845	151	146 (96.7)	-0.3 (0.9)	-4	0.0	3
		Pre: Placebo	162	152 (93.8)	-0.4(1.3)	-4	0.0	4
	OL Week 8	Pre: CR845	151	141 (93.4)	-0.3 (1.0)	-4	0.0	4
		Pre: Placebo	162	150 (92.6)	-0.6(1.3)	-4	0.0	4
	OL Week 12	Pre: CR845	151	134 (88.7)	-0.3 (0.9)	-4	0.0	4
		Pre: Placebo	162	142 (87.7)	-0.5(1.2)	-4	0.0	4
	OL Week 24	Pre: CR845	151	125 (82.8)	-0.2 (1.1)	-4	0.0	4
		Pre: Placebo	162	130 (80.2)	-0.6 (1.2)	-4	0.0	2
	OL Week 36	Pre: CR845	151	120 (79.5)	-0.4(0.9)	-4	0.0	2
		Pre: Placebo	162	123 (75.9)	-0.6(1.4)	-4	0.0	3
	OL Week 52	Pre: CR845	151	92 (60.9)	-0.5 (1.0)	-4	0.0	3
		Pre: Placebo	162	94 (58.0)	-0.8 (1.5)	-4	0.0	3
				()		-		-

Note: SAF-L = Week 52 Safety set.

Table CT3DLO_LMD0:	Change	from	OL-baseline	in	5-D	duration	score	-	LSMEANS	confidence	intervals
				S	SAF-I	L					

duration scor	L-baseline in 5-D e			Change fr	om Baseline
Time	Treatment	N	n (%)	LS-Mean (SE)	95% CI
OL Week 4	Pre: CR845	151	146 (96.7)	-0.3 (0.1)	(-0.4, -0.1)
	Pre: Placebo	162	152 (93.8)	· · · ·	, , ,
OL Week 8	Pre: CR845	151	141 (93.4)	-0.3 (0.1)	(-0.5, -0.2)
	Pre: Placebo	162	150 (92.6)	-0.6 (0.1)	(-0.7, -0.4)
OL Week 12	Pre: CR845	151	134 (88.7)	-0.3 (0.1)	(-0.5, -0.2)
	Pre: Placebo	162	142 (87.7)	-0.6 (0.1)	(-0.7, -0.4)
OL Week 24	Pre: CR845	151	125 (82.8)	-0.3 (0.1)	(-0.4, -0.1)
	Pre: Placebo	162	130 (80.2)	-0.6 (0.1)	(-0.8, -0.4)
OL Week 36	Pre: CR845	151	120 (79.5)	-0.4 (0.1)	(-0.5, -0.2)
	Pre: Placebo	162	123 (75.9)	-0.6 (0.1)	(-0.8, -0.4)
OL Week 52	Pre: CR845	151	92 (60.9)	-0.5 (0.1)	(-0.6, -0.3)
	Pre: Placebo	162	94 (58.0)	-0.7(0.1)	(-0.9, -0.5)

Note: SAF-L = Week 52 Safety set.

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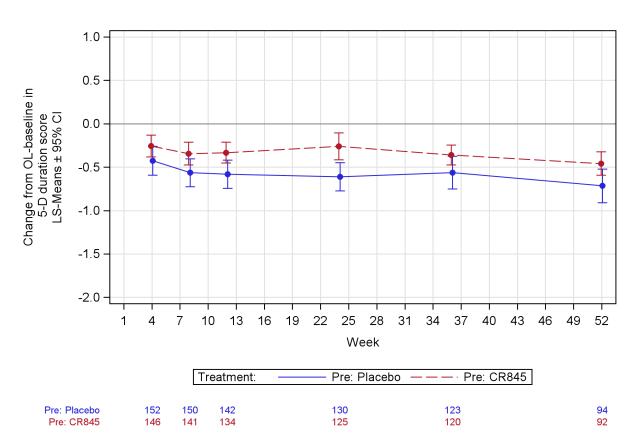


Figure CF3DLO_LMG0: Change from OL-baseline in 5-D duration score - Course of LSMEANS SAF-L

Note: SAF-L = Week 52 Safety set.

Symbols present least square mean (LS-Mean), bars present 95% confidence intervals (CI).

CR845 = Difelikefalin, OL - baseline = Baseline of open label period.

Source Table: CT3DLO LMD0

Table CT3DWO_LMHO: Change from OL-baseline in 5-D direction score SAF-L

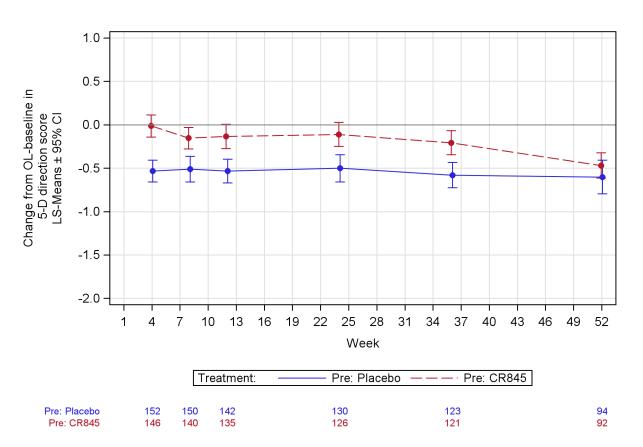
		Treatment	Ν	n (%)	Mean (SD)	Min	Q50	Max
5-D direction score	OL Baseline	Pre: CR845	151	151 (100.0)	2.5 (0.8)	1	2.0	5
5-D direction score	OL DASEIINE	Pre: Placebo	162	162 (100.0)	2.3 (0.8) 2.9 (1.0)	1	2.0	5
	OL Week 4	Pre: CR845	151	146 (96.7)	2.5 (0.9)	1	2.0	5
	OL WEEK 4	Pre: Placebo	162	152 (93.8)	2.3 (0.3) 2.4 (0.8)	1	2.0	5
	OL Week 8	Pre: CR845	151	140 (92.7)	2.3 (0.8)	1	2.0	5
		Pre: Placebo	162	150 (92.6)	2.4 (1.0)	1	2.0	5
	OL Week 12	Pre: CR845	151	135 (89.4)	2.4 (0.9)	1	2.0	5
		Pre: Placebo	162	142 (87.7)	2.4 (0.9)	1	2.0	5
	OL Week 24	Pre: CR845	151	126 (83.4)	2.4 (0.8)	1	2.0	5
		Pre: Placebo	162	130 (80.2)	2.4 (1.0)	1	2.0	5
	OL Week 36	Pre: CR845	151	121 (80.1)	2.3 (0.8)	1	2.0	5
		Pre: Placebo	162	123 (75.9)	2.3 (0.9)	1	2.0	5
	OL Week 52	Pre: CR845	151	92 (60.9)	2.0 (0.8)	1	2.0	4
		Pre: Placebo	162	94 (58.0)	2.3 (1.0)	1	2.0	5
Change from OL-baseline in 5-D direction score	OL Week 4	Pre: CR845	151	146 (96.7)	-0.0 (0.9)	-2	0.0	3
		Pre: Placebo	162	152 (93.8)	-0.5(1.1)	-3	0.0	2
	OL Week 8	Pre: CR845	151	140 (92.7)	-0.2 (0.9)	-2	0.0	3
		Pre: Placebo	162	150 (92.6)	-0.5 (1.2)	-4	0.0	3
	OL Week 12	Pre: CR845	151	135 (89.4)	-0.1 (1.0)	-3	0.0	3
		Pre: Placebo	162	142 (87.7)	-0.5 (1.1)	-4	0.0	2
	OL Week 24	Pre: CR845	151	126 (83.4)	-0.1 (1.0)	-3	0.0	3
		Pre: Placebo	162	130 (80.2)	-0.5 (1.1)	-3	0.0	4
	OL Week 36	Pre: CR845	151	121 (80.1)	-0.2 (0.9)	-2	0.0	2
		Pre: Placebo	162	123 (75.9)	-0.6 (1.0)	-3	-1.0	2
	OL Week 52	Pre: CR845	151	92 (60.9)	-0.4 (0.9)	-3	0.0	1
		Pre: Placebo	162	94 (58.0)	-0.7 (1.3)	-4	-1.0	3

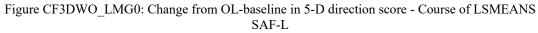
Note: SAF-L = Week 52 Safety set.

Table CT3DWO_LMD0:	Change from	OL-baseline	in	5-D	direction	score	- LSME	ANS	confidence i	ntervals	
			:	SAF-	L						

Chango from O	L-baseline in 5-D			Repeated mea	sures analysis
direction sco				Change fr	om Baseline
Time	Treatment	N	n (%)	LS-Mean (SE)	95% CI
OL Week 4	Pre: CR845	151	146 (96.7)	-0.0 (0.1)	(-0.1, 0.1)
	Pre: Placebo	162	152 (93.8)	-0.5 (0.1)	(-0.7, -0.4)
OL Week 8	Pre: CR845	151	140 (92.7)	-0.2 (0.1)	(-0.3, -0.0)
	Pre: Placebo	162	150 (92.6)	-0.5 (0.1)	(-0.7, -0.4)
OL Week 12	Pre: CR845	151	135 (89.4)	-0.1 (0.1)	(-0.3, 0.0)
	Pre: Placebo	162	142 (87.7)	-0.5 (0.1)	(-0.7, -0.4)
OL Week 24	Pre: CR845	151	126 (83.4)	-0.1 (0.1)	(-0.2, 0.0)
	Pre: Placebo	162	130 (80.2)	-0.5 (0.1)	(-0.7, -0.3)
OL Week 36	Pre: CR845	151	121 (80.1)	-0.2 (0.1)	(-0.3, -0.1)
	Pre: Placebo	162	123 (75.9)	-0.6 (0.1)	(-0.7, -0.4)
OL Week 52	Pre: CR845	151	92 (60.9)	-0.5 (0.1)	(-0.6, -0.3)
	Pre: Placebo	162	94 (58.0)	-0.6 (0.1)	(-0.8, -0.4)

Note: SAF-L = Week 52 Safety set.





Note: SAF-L = Week 52 Safety set.

Symbols present least square mean (LS-Mean), bars present 95% confidence intervals (CI).

CR845 = Difelikefalin, OL - baseline = Baseline of open label period.

Source Table: CT3DWO LMD0

Source Data: afived, created on: 07MAR2022

Table CT3DNO_LMHO: Change from OL-baseline in 5-D disability score SAF-L

		Treatment	N	n (%)	Mean (SD)	Min	Q50	Max
5-D disability score	OL Baseline	Pre: CR845	151	151 (100.0)	2.5 (1.2)	1	2.0	5
5-D disability score	OL DASEIINE	Pre: Placebo	162	151 (100.0) 162 (100.0)	2.3 (1.2) 2.8 (1.2)	1	3.0	5
	OL Week 4	Pre: CR845	151	146 (96.7)	2.4(1.2)	1	2.0	5
	OL WEEK I	Pre: Placebo	162	152 (93.8)	2.3 (1.2)	1	2.0	5
	OL Week 8	Pre: CR845	151	141 (93.4)	2.2 (1.2)	1	2.0	5
		Pre: Placebo	162	150 (92.6)	2.3 (1.2)	1	2.0	5
	OL Week 12	Pre: CR845	151	135 (89.4)	2.2 (1.1)	1	2.0	5
		Pre: Placebo	162	142 (87.7)	2.3 (1.1)	1	2.0	5
	OL Week 24	Pre: CR845	151	126 (83.4)	2.1 (1.1)	1	2.0	5
		Pre: Placebo	162	130 (80.2)	2.4 (1.2)	1	2.0	5
	OL Week 36	Pre: CR845	151	121 (80.1)	2.1 (1.1)	1	2.0	5
		Pre: Placebo	162	123 (75.9)	2.2 (1.2)	1	2.0	5
	OL Week 52	Pre: CR845	151	92 (60.9)	1.9 (1.1)	1	2.0	5
		Pre: Placebo	162	94 (58.0)	2.2 (1.2)	1	2.0	5
Change from OL-baseline in 5-D disability score	OL Week 4	Pre: CR845	151	146 (96.7)	-0.1 (1.0)	-2	0.0	3
-		Pre: Placebo	162	152 (93.8)	-0.5(1.3)	-4	0.0	3
	OL Week 8	Pre: CR845	151	141 (93.4)	-0.3 (1.1)	-3	0.0	3
		Pre: Placebo	162	150 (92.6)	-0.5 (1.3)	-4	0.0	4
	OL Week 12	Pre: CR845	151	135 (89.4)	-0.3 (1.1)	-3	0.0	3
		Pre: Placebo	162	142 (87.7)	-0.5 (1.3)	-4	0.0	3
	OL Week 24	Pre: CR845	151	126 (83.4)	-0.4 (1.1)	-3	0.0	3
		Pre: Placebo	162	130 (80.2)	-0.4 (1.4)	-4	0.0	3
	OL Week 36	Pre: CR845	151	121 (80.1)	-0.4 (1.1)	-3	0.0	3
		Pre: Placebo	162	123 (75.9)	-0.6 (1.5)	-4	-1.0	3
	OL Week 52	Pre: CR845	151	92 (60.9)	-0.5 (1.3)	-4	0.0	4
		Pre: Placebo	162	94 (58.0)	-0.7 (1.4)	-4	-1.0	4

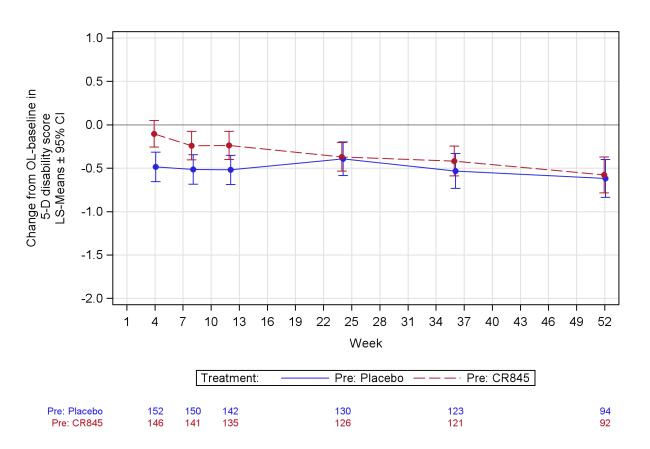
Note: SAF-L = Week 52 Safety set.

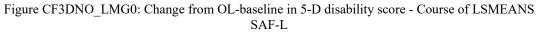
Table CT3DNO_LMD0:	Change	from OL-baseline	in	5-D disability	score	- LSMEANS	confidence	intervals
				SAF-L				

Change from O disability sc	L-baseline in 5-D ore			Change fr	om Baseline
Time	Treatment	Ν	n (%)	LS-Mean (SE)	95% CI
OL Week 4	Pre: CR845	151	146 (96.7)	-0.1(0.1)	(-0.3, 0.1)
	Pre: Placebo	162	152 (93.8)		(-0.7, -0.3)
DL Week 8	Pre: CR845	151	141 (93.4)	-0.2 (0.1)	(-0.4, -0.1)
	Pre: Placebo	162	150 (92.6)	-0.5 (0.1)	(-0.7, -0.3)
OL Week 12	Pre: CR845	151	135 (89.4)	-0.2 (0.1)	(-0.4, -0.1)
	Pre: Placebo	162	142 (87.7)	-0.5 (0.1)	(-0.7, -0.4)
OL Week 24	Pre: CR845	151	126 (83.4)	-0.4 (0.1)	(-0.5, -0.2)
	Pre: Placebo	162	130 (80.2)	-0.4 (0.1)	(-0.6, -0.2)
OL Week 36	Pre: CR845	151	121 (80.1)	-0.4 (0.1)	(-0.6, -0.2)
	Pre: Placebo	162	123 (75.9)	-0.5 (0.1)	(-0.7, -0.3)
OL Week 52	Pre: CR845	151	92 (60.9)	-0.6 (0.1)	(-0.8, -0.4)
	Pre: Placebo	162	94 (58.0)	-0.6 (0.1)	(-0.8, -0.4)

Note: SAF-L = Week 52 Safety set.

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Note: SAF-L = Week 52 Safety set.

Symbols present least square mean (LS-Mean), bars present 95% confidence intervals (CI).

CR845 = Difelikefalin, OL - baseline = Baseline of open label period.

Source Table: CT3DNO LMD0

Table CT3DVO_LMHO: Change from OL-baseline in 5-D distribution score SAF-L

		Treatment	Ν	n (%)	Mean (SD)	Min	Q50	Max
5-D distribution score	OL Baseline	Pre: CR845	151	151 (100.0)	2.7 (1.2)	1	3.0	5
5 D distribution score	Of Dascrine	Pre: Placebo	162	162 (100.0)	3.1 (1.2)	1	3.0	5
	OL Week 4	Pre: CR845	151	146 (96.7)	2.5 (1.2)	1	2.0	5
		Pre: Placebo	162	152 (93.8)	2.7 (1.3)	1	3.0	5
	OL Week 8	Pre: CR845	151	141 (93.4)	2.3 (1.1)	1	2.0	5
		Pre: Placebo	162	150 (92.6)	2.6 (1.2)	1	2.0	5
	OL Week 12	Pre: CR845	151	135 (89.4)	2.4 (1.3)	1	2.0	5
		Pre: Placebo	162	142 (87.7)	2.6 (1.2)	1	3.0	5
	OL Week 24	Pre: CR845	151	126 (83.4)	2.3 (1.2)	1	2.0	5
		Pre: Placebo	162	130 (80.2)	2.4 (1.2)	1	2.0	5
	OL Week 36	Pre: CR845	151	122 (80.8)	2.2 (1.2)	1	2.0	5
		Pre: Placebo	162	123 (75.9)	2.3 (1.2)	1	2.0	5
	OL Week 52	Pre: CR845	151	92 (60.9)	2.1 (1.1)	1	2.0	5
		Pre: Placebo	162	94 (58.0)	2.2 (1.2)	1	2.0	5
Change from OL-baseline in 5-D distribution score	OL Week 4	Pre: CR845	151	146 (96.7)	-0.2 (1.0)	-3	0.0	2
		Pre: Placebo	162	152 (93.8)	-0.4 (1.1)	-4	0.0	2
	OL Week 8	Pre: CR845	151	141 (93.4)	-0.4(1.0)	-4	0.0	2
		Pre: Placebo	162	150 (92.6)	-0.5(1.2)	-4	0.0	4
	OL Week 12	Pre: CR845	151	135 (89.4)	-0.4 (1.2)	-4	0.0	3
		Pre: Placebo	162	142 (87.7)	-0.5(1.1)	-4	0.0	4
	OL Week 24	Pre: CR845	151	126 (83.4)	-0.5(1.0)	-4	0.0	2
		Pre: Placebo	162	130 (80.2)	-0.7 (1.2)	-4	-1.0	4
	OL Week 36	Pre: CR845	151	122 (80.8)	-0.6 (1.0)	-3	-0.5	3
		Pre: Placebo	162	123 (75.9)	-0.9 (1.3)	-4	-1.0	4
	OL Week 52	Pre: CR845	151	92 (60.9)	-0.8 (1.1)	-4	-1.0	3
		Pre: Placebo	162	94 (58.0)	-1.0(1.3)	-4	-1.0	2

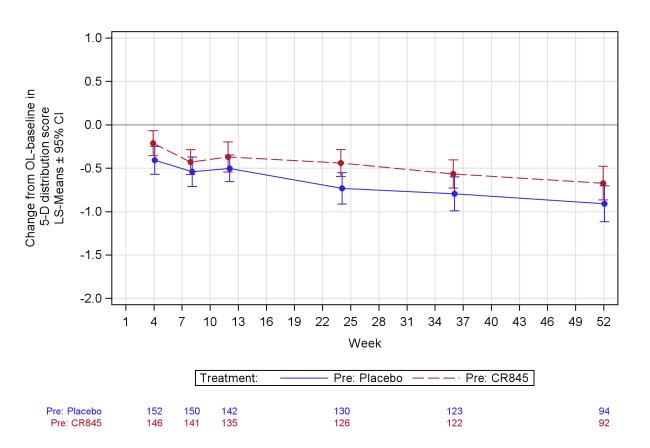
Note: SAF-L = Week 52 Safety set.

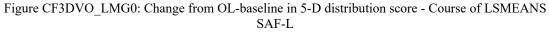
Table CT3DVO_LMD0:	Change fr	rom OL-baseline	in	5-D	distribution	score	-	LSMEANS	confidence	intervals
				SAI	F-L					

Change from 0	t bagaling in 5 D			Repeated mea	sures analysis
distribution	L-baseline in 5-D score			Change fr	om Baseline
Time	Treatment	N	n (%)	LS-Mean (SE)	95% CI
OL Week 4	Pre: CR845	151	146 (96.7)	-0.2 (0.1)	(-0.4, -0.1)
	Pre: Placebo	162	152 (93.8)	-0.4 (0.1)	(-0.6, -0.2)
OL Week 8	Pre: CR845	151	141 (93.4)	-0.4 (0.1)	(-0.6, -0.3)
	Pre: Placebo	162	150 (92.6)	-0.5 (0.1)	(-0.7, -0.4)
OL Week 12	Pre: CR845	151	135 (89.4)	-0.4 (0.1)	(-0.5, -0.2)
	Pre: Placebo	162	142 (87.7)	-0.5 (0.1)	(-0.7, -0.3)
OL Week 24	Pre: CR845	151	126 (83.4)	-0.4 (0.1)	(-0.6, -0.3)
	Pre: Placebo	162	130 (80.2)	-0.7 (0.1)	(-0.9, -0.5)
OL Week 36	Pre: CR845	151	122 (80.8)	-0.6 (0.1)	(-0.7, -0.4)
	Pre: Placebo	162	123 (75.9)	-0.8 (0.1)	(-1.0, -0.6)
OL Week 52	Pre: CR845	151	92 (60.9)	-0.7 (0.1)	(-0.9, -0.5)
	Pre: Placebo	162	94 (58.0)	-0.9 (0.1)	(-1.1, -0.7)

Note: SAF-L = Week 52 Safety set.

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Note: SAF-L = Week 52 Safety set.

Symbols present least square mean (LS-Mean), bars present 95% confidence intervals (CI).

CR845 = Difelikefalin, OL - baseline = Baseline of open label period.

Source Table: CT3DVO LMD0

Table CT3DDO_CMHO: Change from OL-baseline in 5-D degree score SAF-C

		Treatment	Ν	n (%)	Mean (SD)	Min	Q50	Max
		D	122	122 (100 0)		4	2 0	F
5-D degree score	OL Baseline	Pre: CR845 Pre: Placebo	122 122	122 (100.0)	2.5 (0.8)	1	2.0 3.0	5
	OT Usels 4		122	122 (100.0)	2.9(0.9)	1		5
	OL Week 4	Pre: CR845		121 (99.2)	2.3 (0.8) 2.5 (0.8)	1	2.0	5 5
	OL Week 8	Pre: Placebo Pre: CR845	122 122	117 (95.9)	· · ·	1 1	2.0 2.0	
	OL week o	Pre: Placebo		119 (97.5) 119 (97.5)	2.3 (0.8)		2.0	5
	OL Week 12	Pre: CR845	122 122	119 (97.5)	2.4(0.8)	1 1	2.0	5
	OL WEEK 12			, ,	2.3 (0.8)	_	2.0	5
	OT Usels 24	Pre: Placebo Pre: CR845	122	116 (95.1)	2.3 (0.8)	1	2.0	4
	OL Week 24		122	119 (97.5)	2.2 (0.8)	1		5
		Pre: Placebo	122	122 (100.0)	2.3 (0.9)	1	2.0	5
	OL Week 36	Pre: CR845	122	119 (97.5)	2.2 (0.8)	1	2.0	5
	01 11 1 50	Pre: Placebo	122	121 (99.2)	2.3 (0.8)	1	2.0	5
	OL Week 52	Pre: CR845	122	92 (75.4)	2.1 (0.9)	1	2.0	4
		Pre: Placebo	122	94 (77.0)	2.3 (0.9)	1	2.0	5
Change from OL-baseline in 5-D degree score	OL Week 4	Pre: CR845	122	121 (99.2)	-0.2 (0.8)	-3	0.0	2
		Pre: Placebo	122	117 (95.9)	-0.3 (1.0)	-3	0.0	2
	OL Week 8	Pre: CR845	122	119 (97.5)	-0.2 (0.8)	-3	0.0	2
		Pre: Placebo	122	119 (97.5)	-0.5 (1.0)	-3	0.0	2
	OL Week 12	Pre: CR845	122	119 (97.5)	-0.2 (0.9)	-3	0.0	2
		Pre: Placebo	122	116 (95.1)	-0.6 (1.0)	-3	-1.0	2
	OL Week 24	Pre: CR845	122	119 (97.5)	-0.3 (0.9)	-4	0.0	2
		Pre: Placebo	122	122 (100.0)	-0.5 (1.2)	-3	0.0	3
	OL Week 36	Pre: CR845	122	119 (97.5)	-0.3 (0.8)	-3	0.0	2
		Pre: Placebo	122	121 (99.2)	-0.6 (1.1)	-3	-1.0	3
	OL Week 52	Pre: CR845	122	92 (75.4)	-0.4 (1.0)	-4	0.0	2
		Pre: Placebo	122	94 (77.0)	-0.6 (1.2)	-3	-1.0	3

Note: SAF-C = Week 52 Study Completer Set.

Table CT3DDO_CMD0:	Change from	OL-baseline	in 5-D	degree	score -	LSMEANS	confidence	intervals
			SAF-C					

Change from (degree score	DL-baseline in 5-D			Change fr	om Baseline
Time	Treatment	N	n (%)	LS-Mean (SE)	95% CI
OL Week 4	Pre: CR845	122	121 (99.2)	-0.2 (0.1)	(-0.3, -0.1)
	Pre: Placebo	122	117 (95.9)	-0.3 (0.1)	(-0.5, -0.2)
OL Week 8	Pre: CR845	122	119 (97.5)	-0.2 (0.1)	(-0.3, -0.1)
	Pre: Placebo	122	119 (97.5)	-0.5 (0.1)	(-0.6, -0.4)
OL Week 12	Pre: CR845	122	119 (97.5)	-0.2 (0.1)	(-0.4, -0.1)
	Pre: Placebo	122	116 (95.1)	-0.6 (0.1)	(-0.7, -0.4)
OL Week 24	Pre: CR845	122	119 (97.5)	-0.3 (0.1)	(-0.4, -0.1)
	Pre: Placebo	122	122 (100.0)	-0.5 (0.1)	(-0.7, -0.4)
OL Week 36	Pre: CR845	122	119 (97.5)	-0.3 (0.1)	(-0.4, -0.2)
	Pre: Placebo	122	121 (99.2)	-0.6 (0.1)	(-0.7, -0.4)
OL Week 52	Pre: CR845	122	92 (75.4)	-0.4 (0.1)	(-0.6, -0.2)
	Pre: Placebo	122	94 (77.0)	-0.6(0.1)	(-0.8, -0.4)

Note: SAF-C = Week 52 Study Completer Set.

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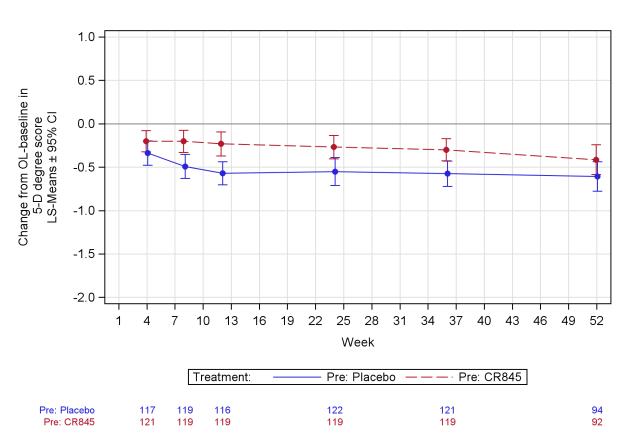


Figure CF3DDO_CMG0: Change from OL-baseline in 5-D degree score - Course of LSMEANS SAF-C

Note: SAF-C = Week 52 Study Completer Set.

Symbols present least square mean (LS-Mean), bars present 95% confidence intervals (CI).

CR845 = Difelikefalin, OL - baseline = Baseline of open label period.

Source Table: CT3DDO CMD0

Table CT3DLO_CMHO:	Change	from	OL-baseline	in	5-D	duration	score	
		S	AF-C					

		Treatment	N n (%)	Mean (SD)	Min	Q50	Max
							_
5-D duration score	OL Baseline	Pre: CR845	122 122 (100.0)	1.7 (1.0)	1	1.0	5
		Pre: Placebo	122 122 (100.0)	2.3 (1.3)	1	2.0	5
	OL Week 4	Pre: CR845	122 121 (99.2)	1.5 (1.0)	1	1.0	5
		Pre: Placebo	122 117 (95.9)	1.9 (1.1)	1	1.0	5
	OL Week 8	Pre: CR845	122 119 (97.5)	1.4 (0.9)	1	1.0	5
		Pre: Placebo	122 119 (97.5)	1.7 (1.1)	1	1.0	5
	OL Week 12	Pre: CR845	122 119 (97.5)	1.4 (0.8)	1	1.0	5
		Pre: Placebo	122 116 (95.1)	1.8 (1.2)	1	1.0	5
	OL Week 24	Pre: CR845	122 118 (96.7)	1.4 (0.9)	1	1.0	5
		Pre: Placebo	122 122 (100.0)	1.7 (1.1)	1	1.0	5
	OL Week 36	Pre: CR845	122 119 (97.5)	1.4 (0.8)	1	1.0	5
		Pre: Placebo	122 121 (99.2)	1.7 (1.1)	1	1.0	5
	OL Week 52	Pre: CR845	122 92 (75.4)	1.3 (0.8)	1	1.0	5
		Pre: Placebo	122 94 (77.0)	1.5 (1.0)	1	1.0	5
Change from OL-baseline in 5-D duration score	OL Week 4	Pre: CR845	122 121 (99.2)	-0.2 (0.9)	-4	0.0	3
		Pre: Placebo	122 117 (95.9)	-0.4(1.4)	-4	0.0	4
	OL Week 8	Pre: CR845	122 119 (97.5)	-0.3 (1.0)	-4	0.0	4
		Pre: Placebo	122 119 (97.5)	-0.6 (1.4)	-4	0.0	2
	OL Week 12	Pre: CR845	122 119 (97.5)	-0.3 (1.0)	-4	0.0	4
		Pre: Placebo	122 116 (95.1)	-0.5 (1.3)	-4	0.0	4
	OL Week 24	Pre: CR845	122 118 (96.7)	-0.3 (1.1)	-4	0.0	4
		Pre: Placebo	122 122 (100.0)	-0.6 (1.2)	-4	0.0	2
	OL Week 36	Pre: CR845	122 119 (97.5)	-0.4(0.9)	-4	0.0	2
		Pre: Placebo	122 121 (99.2)	-0.6 (1.4)	-4	0.0	3
	OL Week 52	Pre: CR845	122 92 (75.4)	-0.5 (1.0)	-4	0.0	3
		Pre: Placebo	122 94 (77.0)	-0.8 (1.5)	-4	0.0	3

Note: SAF-C = Week 52 Study Completer Set.

Table CT3DLO_CMD0:	Change	from	OL-baseline	in	5-D	duration	score	_	LSMEANS	confidence	intervals
				S	SAF-0	2					

Change from C	DL-baseline in 5-D			Repeated meas	sures analysis
duration scor				Change fr	om Baseline
Time	Treatment	Ν	n (%)	LS-Mean (SE)	95% CI
OL Week 4	Pre: CR845	122	121 (99.2)	-0.2 (0.1)	(-0.4, -0.1)
OL WEEK 4	Pre: Placebo	122	117 (95.9)		(-0.4, -0.1) (-0.6, -0.3)
OL Week 8	Pre: CR845	122	119 (97.5)	-0.3 (0.1)	(-0.5, -0.2)
	Pre: Placebo	122	119 (97.5)	-0.6 (0.1)	(-0.8, -0.4)
OL Week 12	Pre: CR845	122	119 (97.5)	-0.3 (0.1)	(-0.5, -0.2)
	Pre: Placebo	122	116 (95.1)	-0.5 (0.1)	(-0.7, -0.4)
OL Week 24	Pre: CR845	122	118 (96.7)	-0.3 (0.1)	(-0.4, -0.1)
	Pre: Placebo	122	122 (100.0)	-0.6 (0.1)	(-0.8, -0.4)
OL Week 36	Pre: CR845	122	119 (97.5)	-0.4 (0.1)	(-0.5, -0.2)
	Pre: Placebo	122	121 (99.2)	-0.6 (0.1)	(-0.8, -0.4)
OL Week 52	Pre: CR845	122	92 (75.4)	-0.5 (0.1)	(-0.6, -0.3)
	Pre: Placebo	122	94 (77.0)	-0.7(0.1)	(-0.9, -0.5)

Note: SAF-C = Week 52 Study Completer Set.

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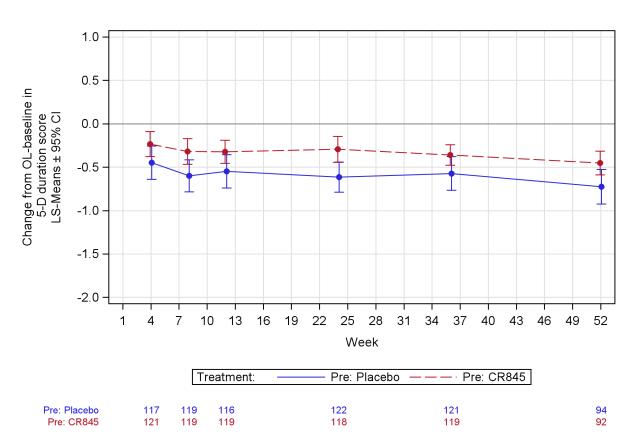


Figure CF3DLO_CMG0: Change from OL-baseline in 5-D duration score - Course of LSMEANS SAF-C

Note: SAF-C = Week 52 Study Completer Set.

Symbols present least square mean (LS-Mean), bars present 95% confidence intervals (CI).

CR845 = Difelikefalin, OL - baseline = Baseline of open label period.

Source Table: CT3DLO CMD0

Table CT3DWO_CMHO: Change from OL-baseline in 5-D direction score SAF-C

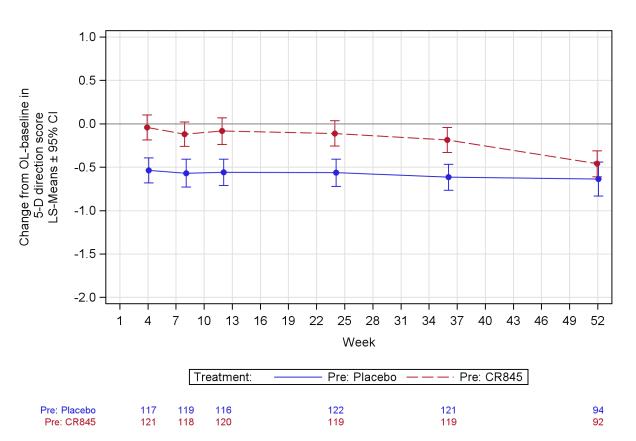
		Treatment	N	n (%)	Mean (SD)	Min	Q50	Max
5-D direction score	OL Baseline	Pre: CR845	177	122 (100 0)		1	2.0	E
5-D direction score	OL Baseline	Pre: CR845 Pre: Placebo	122 122	122 (100.0) 122 (100.0)	2.5 (0.8) 2.9 (1.0)	1 1	2.0 3.0	5 5
	OL Week 4	Pre: CR845	122	122 (100.0)	2.9(1.0) 2.4(0.9)	1	2.0	5
	OL Week 4	Pre: Placebo	122	121 (99.2) 117 (95.9)	2.4 (0.9) 2.4 (0.8)	1	2.0	5
	OL Week 8	Pre: CR845	122	117 (95.9)	2.3 (0.8)	1	2.0	5
	OL WEEK 0	Pre: Placebo	122	119 (97.5)	2.3 (0.8) 2.4 (0.9)	1	2.0	5
	OL Week 12	Pre: CR845	122	120 (98.4)	2.4 (0.9) 2.4 (0.9)	1	2.0	5
	OL Week 12	Pre: Placebo				1	2.0	5
	OL Week 24	Pre: CR845	122 122	116 (95.1) 119 (97.5)	2.4(0.9)		2.0	
	OL Week 24	Pre: CR845 Pre: Placebo		, ,	2.4(0.8)	1	2.0	5 5
	OT Usels 20		122	122 (100.0)	2.4 (0.9)	1		
	OL Week 36	Pre: CR845 Pre: Placebo	122	119 (97.5)	2.3 (0.8)	1	2.0 2.0	5
			122	121 (99.2)	2.3 (0.9)	1		5
	OL Week 52	Pre: CR845	122	92 (75.4)	2.0 (0.8)	1	2.0	4
		Pre: Placebo	122	94 (77.0)	2.3 (1.0)	1	2.0	5
Change from OL-baseline in 5-D direction score	OL Week 4	Pre: CR845	122	121 (99.2)	-0.0 (0.9)	-2	0.0	3
		Pre: Placebo	122	117 (95.9)	-0.5(1.0)	-3	0.0	2
	OL Week 8	Pre: CR845	122	118 (96.7)	-0.1(0.9)	-2	0.0	3
		Pre: Placebo	122	119 (97.5)	-0.6(1.2)	-4	0.0	3
	OL Week 12	Pre: CR845	122	120 (98.4)	-0.1 (1.0)	-2	0.0	3
		Pre: Placebo	122	116 (95.1)	-0.6(1.1)	-4	0.0	2
	OL Week 24	Pre: CR845	122	119 (97.5)	-0.1 (1.0)	-3	0.0	3
		Pre: Placebo	122	122 (100.0)	-0.6 (1.1)	-3	0.0	3
	OL Week 36	Pre: CR845	122	119 (97.5)	-0.2 (0.9)	-2	0.0	2
		Pre: Placebo	122	121 (99.2)	-0.6 (1.0)	-3	-1.0	2
	OL Week 52	Pre: CR845	122	92 (75.4)	-0.4(0.9)	-3	0.0	1
		Pre: Placebo	122	94 (77.0)	-0.7 (1.3)	-4	-1.0	3
					()			

Note: SAF-C = Week 52 Study Completer Set.

Table CT3DWO_CMD0:	Change fro	om OL-baseline	in 5-I	direction	score	- LSMEANS	confidence	intervals
			SAF	-C				

Change from O	L-baseline in 5-D			Repeated mea	sures analysis
direction sco		_		Change fr	om Baseline
Time	Treatment	N	n (%)	LS-Mean (SE)	95% CI
OL Week 4	Pre: CR845	122	121 (99.2)	-0.0 (0.1)	(-0.2, 0.1)
OL WEEK 4	Pre: Placebo	122	117 (95.9)		(-0.2, 0.1)
OL Week 8	Pre: CR845	122	118 (96.7)	-0.1 (0.1)	(-0.3, 0.0)
	Pre: Placebo	122	119 (97.5)	-0.6 (0.1)	(-0.7, -0.4)
OL Week 12	Pre: CR845	122	120 (98.4)	-0.1 (0.1)	(-0.2, 0.1)
	Pre: Placebo	122	116 (95.1)	-0.6 (0.1)	(-0.7, -0.4)
OL Week 24	Pre: CR845	122	119 (97.5)	-0.1 (0.1)	(-0.3, 0.0)
	Pre: Placebo	122	122 (100.0)	-0.6 (0.1)	(-0.7, -0.4)
OL Week 36	Pre: CR845	122	119 (97.5)	-0.2 (0.1)	(-0.3, -0.0)
	Pre: Placebo	122	121 (99.2)	-0.6 (0.1)	(-0.8, -0.5)
OL Week 52	Pre: CR845	122	92 (75.4)	-0.5 (0.1)	(-0.6, -0.3)
	Pre: Placebo	122	94 (77.0)	-0.6 (0.1)	(-0.8, -0.4)

Note: SAF-C = Week 52 Study Completer Set.





Note: SAF-C = Week 52 Study Completer Set.

Symbols present least square mean (LS-Mean), bars present 95% confidence intervals (CI).

CR845 = Difelikefalin, OL - baseline = Baseline of open label period.

Source Table: CT3DWO CMD0

Table CT3DNO_CMHO: Change from OL-baseline in 5-D disability score SAF-C

		Treatment	Ν	n (%)	Mean (SD)	Min	Q50	Max
5-D disability score	OL Baseline	Pre: CR845	122	122 (100.0)	2.5 (1.2)	1	2.0	5
J-D disability score	OL DASEIINE	Pre: Placebo	122	122 (100.0) 122 (100.0)	2.3(1.2) 2.8(1.2)	1	3.0	5
	OL Week 4	Pre: CR845	122	121 (99.2)	2.8 (1.2) 2.4 (1.2)	1	2.0	5
	OL WEEK F	Pre: Placebo	122	117 (95.9)	2.3 (1.1)	1	2.0	5
	OL Week 8	Pre: CR845	122	119 (97.5)	2.3(1.1) 2.2(1.2)	1	2.0	5
	OL WEEK O	Pre: Placebo	122	119 (97.5)	2.2(1.2) 2.2(1.1)	1	2.0	5
	OL Week 12	Pre: CR845	122	120 (98.4)	2.2(1.1) 2.3(1.2)	1	2.0	5
	OI WEEK IZ	Pre: Placebo	122	120 (95.1) 116 (95.1)	2.2(1.1)	1	2.0	5
	OL Week 24	Pre: CR845	122	119 (97.5)	2.2 (1.1) 2.1 (1.1)	1	2.0	5
	OL WEEK 24	Pre: Placebo	122	122 (100.0)	2.3 (1.2)	1	2.0	5
	OL Week 36	Pre: CR845	122	119 (97.5)	2.3 (1.2) 2.1 (1.1)	1	2.0	5
	OL WEEK 50	Pre: Placebo	122	121 (99.2)	2.2 (1.2)	1	2.0	5
	OL Week 52	Pre: CR845	122	92 (75.4)	1.9 (1.1)	1	2.0	5
	OL WEEK JZ	Pre: Placebo	122	94 (77.0)	2.2(1.2)	1	2.0	5
		iie. iiacebo	166	J= (//.0)	2.2 (1.2)	T	2.0	5
Change from OL-baseline in 5-D disability score	OL Week 4	Pre: CR845	122	121 (99.2)	-0.1 (0.9)	-2	0.0	2
-		Pre: Placebo	122	117 (95.9)	-0.5(1.4)	-4	0.0	3
	OL Week 8	Pre: CR845	122	119 (97.5)	-0.2 (1.1)	-3	0.0	3
		Pre: Placebo	122	119 (97.5)	-0.6(1.3)	-4	0.0	2
	OL Week 12	Pre: CR845	122	120 (98.4)	-0.2(1.1)	-3	0.0	3
		Pre: Placebo	122	116 (95.1)	-0.6(1.4)	-4	-1.0	3
	OL Week 24	Pre: CR845	122	119 (97.5)	-0.4(1.1)	-3	0.0	3
		Pre: Placebo	122	122 (100.0)	-0.5 (1.3)	-4	0.0	3
	OL Week 36	Pre: CR845	122	119 (97.5)	-0.4(1.1)	-3	0.0	3
		Pre: Placebo	122	121 (99.2)	-0.6 (1.4)	-4	-1.0	3
	OL Week 52	Pre: CR845	122	92 (75.4)	-0.5 (1.3)	-4	0.0	4
		Pre: Placebo	122	94 (77.0)	-0.7(1.4)	-4	-1.0	4
				. ,	. ,			

Note: SAF-C = Week 52 Study Completer Set.

		SAF-C				
			Repeated r	measures an	alysis	
Change	from OL-baseline in 5-D					

Table CT3DNO_CMD0:	Change	from	OL-baseline	in	5-D	disability	score	-	LSMEANS	confidence	intervals
					SAF	-C					

Change from O disability sc	L-baseline in 5-D ore	_		Change fr	om Baseline
Time	Treatment	n (%)	LS-Mean (SE)	95% CI	
OL Week 4	Pre: CR845	122	121 (99.2)	-0.1 (0.1)	(-0.3, 0.0)
	Pre: Placebo	122	117 (95.9)	-0.5 (0.1)	(-0.7, -0.3)
OL Week 8	Pre: CR845	122	110 (07 E)	0 2 (0 1)	
OL week o			119 (97.5)		(-0.4, -0.1)
	Pre: Placebo	122	119 (97.5)	-0.6 (0.1)	(-0.8, -0.5)
OL Week 12	Pre: CR845	122	120 (98.4)	-0.2(0.1)	(-0.4, -0.0)
01 10011 11	Pre: Placebo	122	116 (95.1)		(-0.8, -0.4)
	FIE. FIACEDO	122	110 (95.1)	-0.0 (0.1)	(-0.8, -0.4)
OL Week 24	Pre: CR845	122	119 (97.5)	-0.4 (0.1)	(-0.5, -0.2)
	Pre: Placebo	122	122 (100.0)	-0.5 (0.1)	(-0.7, -0.3)
OL Week 36	Pre: CR845	122	119 (97.5)	-0.4(0.1)	(-0.6, -0.2)
	Pre: Placebo	122	121 (99.2)	-0.6 (0.1)	(-0.8, -0.4)
OL Week 52	Pre: CR845	122	92 (75.4)	-0.6 (0.1)	(-0.8, -0.4)
OL NCCK JL			· ,	, ,	. , ,
	Pre: Placebo	122	94 (77.0)	-0.7(0.1)	(-0.9, -0.5)

Note: SAF-C = Week 52 Study Completer Set.

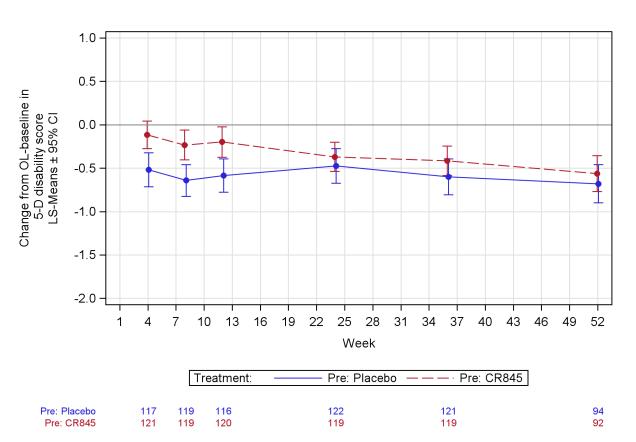


Figure CF3DNO_CMG0: Change from OL-baseline in 5-D disability score - Course of LSMEANS SAF-C

Note: SAF-C = Week 52 Study Completer Set.

Symbols present least square mean (LS-Mean), bars present 95% confidence intervals (CI).

CR845 = Difelikefalin, OL - baseline = Baseline of open label period.

Source Table: CT3DNO CMD0

Table CT3DVO_CMHO: Change from OL-baseline in 5-D distribution score SAF-C

5-D distribution score OL Baseline Pre: CR845 122 122 100.0) 2.7 1.2 Pre: Placebo 122 122 100.0) 3.2 1.2 OL Week 4 Pre: CR845 122 121 09.2) 2.5 1.2 Pre: Placebo 122 117 09.5) 2.8 1.1 OL Week 8 Pre: CR845 122 119 07.5) 2.4 1.2 Pre: Placebo 122 119 07.5) 2.6 (1.1)	2) 1 2) 1 3) 1 3) 1 3) 1	3.0 3.0 2.0 3.0 2.0	5 5 5 5 5
Pre: Placebo 122 122 100.0) 3.2 11.2 OL Week 4 Pre: CR845 122 121 (99.2) 2.5 (1.2) Pre: Placebo 122 117 (95.9) 2.8 (1.2) OL Week 8 Pre: CR845 122 119 (97.5) 2.4 (1.2)	2) 1 2) 1 3) 1 3) 1 3) 1	3.0 2.0 3.0 2.0	5 5 5
OL Week 4Pre: CR845122121(99.2)2.5(1.2)Pre: Placebo122117(95.9)2.8(1.2)OL Week 8Pre: CR845122119(97.5)2.4(1.2)	2) 1 3) 1 2) 1 3) 1	2.0 3.0 2.0	5 5
Pre: Placebo122117 (95.9)2.8 (1.3)OL Week 8Pre: CR845122119 (97.5)2.4 (1.3)	3) 1 2) 1 3) 1	3.0 2.0	5
OL Week 8 Pre: CR845 122 119 (97.5) 2.4 (1.3	2) 1 3) 1	2.0	
	3) 1		
		2.0	5
OL Week 12 Pre: CR845 122 120 (98.4) 2.4 (1.)	3) 1	2.0	5
Pre: Placebo 122 116 (95.1) 2.7 (1.3	2) 1	3.0	5
OL Week 24 Pre: CR845 122 119 (97.5) 2.3 (1.3	2) 1	2.0	5
Pre: Placebo 122 122 (100.0) 2.4 (1.3	2) 1	2.0	5
OL Week 36 Pre: CR845 122 120 (98.4) 2.2 (1.3	?) 1	2.0	5
Pre: Placebo 122 121 (99.2) 2.3 (1.2	2) 1	2.0	5
OL Week 52 Pre: CR845 122 92 (75.4) 2.1 (1.3	.) 1	2.0	5
Pre: Placebo 122 94 (77.0) 2.2 (1.3	2) 1	2.0	5
Change from OL-baseline in 5-D OL Week 4 Pre: CR845 122 121 (99.2) -0.2 (1. distribution score	0) -3	0.0	2
Pre: Placebo 122 117 (95.9) -0.4 (1.	1) -4	0.0	2
OL Week 8 Pre: CR845 122 119 (97.5) -0.4 (1.	0) -4	0.0	2
Pre: Placebo 122 119 (97.5) -0.7 (1.	1) -4	0.0	2
OL Week 12 Pre: CR845 122 120 (98.4) -0.4 (1.	1) -4	0.0	3
Pre: Placebo 122 116 (95.1) -0.6 (1.	0) -4	0.0	2
OL Week 24 Pre: CR845 122 119 (97.5) -0.4 (1.	0) -4	0.0	2
Pre: Placebo 122 122 (100.0) -0.8 (1.	2) -4	-1.0	4
OL Week 36 Pre: CR845 122 120 (98.4) -0.6 (1.	0) -3	-0.5	3
Pre: Placebo 122 121 (99.2) -0.9 (1.	3) -4	-1.0	4
OL Week 52 Pre: CR845 122 92 (75.4) -0.8 (1.	1) -4	-1.0	3
Pre: Placebo 122 94 (77.0) -1.0 (1.	3) -4	-1.0	2

Note: SAF-C = Week 52 Study Completer Set.

Table CT3DVO_CMD0:	Change fro	m OL-baseline	in	5-D	distribution	score	-	LSMEANS	confidence	intervals
				SAI	F-C					

Change from O	L-baseline in 5-D			Repeated mea	sures analysis
distribution		_		Change fr	om Baseline
Time	Treatment	N	n (%)	LS-Mean (SE)	95% CI
OL Week 4	Pre: CR845	122	121 (99.2)	-0.2 (0.1)	(-0.4, -0.1)
	Pre: Placebo	122	117 (95.9)		(-0.6, -0.3)
OL Week 8	Pre: CR845	122	119 (97.5)	-0.4 (0.1)	(-0.6, -0.2)
	Pre: Placebo	122	119 (97.5)	-0.6 (0.1)	(-0.8, -0.5)
OL Week 12	Pre: CR845	122	120 (98.4)	-0.4 (0.1)	(-0.5, -0.2)
	Pre: Placebo	122	116 (95.1)	-0.5 (0.1)	(-0.7, -0.4)
OL Week 24	Pre: CR845	122	119 (97.5)	-0.4 (0.1)	(-0.6, -0.3)
	Pre: Placebo	122	122 (100.0)	-0.8 (0.1)	(-1.0, -0.6)
OL Week 36	Pre: CR845	122	120 (98.4)	-0.6 (0.1)	(-0.7, -0.4)
	Pre: Placebo	122	121 (99.2)	-0.9 (0.1)	(-1.1, -0.7)
OL Week 52	Pre: CR845	122	92 (75.4)	-0.7 (0.1)	(-0.9, -0.5)
	Pre: Placebo	122	94 (77.0)	-1.0 (0.1)	(-1.2, -0.8)

Note: SAF-C = Week 52 Study Completer Set.

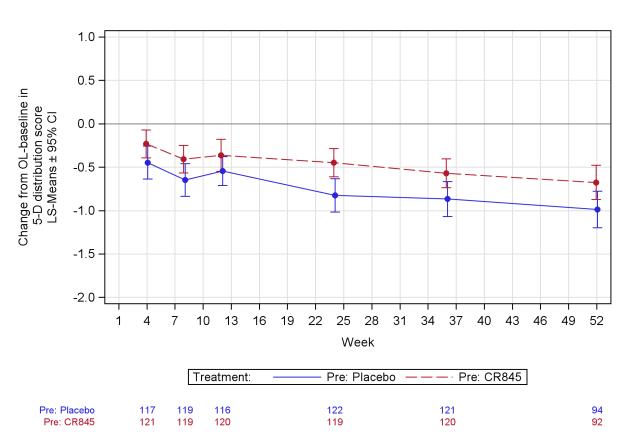


Figure CF3DVO_CMG0: Change from OL-baseline in 5-D distribution score - Course of LSMEANS SAF-C

Note: SAF-C = Week 52 Study Completer Set.

Symbols present least square mean (LS-Mean), bars present 95% confidence intervals (CI).

CR845 = Difelikefalin, OL - baseline = Baseline of open label period.

Source Table: CT3DVO CMD0

		Pre: CR845	P	re: Placebo
TEAEs during OLP	N	n (%) [95 % CI]	N	n (%) [95 % CI]
SOC: Cardiac disorders	151	13 (8.6) [4.7, 14.3]	162	15 (9.3) [5.3, 14.8]
SOC: Gastrointestinal disorders	151	32 (21.2) [15.0, 28.6]	162	37 (22.8) [16.6, 30.1]
Diarrhoea	151	8 (5.3) [2.3, 10.2]	162	12 (7.4) [3.9, 12.6]
Nausea	151	11 (7.3) [3.7, 12.7]	162	6 (3.7) [1.4, 7.9]
SOC: General disorders and administration site conditions	151	17 (11.3) [6.7, 17.4]	162	14 (8.6) [4.8, 14.1]
SOC: Infections and infestations	151	28 (18.5) [12.7, 25.7]	162	33 (20.4) [14.5, 27.4]
SOC: Injury, poisoning and procedural complications	151	17 (11.3) [6.7, 17.4]	162	27 (16.7) [11.3, 23.3]
Fall	151	5 (3.3) [1.1, 7.6]	162	10 (6.2) [3.0, 11.1]
SOC: Metabolism and nutrition disorders	151	13 (8.6) [4.7, 14.3]	162	11 (6.8) [3.4, 11.8]
SOC: Musculoskeletal and connective tissue disorders	151	11 (7.3) [3.7, 12.7]	162	26 (16.0) [10.8, 22.6]
Muscle spasms	151	2 (1.3) [0.2, 4.7]	162	10 (6.2) [3.0, 11.1]
SOC: Nervous system disorders	151	18 (11.9) [7.2, 18.2]	162	14 (8.6) [4.8, 14.1]
SOC: Respiratory, thoracic and mediastinal disorders	151	22 (14.6) [9.4, 21.2]	162	20 (12.3) [7.7, 18.4]

Table CT3LA_LMS1: TEAEs during first quarter of OLP by SOC and PT SAF-L

Note: SAF-L = Week 52 Safety set. Only events are displayed with an incidence of at least 10 percent in a treatment group or 10 patients with an incidence of at least 1 percent in a treatment group.

N = total number of patients in analysis set. n = number of patients with events during OLP. OLP = open label period.

95% CI = 95% confidence interval according to Clopper Pearson. TEAE = treatment emergent adverse event. SOC = system organ class. PT = preferred term.

Source Data: aae, created on: 03MAR2022

Table CT3LA_LMS1: TEAEs during first quarter of OLP by SOC and PT $$\rm SAF-L$$

	Pre: CR845		Pı	re: Placebo
		n (%)		n (%)
TEAEs during OLP	Ν	[95 % CI]	Ν	[95 % CI]
SOC: Vascular disorders	151	15 (9.9)	162	11 (6.8)
		[5.7, 15.9]		[3.4, 11.8]

Note: SAF-L = Week 52 Safety set. Only events are displayed with an incidence of at least 10 percent in a treatment group or 10 patients with an incidence of at least 1 percent in a treatment group.

N = total number of patients in analysis set. n = number of patients with events during OLP. OLP = open label period.

95% CI = 95% confidence interval according to Clopper Pearson. TEAE = treatment emergent adverse event. SOC = system organ class. PT = preferred term.

Source Data: aae, created on: 03MAR2022

		Pre: CR845	P	re: Placebo
TEAEs during OLP	N	n (%) [95 % CI]	N	n (%) [95 % CI]
SOC: Blood and lymphatic system disorders	151	10 (6.6) [3.2, 11.8]	162	10 (6.2) [3.0, 11.1]
SOC: Cardiac disorders	151	32 (21.2) [15.0, 28.6]	162	37 (22.8) [16.6, 30.1]
SOC: Gastrointestinal disorders	151	67 (44.4) [36.3, 52.7]	162	76 (46.9) [39.0, 54.9]
Abdominal pain	151	10 (6.6) [3.2, 11.8]	162	14 (8.6) [4.8, 14.1]
Abdominal pain upper	151	4 (2.6) [0.7, 6.6]	162	10 (6.2) [3.0, 11.1]
Constipation	151	12 (7.9) [4.2, 13.5]	162	11 (6.8) [3.4, 11.8]
Diarrhoea	151	26 (17.2) [11.6, 24.2]	162	23 (14.2) [9.2, 20.5]
Nausea	151	24 (15.9) [10.5, 22.7]	162	23 (14.2) [9.2, 20.5]
Vomiting	151	14 (9.3) [5.2, 15.1]	162	23 (14.2) [9.2, 20.5]
SOC: General disorders and administration site conditions	151	43 (28.5) [21.4, 36.4]	162	36 (22.2) [16.1, 29.4]
Non-cardiac chest pain	151	13 (8.6) [4.7, 14.3]	162	5 (3.1) [1.0, 7.1]
SOC: Infections and infestations	151	55 (36.4) [28.8, 44.6]	162	61 (37.7) [30.2, 45.6]
Pneumonia	151	18 (11.9) [7.2, 18.2]	162	15 (9.3) [5.3, 14.8]
SOC: Injury, poisoning and procedural complications	151	50 (33.1) [25.7, 41.2]	162	57 (35.2) [27.9, 43.1]
Fall	151	21 (13.9) [8.8, 20.5]	162	27 (16.7) [11.3, 23.3]

Table CT3LA_LMSO: TEAEs during OLP by SOC and PT $_{\rm SAF-L}$

Note: SAF-L = Week 52 Safety set. Only events are displayed with an incidence of at least 10 percent in a treatment group or 10 patients with an incidence of at least 1 percent in a treatment group.

N = total number of patients in analysis set. n = number of patients with events during OLP. OLP = open label period.

- 95% CI = 95% confidence interval according to Clopper Pearson. TEAE = treatment emergent adverse event. SOC = system organ class. PT = preferred term.
- Source Data: aae, created on: 03MAR2022

Table CT3LA_LMSO: TEAEs during OLP by SOC and PT SAF-L

		Pre: CR845		re: Placebo
TEAEs during OLP	N	n (%) [95 % CI]	N	n (%) [95 % CI]
SOC: Investigations	151	13 (8.6) [4.7, 14.3]	162	21 (13.0) [8.2, 19.1]
SOC: Metabolism and nutrition disorders	151	36 (23.8) [17.3, 31.4]	162	43 (26.5) [19.9, 34.0]
Fluid overload	151	12 (7.9) [4.2, 13.5]	162	9 (5.6) [2.6, 10.3]
Hyperkalaemia	151	15 (9.9) [5.7, 15.9]	162	23 (14.2) [9.2, 20.5]
SOC: Musculoskeletal and connective tissue disorders	151	36 (23.8) [17.3, 31.4]	162	51 (31.5) [24.4, 39.2]
Back pain	151	7 (4.6) [1.9, 9.3]	162	14 (8.6) [4.8, 14.1]
Muscle spasms	151	12 (7.9) [4.2, 13.5]	162	14 (8.6) [4.8, 14.1]
Pain in extremity	151	7 (4.6) [1.9, 9.3]	162	16 (9.9) [5.8, 15.5]
SOC: Nervous system disorders	151	49 (32.5) [25.1, 40.5]	162	46 (28.4) [21.6, 36.0]
Dizziness	151	16 (10.6) [6.2, 16.6]	162	13 (8.0) [4.3, 13.3]
Headache	151	22 (14.6) [9.4, 21.2]	162	7 (4.3) [1.8, 8.7]
SOC: Psychiatric disorders	151	25 (16.6) [11.0, 23.5]	162	17 (10.5) [6.2, 16.3]
Mental status changes	151	12 (7.9) [4.2, 13.5]	162	5 (3.1) [1.0, 7.1]
SOC: Respiratory, thoracic and mediastinal disorders	151	48 (31.8) [24.5, 39.9]	162	55 (34.0) [26.7, 41.8]
Cough	151	15 (9.9) [5.7, 15.9]	162	11 (6.8) [3.4, 11.8]

Note: SAF-L = Week 52 Safety set. Only events are displayed with an incidence of at least 10 percent in a treatment group or 10 patients with an incidence of at least 1 percent in a treatment group.

N = total number of patients in analysis set. n = number of patients with events during OLP. OLP = open label period.

- 95% CI = 95% confidence interval according to Clopper Pearson. TEAE = treatment emergent adverse event. SOC = system organ class. PT = preferred term.
- Source Data: aae, created on: 03MAR2022

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Table CT3LA_LMSO:	TEAEs	during	OLP	by	SOC	and	\mathbf{PT}	
	SA	F-L						

		Pre: CR845	Р	re: Placebo
TEAEs during OLP	N	n (%) [95 % CI]	N	n (%) [95 % CI]
Dyspnoea	151	19 (12.6)	162	- ()
Respiratory failure	151	[7.7, 19.0] 6 (4.0) [1.5, 8.4]	162	[5.3, 14.8] 12 (7.4) [3.9, 12.6]
SOC: Skin and subcutaneous tissue	151	17 (11.3)	162	- , -
disorders		[6.7, 17.4]		[5.8, 15.5]
SOC: Vascular disorders	151	42 (27.8) [20.8, 35.7]	162	37 (22.8) [16.6, 30.1]
Hypotension	151	24 (15.9) [10.5, 22.7]	162	19 (11.7) [7.2, 17.7]

Note: SAF-L = Week 52 Safety set. Only events are displayed with an incidence of at least 10 percent in a treatment group or 10 patients with an incidence of at least 1 percent in a treatment group.

N = total number of patients in analysis set. n = number of patients with events during OLP. OLP = open label period.

95% CI = 95% confidence interval according to Clopper Pearson. TEAE = treatment emergent adverse event. SOC = system organ class. PT = preferred term.

Source Data: aae, created on: 03MAR2022

	Pre: CR845		Pre: Placebo		
		n (%)		n (%)	
TEAEs during OLP	N	[95 % CI]	N	[95 % CI]	
SOC: Cardiac disorders	122	23 (18.9) [12.3, 26.9]	122	26 (21.3) [14.4, 29.6]	
SOC: Gastrointestinal disorders	122	60 (49.2) [40.0, 58.4]	122	58 (47.5) [38.4, 56.8]	
Abdominal pain	122	8 (6.6) [2.9, 12.5]	122	11 (9.0) [4.6, 15.6]	
Constipation	122	10 (8.2) [4.0, 14.6]	122	10 (8.2) [4.0, 14.6]	
Diarrhoea	122	24 (19.7) [13.0, 27.8]	122	18 (14.8) [9.0, 22.3]	
Nausea	122	23 (18.9) [12.3, 26.9]	122	19 (15.6) [9.6, 23.2]	
Vomiting	122	13 (10.7) [5.8, 17.5]	122	16 (13.1) [7.7, 20.4]	
SOC: General disorders and administration site conditions	122	37 (30.3) [22.3, 39.3]	122	30 (24.6) [17.2, 33.2]	
Non-cardiac chest pain	122	12 (9.8) [5.2, 16.6]	122	5 (4.1) [1.3, 9.3]	
SOC: Infections and infestations	122	44 (36.1) [27.6, 45.3]	122	46 (37.7) [29.1, 46.9]	
Pneumonia	122	12 (9.8) [5.2, 16.6]	122	9 (7.4) [3.4, 13.5]	
SOC: Injury, poisoning and procedural complications	122	39 (32.0) [23.8, 41.0]	122	49 (40.2) [31.4, 49.4]	
Fall	122	18 (14.8) [9.0, 22.3]	122	24 (19.7) [13.0, 27.8]	
SOC: Investigations	122	9 (7.4) [3.4, 13.5]	122	14 (11.5) [6.4, 18.5]	
SOC: Metabolism and nutrition disorders	122	25 (20.5) [13.7, 28.7]	122	32 (26.2) [18.7, 35.0]	

Table CT3LA_CMSO: TEAEs during OLP by SOC and PT $_{\rm SAF-C}$

Note: SAF-C = Week 52 Study Completer Set. Only events are displayed with an incidence of at least 10 percent in a treatment group or 10 patients with an incidence of at least 1 percent in a treatment group.

N = total number of patients in analysis set. n = number of patients with events during OLP. OLP = open label period.

- 95% CI = 95% confidence interval according to Clopper Pearson. TEAE = treatment emergent adverse event. SOC = system organ class. PT = preferred term.
- Source Data: aae, created on: 03MAR2022

		Pre: CR845		Pre: Placebo		
		n (%)		n (%)		
TEAEs during OLP	N	[95 % CI]	N	[95 % CI]		
Hyperkalaemia	122	10 (8.2) [4.0, 14.6]	122	18 (14.8) [9.0, 22.3]		
SOC: Musculoskeletal and connective tissue disorders	122	34 (27.9) [20.1, 36.7]	122	41 (33.6) [25.3, 42.7]		
Back pain	122	5 (4.1) [1.3, 9.3]	122	11 (9.0) [4.6, 15.6]		
Muscle spasms	122	12 (9.8) [5.2, 16.6]	122	9 (7.4) [3.4, 13.5]		
Pain in extremity	122	7 (5.7) [2.3, 11.5]	122	12 (9.8) [5.2, 16.6]		
SOC: Nervous system disorders	122	39 (32.0) [23.8, 41.0]	122	38 (31.1) [23.1, 40.2]		
Dizziness	122	15 (12.3) [7.0, 19.5]	122	12 (9.8) [5.2, 16.6]		
Headache	122	19 (15.6) [9.6, 23.2]	122	7 (5.7) [2.3, 11.5]		
SOC: Psychiatric disorders	122	17 (13.9) [8.3, 21.4]	122	11 (9.0) [4.6, 15.6]		
SOC: Respiratory, thoracic and mediastinal disorders	122	39 (32.0) [23.8, 41.0]	122	45 (36.9) [28.3, 46.1]		
Cough	122	14 (11.5) [6.4, 18.5]	122	11 (9.0) [4.6, 15.6]		
Dyspnoea	122	14 (11.5) [6.4, 18.5]	122	10 (8.2) [4.0, 14.6]		
SOC: Skin and subcutaneous tissue disorders	122	15 (12.3) [7.0, 19.5]	122	13 (10.7) [5.8, 17.5]		
SOC: Vascular disorders	122	35 (28.7) [20.9, 37.6]	122	32 (26.2) [18.7, 35.0]		

Table CT3LA_CMSO: TEAEs during OLP by SOC and PT $${\rm SAF-C}$$

Note: SAF-C = Week 52 Study Completer Set. Only events are displayed with an incidence of at least 10 percent in a treatment group or 10 patients with an incidence of at least 1 percent in a treatment group.

N = total number of patients in analysis set. n = number of patients with events during OLP. OLP = open label period.

- 95% CI = 95% confidence interval according to Clopper Pearson. TEAE = treatment emergent adverse event. SOC = system organ class. PT = preferred term.
- Source Data: aae, created on: 03MAR2022

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Table CT3LA_CMSO: TEAEs during OLP by SOC and PT $_{\rm SAF-C}$

	Pre: CR845		Pi	re: Placebo
		n (%)		n (%)
TEAEs during OLP	Ν	[95 % CI]	Ν	[95 % CI]
Hypotension	122	22 (18.0)	122	16 (13.1)
		[11.7, 26.0]		[7.7, 20.4]

Note: SAF-C = Week 52 Study Completer Set. Only events are displayed with an incidence of at least 10 percent in a treatment group or 10 patients with an incidence of at least 1 percent in a treatment group.

N = total number of patients in analysis set. n = number of patients with events during OLP. OLP = open label period.

95% CI = 95% confidence interval according to Clopper Pearson. TEAE = treatment emergent adverse event. SOC = system organ class. PT = preferred term.

Source Data: aae, created on: 03MAR2022

Table CT3LAEGN_LMI1: AESI gait disturbance - non-severe during first quarter of OLP SAF-L

	F	Pre: CR845		e: Placebo
	N	n (%) [95 % CI]	N	n (%) [95 % CI]
AESI gait disturbance - non-severe	151	0 (0.0)	162	0 (0.0)
during OLP		[0.0, 2.4]		[0.0, 2.3]

Table CT3LAEFN_LMI1: AESI falls/injuries - non-severe during first quarter of OLP SAF-L

	H	Pre: CR845		re: Placebo
		n (%)		n (%)
	Ν	[95 % CI]	Ν	[95 % CI]
AESI falls/injuries - non-severe during OLP	151	6 (4.0) [1.5, 8.4]	162	13 (8.0) [4.3, 13.3]

Table CT3LAEVN_LMI1: AESI dizziness - non-severe during first quarter of OLP SAF-L

	Pre: CR845		Pre: Placebo	
	N	n (%) [95 % CI]	N	n (%) [95 % CI]
AESI dizziness - non-severe during OLP	151	7 (4.6)	162	4 (2.5) [0.7, 6.2]

Table CT3LAEYN_LMI1: AESI syncope - non-severe during first quarter of OLP SAF-L

	Pre: CR845		Pre: Placebo	
	N	n (%) [95 % CI]	N	n (%) [95 % CI]
AESI syncope - non-severe during OLP	151	3 (2.0) [0.4, 5.7]	162	1 (0.6) [0.0, 3.4]

Table CT3LAEON_LMI1: AESI somnolence - non-severe during first quarter of OLP SAF-L

	Pre: CR845		Pre: Placebo	
	N	n (%) [95 % CI]	N	n (%) [95 % CI]
AESI somnolence - non-severe during OLP	151	$0 (0.0) \\ [0.0, 2.4]$	162	0 (0.0) [0.0, 2.3]

Table CT3LAEKN_LMI1: AESI seizures - non-severe during first quarter of OLP SAF-L

	Pre: CR845		Pre: Placebo	
	N	n (%) [95 % CI]	N	n (%) [95 % CI]
AESI seizures - non-severe during OLP	151	0 (0.0) [0.0, 2.4]	162	0 (0.0) [0.0, 2.3]

Table CT3LAEMN_LMI1: AESI mental status change - non-severe during first quarter of OLP SAF-L

	Pre: CR845		Pr	Pre: Placebo	
		n (%)		n (%)	
	N	[95 % CI]	N	[95 % CI]	
AESI mental status	151	2 (1.3)	162	3 (1.9)	
change – non-severe during OLP		[0.2, 4.7]		[0.4, 5.3]	

Table CT3LAEEN_LMI1: AESI mood change - non-severe during first quarter of OLP SAF-L

	Pre: CR845		Pre: Placebo	
	N	n (%) [95 % CI]	N	n (%) [95 % CI]
AESI mood change - non-severe	151	4 (2.6)	162	1 (0.6)
during OLP		[0.7, 6.6]		[0.0, 3.4]

Table CT3LAEUN_LMI1: AESI unusual feeling/sensation - non-severe during first quarter of OLP SAF-L

	Pre: CR845		Pr	Pre: Placebo	
	N	n (%) [95 % CI]	N	n (%) [95 % CI]	
AESI unusual feeling/sensation - non-severe during OLP	151	1 (0.7) [0.0, 3.6]	162	0 (0.0)	

Table CT3LAERN_LMI1: AESI tachycardia/palpitation - non-severe during first quarter of OLP SAF-L

	Pre: CR845		Pr	e: Placebo
	N	n (%) [95 % CI]	N	n (%) [95 % CI]
AESI tachycardia/palpitation - non-severe during OLP	151	2 (1.3) [0.2, 4.7]	162	3 (1.9) [0.4, 5.3]

Table CT3LAEGN_LMIO: AESI gait disturbance - non-severe during OLP SAF-L

	Pre: CR845		Pre: Placebo	
	N	n (%) [95 % CI]	N	n (%) [95 % CI]
AESI gait disturbance - non-severe during OLP	151	1 (0.7) [0.0, 3.6]	162	1 (0.6) [0.0, 3.4]

Table CT3LAEFN_LMIO: AESI falls/injuries - non-severe during OLP SAF-L

	Pre: CR845		Pre: Placebo	
	N	n (%) [95 % CI]	N	n (%) [95 % CI]
	N	[93 % C1]	N	[95 % C1]
AESI falls/injuries - non-severe during OLP	151	25 (16.6) [11.0, 23.5]	162	28 (17.3) [11.8, 24.0]

Table CT3LAEVN_LMIO: AESI dizziness - non-severe during OLP SAF-L

	Pre: CR845		Pre: Placebo	
	N	n (%) [95 % CI]	N	n (%) [95 % CI]
AESI dizziness - non-severe during OLP	151	16 (10.6) [6.2, 16.6]	162	13 (8.0) [4.3, 13.3]

Table CT3LAEYN_LMIO: AESI syncope - non-severe during OLP SAF-L

	Pre: CR845		Pre: Placebo	
	N	n (%) [95 % CI]	N	n (%) [95 % CI]
AESI syncope - non-severe during OLP	151	8 (5.3) [2.3, 10.2]	162	4 (2.5) [0.7, 6.2]

Table CT3LAEON_LMIO: AESI somnolence - non-severe during OLP SAF-L

	Pre: CR845		Pre: Placebo	
	N	n (%) [95 % CI]	N	n (%) [95 % CI]
AESI somnolence - non-severe during OLP	151	1 (0.7) [0.0, 3.6]	162	0 (0.0) [0.0, 2.3]

Table CT3LAEKN_LMIO: AESI seizures - non-severe during OLP SAF-L

	Pre: CR845		Pre: Placebo	
	N	n (%) [95 % CI]	N	n (%) [95 % CI]
AESI seizures - non-severe during OLP	151	1 (0.7) [0.0, 3.6]	162	2 (1.2) [0.1, 4.4]

Table CT3LAEMN_LMIO: AESI mental status change - non-severe during OLP SAF-L

	Pre: CR845		Pr	Pre: Placebo	
		n (%)		n (%)	
	N	[95 % CI]	N	[95 % CI]	
AESI mental status	151	13 (8.6)	162	7 (4.3)	
change - non-severe during OLP	151	[4.7, 14.3]	102	[1.8, 8.7]	

Table CT3LAEEN_LMIO: AESI mood change - non-severe during OLP SAF-L

	Pre: CR845		Pre: Placebo	
	N	n (%) [95 % CI]	N	n (%) [95 % CI]
AESI mood change - non-severe	151	7 (4.6)	162	5 (3.1)
during OLP		[1.9, 9.3]		[1.0, 7.1]

Table CT3LAEUN_LMIO: AESI unusual feeling/sensation - non-severe during OLP SAF-L

	Pre: CR845		Pr	Pre: Placebo	
		n (%)		n (%)	
	N	[95 % CI]	N	[95 % CI]	
AESI unusual feeling/sensation - non-severe during OLP	151	8 (5.3) [2.3, 10.2]	162	5 (3.1) [1.0, 7.1]	

Table CT3LAERN_LMIO: AESI tachycardia/palpitation - non-severe during OLP SAF-L

	I	Pre: CR845		Pre: Placebo	
		n (%)		n (%)	
	N	[95 % CI]	N	[95 % CI]	
AESI tachycardia/palpitation - non-severe during OLP	151	10 (6.6) [3.2, 11.8]	162	10 (6.2) [3.0, 11.1]	

Table CT3LAEGN_CMIO: AESI gait disturbance - non-severe during OLP SAF-C

	Pre: CR845		Pre: Placebo	
		n (%)	N	n (%)
	N	[95 % CI]	N	[95 % CI]
AESI gait disturbance - non-severe during OLP	122	0 (0.0) [0.0, 3.0]	122	1 (0.8) [0.0, 4.5]

Table CT3LAEFN_CMIO: AESI falls/injuries - non-severe during OLP SAF-C

	Pre: CR845		Pre: Placebo	
	N	n (%) [95 % CI]	N	n (%) [95 % CI]
AESI falls/injuries - non-severe during OLP	122	20 (16.4) [10.3, 24.2]	122	24 (19.7) [13.0, 27.8]

Table CT3LAEVN_CMIO: AESI dizziness - non-severe during OLP SAF-C

	Pre: CR845		Pre: Placebo	
	N	n (%) [95 % CI]	N	n (%) [95 % CI]
AESI dizziness - non-severe during OLP	122	15 (12.3) [7.0, 19.5]	122	12 (9.8) [5.2, 16.6]

Table CT3LAEYN_CMIO: AESI syncope - non-severe during OLP SAF-C

	Pre: CR845		Pre: Placebo		
	N	n (%) [95 % CI]	N	n (%) [95 % CI]	_
AESI syncope - non-severe during OLP	122	6 (4.9) [1.8, 10.4]	122	4 (3.3) [0.9, 8.2]	-

Table CT3LAEON_CMIO: AESI somnolence - non-severe during OLP SAF-C

	Pre: CR845		Pre: Placebo	
	N	n (%) [95 % CI]	N	n (%) [95 % CI]
AESI somnolence - non-severe during OLP	122	1 (0.8) [0.0, 4.5]	122	0 (0.0) [0.0, 3.0]

Table CT3LAEKN_CMIO: AESI seizures - non-severe during OLP SAF-C

	Pre: CR845		Pre: Placebo	
	N	n (%) [95 % CI]	N	n (%) [95 % CI]
AESI seizures - non-severe during OLP	122	0 (0.0)	122	1 (0.8) [0.0, 4.5]

Table CT3LAEMN_CMIO: AESI mental status change - non-severe during OLP SAF-C

	Pre: CR845		Pre: Placebo	
		n (%)		n (%)
	N	[95 % CI]	N	[95 % CI]
AESI mental status change - non-severe during OLP	122	8 (6.6) [2.9, 12.5]	122	4 (3.3) [0.9, 8.2]
change – non-severe during OLP		[2.9, 12.5]		[0.9, 8.2]

Table CT3LAEEN_CMIO: AESI mood change - non-severe during OLP SAF-C

	Pre: CR845		Pre: Placebo	
	N	n (%) [95 % CI]	N	n (%) [95 % CI]
AESI mood change - non-severe	122	4 (3.3)	122	3 (2.5)
during OLP		[0.9, 8.2]		[0.5, 7.0]

Table CT3LAEUN_CMIO: AESI unusual feeling/sensation - non-severe during OLP SAF-C

	I	Pre: CR845	Pr	re: Placebo
		n (%)		n (%)
	N	[95 % CI]	N	[95 % CI]
AESI unusual feeling/sensation - non-severe during OLP	122	7 (5.7) [2.3, 11.5]	122	4 (3.3) [0.9, 8.2]

Note: SAF-C = Week 52 Study Completer Set. N = total number of patients in analysis set. n = number of patients with events during OLP. OLP = open label period. 95% CI = 95% confidence interval according to Clopper Pearson. AESI = adverse event of special interest. Source Data: aae, created on: 03MAR2022

Table CT3LAERN_CMIO: AESI tachycardia/palpitation - non-severe during OLP SAF-C

	I	Pre: CR845	Pre: Placebo		
	N	n (%) [95 % CI]	N	n (%) [95 % CI]	
AESI tachycardia/palpitation - non-severe during OLP	122	9 (7.4) [3.4, 13.5]	122	8 (6.6) [2.9, 12.5]	

Note: SAF-C = Week 52 Study Completer Set. N = total number of patients in analysis set. n = number of patients with events during OLP. OLP = open label period. 95% CI = 95% confidence interval according to Clopper Pearson. AESI = adverse event of special interest. Source Data: aae, created on: 03MAR2022

Anhang 4-I-2: Zusatzauswertungen der Studie KALM-2 (OL)

DT3DDO_LMHO: Change from OL-baseline in 5-D degree score - Cohort SAF-L	4
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DT3DLO_LMHO: Change from OL-baseline in 5-D duration score - Cohort SAF-L	7
DT3DLO_LMD0: Change from OL-baseline in 5-D duration score - LSMEANS confidence intervals - Cohort SAF-L	
DF3DLO_LMG0: Change from OL-baseline in 5-D duration score - Course of LSMEANS - Cohort SAF-L	
DT3DWO_LMHO: Change from OL-baseline in 5-D direction score - Cohort SAF-L	10
DT3DWO_LMD0: Change from OL-baseline in 5-D direction score - LSMEANS confidence intervals - Cohort SAF-L	11
DF3DWO_LMG0: Change from OL-baseline in 5-D direction score - Course of LSMEANS - Cohort SAF-L	
DT3DNO_LMHO: Change from OL-baseline in 5-D disability score - Cohort SAF-L	13
DT3DNO_LMD0: Change from OL-baseline in 5-D disability score - LSMEANS confidence intervals - Cohort SAF-L	14
DF3DNO_LMG0: Change from OL-baseline in 5-D disability score - Course of LSMEANS - Cohort SAF-L	
DT3DVO_LMHO: Change from OL-baseline in 5-D distribution score - Cohort SAF-L	
DT3DVO_LMD0: Change from OL-baseline in 5-D distribution score - LSMEANS confidence intervals - Cohort SAF-L	
DF3DVO_LMG0: Change from OL-baseline in 5-D distribution score - Course of LSMEANS - Cohort SAF-L	
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DT3DDO_CMD0: Change from OL-baseline in 5-D degree score - LSMEANS confidence intervals - Cohort SAF-C	20
DF3DDO_CMG0: Change from OL-baseline in 5-D degree score - Course of LSMEANS - Cohort SAF-C	21
DT3DLO_CMHO: Change from OL-baseline in 5-D duration score - Cohort SAF-C	22
DT3DLO_CMD0: Change from OL-baseline in 5-D duration score - LSMEANS confidence intervals - Cohort SAF-C	23
DF3DLO_CMG0: Change from OL-baseline in 5-D duration score - Course of LSMEANS - Cohort SAF-C	24
DT3DWO_CMHO: Change from OL-baseline in 5-D direction score - Cohort SAF-C	25
DT3DWO_CMD0: Change from OL-baseline in 5-D direction score - LSMEANS confidence intervals - Cohort SAF-C	26
DF3DWO_CMG0: Change from OL-baseline in 5-D direction score - Course of LSMEANS - Cohort SAF-C	27
DT3DNO_CMHO: Change from OL-baseline in 5-D disability score - Cohort SAF-C	28
DT3DNO_CMD0: Change from OL-baseline in 5-D disability score - LSMEANS confidence intervals - Cohort SAF-C	29
DF3DNO_CMG0: Change from OL-baseline in 5-D disability score - Course of LSMEANS - Cohort SAF-C	30
DT3DVO_CMHO: Change from OL-baseline in 5-D distribution score - Cohort SAF-C	31
DT3DVO_CMD0: Change from OL-baseline in 5-D distribution score - LSMEANS confidence intervals - Cohort SAF-C	32
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DT3LAEGN_LMIO: AESI gait disturbance - non-severe during OLP - Cohort SAF-L	50
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DT3LAEKN_LMIO: AESI seizures - non-severe during OLP - Cohort SAF-L	55
DT3LAEMN_LMIO: AESI mental status change - non-severe during OLP - Cohort SAF-L	56
DT3LAEEN_LMIO: AESI mood change - non-severe during OLP - Cohort SAF-L	57
DT3LAEUN_LMIO: AESI unusual feeling/sensation - non-severe during OLP - Cohort SAF-L	58
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DT3LAEYN_CMIO: AESI syncope - non-severe during OLP - Cohort SAF-C	63
DT3LAEON_CMIO: AESI somnolence - non-severe during OLP - Cohort SAF-C	64
DT3LAEKN_CMIO: AESI seizures - non-severe during OLP - Cohort SAF-C	65
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DT3LAEEN_CMIO: AESI mood change - non-severe during OLP - Cohort SAF-C	67
DT3LAEUN_CMIO: AESI unusual feeling/sensation - non-severe during OLP - Cohort SAF-C	68
DT3LAERN_CMIO: AESI tachycardia/palpitation - non-severe during OLP - Cohort SAF-C	69

Table DT3DDO_LMHO: Change from OL-baseline in 5-D degree score SAF-L

	Treatment	N	n (%)	Mean (SD)	Min	Q50	Max
5-D degree score OL Bas	seline Pre: CR845	189	189 (100.0)	2.6 (0.9)	1	2.0	5
5-D degree score OL Bas	Pre: Placebo		210 (100.0)	2.8 (0.9) 2.8 (0.8)	1	2.0	5
OL Wee		189	173 (91.5)	2.5 (0.9)	1	2.0	5
	Pre: Placebo		200 (95.2)	2.3 (0.8)	1	2.0	5
OL Wee		189	140 (74.1)	2.4 (0.9)	1	2.0	5
	Pre: Placebo		162 (77.1)	2.3 (0.8)	1	2.0	5
OL Wee		189	137 (72.5)	2.3 (0.9)	1	2.0	5
02	Pre: Placebo		158 (75.2)	2.3 (0.8)	1	2.0	5
OL Wee		189	71 (37.6)	2.2 (0.9)	1	2.0	5
02	Pre: Placebo		76 (36.2)	2.2 (0.9)	1	2.0	5
OL Wee		189	23 (12.2)	2.2 (0.8)	1	2.0	4
	Pre: Placebo		30 (14.3)	2.3 (0.9)	1	2.0	4
OL Wee	ek 52 Pre: CR845	189	2 (1.1)	2.0 (0.0)	2	2.0	2
	Pre: Placebo	210	3 (1.4)	2.3 (0.6)	2	2.0	3
Change from OL-baseline in 5-D degree OL Wee	ek 4 Pre: CR845	189	173 (91.5)	-0.1 (0.8)	-2	0.0	2
	Pre: Placebo	210	200 (95.2)	-0.5(0.9)	-4	0.0	2
OL Wee	ek 8 Pre: CR845	189	140 (74.1)	-0.1 (0.8)	-3	0.0	3
	Pre: Placebo	210	162 (77.1)	-0.5 (0.9)	-4	-0.5	1
OL Wee	ek 12 Pre: CR845	189	137 (72.5)	-0.2 (0.9)	-3	0.0	2
	Pre: Placebo	210	158 (75.2)	-0.6 (0.9)	-4	-0.5	2
OL Wee	ek 24 Pre: CR845	189	71 (37.6)	-0.3 (0.9)	-3	0.0	2
	Pre: Placebo	210	76 (36.2)	-0.7 (1.0)	-4	-1.0	2
OL Wee	ek 36 Pre: CR845	189	23 (12.2)	-0.3 (1.2)	-3	0.0	1
	Pre: Placebo	210	30 (14.3)	-0.5 (0.9)	-3	-1.0	1
OL Wee	ek 52 Pre: CR845	189	2 (1.1)	-0.5 (0.7)	-1	-0.5	0
	Pre: Placebo	210	3 (1.4)	-1.0 (0.0)	-1	-1.0	-1

Note: SAF-L = Week 52 Safety set.

Table DT3DDO_LMD0:	Change from OL-baseli	ne in 5-D degree	score - LSMEANS	confidence intervals
		SAF-L		

Change from OL-baseline in 5-D degree score				Change fr	om Baseline
Time	Treatment	Ν	n (%)	LS-Mean (SE)	95% CI
OL Week 4	Pre: CR845	189	173 (91.5)	-0.1 (0.1)	(-0.2, 0.0)
	Pre: Placebo	210	200 (95.2)	-0.5 (0.1)	(-0.6, -0.4)
DL Week 8	Pre: CR845	189	140 (74.1)	-0.1 (0.1)	(-0.3, -0.0)
	Pre: Placebo	210	162 (77.1)	-0.5 (0.1)	(-0.7, -0.4)
DL Week 12	Pre: CR845	189	137 (72.5)	-0.2 (0.1)	(-0.3, -0.1)
	Pre: Placebo	210	158 (75.2)	-0.5 (0.1)	(-0.6, -0.4)
DL Week 24	Pre: CR845	189	71 (37.6)	-0.3 (0.1)	(-0.4, -0.1)
	Pre: Placebo	210	76 (36.2)	-0.6 (0.1)	(-0.8, -0.5)
OL Week 36	Pre: CR845	189	23 (12.2)	-0.3 (0.2)	(-0.7, 0.1)
	Pre: Placebo	210	30 (14.3)	-0.5 (0.2)	(-0.8, -0.2)

Note: SAF-L = Week 52 Safety set.

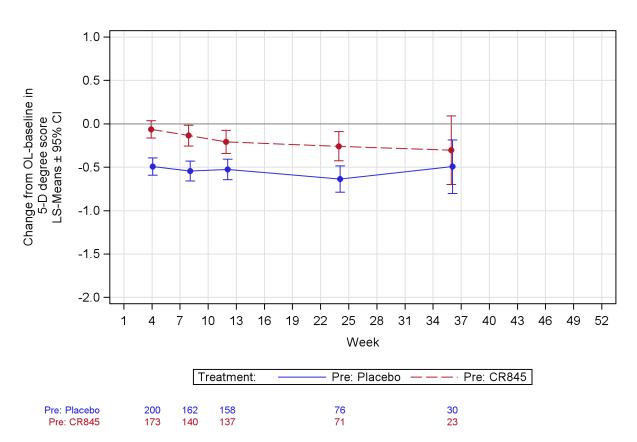
N = total number of patients in analysis set. n = number of non-missing values. MMRM = mixed repeated measures model.

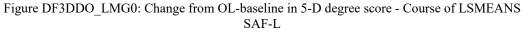
LS-Mean = Least square mean. SE = Standard error. 95% CI = 95% confidence interval.

For each treatment, a separate MMRM was applied with fixed factor time and baseline as covariate.

Due to the low number of patients with values at OL-Week 52, data from this time point were omitted from the analysis to enable convergence of the MMRM.

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Note: SAF-L = Week 52 Safety set.

Symbols present least square mean (LS-Mean), bars present 95% confidence intervals (CI). CR845 = Difelikefalin.

OL - baseline = Baseline of open label period. No display of Week 52 due to the low patient numbers.

Source Table: DT3DDO LMD0

Table DT3DLO_LMHO: Change from OL-baseline in 5-D duration score SAF-L

		Treatment	Ν	n (%)	Mean (SD)	Min	Q50	Max
5-D duration score	OL Baseline	Pre: CR845	189	189 (100.0)	1.8 (1.1)	1	1.0	5
S-D duration score	OL DASEIINE	Pre: Placebo	210	210 (100.0)	1.8 (1.1) 1.9 (1.3)	1	2.0	5
	OL Week 4	Pre: CR845	189	170 (89.9)	1.9 (1.3) 1.7 (1.1)	1	1.0	5
	OL WEEK 4	Pre: Placebo	210	200 (95.2)	1.5 (0.9)	1	1.0	5
	OL Week 8	Pre: CR845	189	140 (74.1)	1.5 (0.9) 1.6 (1.1)	1	1.0	5
	OL WEEK 0	Pre: Placebo	210	162 (77.1)	1.4 (0.8)	1	1.0	5
	OL Week 12	Pre: CR845	189	137 (72.5)	1.4 (0.8) 1.6 (1.1)	1	1.0	5
	OL WEEK IZ	Pre: Placebo	210	158 (75.2)	1.6 (1.1) 1.4 (0.9)	1	1.0	5
	OL Week 24	Pre: CR845	189	70 (37.0)	1.4 (0.9) 1.4 (0.9)	1	1.0	5
	OL Week 24	Pre: Placebo	210	76 (36.2)	1.4 (0.9) 1.4 (1.0)	1	1.0	5
	OL Week 36	Pre: CR845	189	24 (12.7)	1.4 (1.0) 1.2 (0.5)			
	OL Week 36	Pre: CR845 Pre: Placebo	210	. ,	1.2 (0.5) 1.2 (0.4)	1 1	1.0 1.0	3 2
	OT Usels 50			31 (14.8)				
	OL Week 52	Pre: CR845	189	2 (1.1)	1.0 (0.0)	1	1.0	1
		Pre: Placebo	210	3 (1.4)	2.0 (0.0)	2	2.0	2
Change from OL-baseline in 5-D duration score	OL Week 4	Pre: CR845	189	170 (89.9)	0.0 (1.1)	-4	0.0	4
		Pre: Placebo	210	200 (95.2)	-0.5(1.3)	-4	0.0	3
	OL Week 8	Pre: CR845	189	140 (74.1)	-0.0 (1.0)	-3	0.0	4
		Pre: Placebo	210	162 (77.1)	-0.6(1.2)	-4	0.0	2
	OL Week 12	Pre: CR845	189	137 (72.5)	-0.1 (1.0)	-4	0.0	4
		Pre: Placebo	210	158 (75.2)	-0.6(1.3)	-4	0.0	4
	OL Week 24	Pre: CR845	189	70 (37.0)	-0.3 (0.8)	-3	0.0	3
		Pre: Placebo	210	76 (36.2)	-0.7 (1.2)	-4	0.0	1
	OL Week 36	Pre: CR845	189	24 (12.7)	-0.5 (0.9)	-3	0.0	0
		Pre: Placebo	210	31 (14.8)	-0.7 (1.3)	-4	0.0	1
	OL Week 52	Pre: CR845	189	2 (1.1)	-0.5 (0.7)	-1	-0.5	0
		Pre: Placebo	210	3 (1.4)	0.0 (0.0)	0	0.0	0
		111111111111111	210	- (=• 1)	(0.0)	Ũ	2.0	0

Note: SAF-L = Week 52 Safety set.

Table DT3DLO_LMD0:	Change from	OL-baseline	in	5-D	duration	score	-	LSMEANS	confidence	intervals	
			S	SAF-I	Ľ						

Change from OL-baseline in 5-D duration score				Change fr	om Baseline
Time	Treatment	Ν	n (%)	LS-Mean (SE)	95% CI
OL Week 4	Pre: CR845	189	170 (89.9)	0.0 (0.1)	(-0.1, 0.2)
	Pre: Placebo	210	200 (95.2)	-0.5 (0.1)	(-0.6, -0.4)
OL Week 8	Pre: CR845	189	140 (74.1)	-0.0 (0.1)	(-0.2, 0.1)
	Pre: Placebo	210	162 (77.1)	-0.6 (0.1)	(-0.7, -0.5)
OL Week 12	Pre: CR845	189	137 (72.5)	-0.1 (0.1)	(-0.3, 0.1)
	Pre: Placebo	210	158 (75.2)	-0.6 (0.1)	(-0.7, -0.5)
OL Week 24	Pre: CR845	189	70 (37.0)	-0.2 (0.1)	(-0.4, -0.1)
	Pre: Placebo	210	76 (36.2)	-0.6 (0.1)	(-0.8, -0.5)
OL Week 36	Pre: CR845	189	24 (12.7)	-0.5 (0.0)	(-0.6, -0.4)
	Pre: Placebo	210	31 (14.8)	-0.7 (0.1)	(-0.9, -0.5)

Note: SAF-L = Week 52 Safety set.

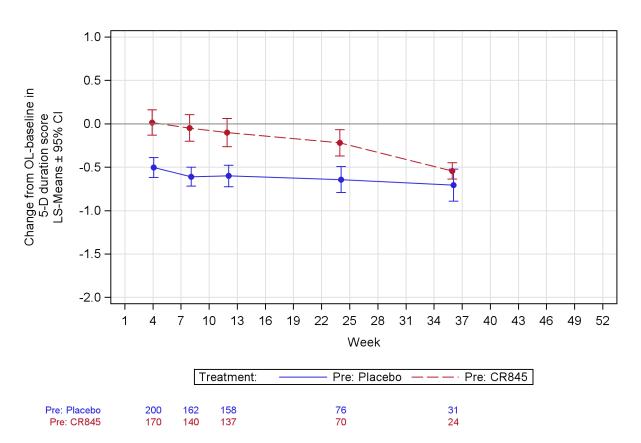
N = total number of patients in analysis set. n = number of non-missing values. MMRM = mixed repeated measures model.

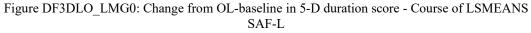
LS-Mean = Least square mean. SE = Standard error. 95% CI = 95% confidence interval.

For each treatment, a separate MMRM was applied with fixed factor time and baseline as covariate.

Due to the low number of patients with values at OL-Week 52, data from this time point were omitted from the analysis to enable convergence of the MMRM.

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Note: SAF-L = Week 52 Safety set.

Symbols present least square mean (LS-Mean), bars present 95% confidence intervals (CI). CR845 = Difelikefalin.

OL - baseline = Baseline of open label period. No display of Week 52 due to the low patient numbers.

Source Table: DT3DLO LMD0

Table DT3DWO_LMHO: Change from OL-baseline in 5-D direction score SAF-L

		Treatment	N	n (%)	Mean (SD)	Min	Q50	Max
		5 (50.45	100	100 (100 0)				_
5-D direction score	OL Baseline	Pre: CR845	189	189 (100.0)	2.6 (1.0)	1	2.0	5
		Pre: Placebo	210	210 (100.0)	2.9 (1.0)	1	3.0	5
	OL Week 4	Pre: CR845	189	172 (91.0)	2.4 (0.9)	1	2.0	5
		Pre: Placebo	210	200 (95.2)	2.4 (0.9)	1	2.0	5
	OL Week 8	Pre: CR845	189	140 (74.1)	2.5 (1.1)	1	2.0	5
		Pre: Placebo	210	162 (77.1)	2.3 (0.9)	1	2.0	5
	OL Week 12	Pre: CR845	189	137 (72.5)	2.5 (1.1)	1	2.0	5
		Pre: Placebo	210	158 (75.2)	2.3 (0.9)	1	2.0	5
	OL Week 24	Pre: CR845	189	71 (37.6)	2.3 (0.9)	1	2.0	4
		Pre: Placebo	210	76 (36.2)	2.4 (1.0)	1	2.0	5
	OL Week 36	Pre: CR845	189	23 (12.2)	2.4 (0.9)	1	2.0	4
		Pre: Placebo	210	30 (14.3)	2.3 (1.0)	1	2.0	5
	OL Week 52	Pre: CR845	189	2 (1.1)	2.0 (0.0)	2	2.0	2
		Pre: Placebo	210	3 (1.4)	2.3 (0.6)	2	2.0	3
Change from OL-baseline in 5-D direction score	OL Week 4	Pre: CR845	189	172 (91.0)	-0.1 (1.0)	-3	0.0	3
		Pre: Placebo	210	200 (95.2)	-0.6 (1.1)	-4	0.0	2
	OL Week 8	Pre: CR845	189	140 (74.1)	-0.1 (1.2)	-3	0.0	4
		Pre: Placebo	210	162 (77.1)	-0.7 (1.1)	-4	-1.0	2
	OL Week 12	Pre: CR845	189	137 (72.5)	-0.1 (1.3)	-3	0.0	3
		Pre: Placebo	210	158 (75.2)	-0.7 (1.2)	-3	-1.0	3
	OL Week 24	Pre: CR845	189	71 (37.6)	-0.3 (1.1)	-3	0.0	2
		Pre: Placebo	210	76 (36.2)	-0.7 (1.1)	-3	-1.0	3
	OL Week 36	Pre: CR845	189	23 (12.2)	-0.3 (1.5)	-3	0.0	2
		Pre: Placebo	210	30 (14.3)	-0.8(1.0)	-3	-1.0	1
	OL Week 52	Pre: CR845	189	2 (1.1)	-0.5 (0.7)	-1	-0.5	0
		Pre: Placebo	210	3 (1.4)	-1.3 (0.6)	-2	-1.0	-1

Note: SAF-L = Week 52 Safety set.

Table DT3DWO_LMD0:	Change from	OL-baseline i	n 5-D	direction	score	- LSMEANS	confidence	intervals
			SAF-	L				

Change from C direction sco	DL-baseline in 5-D			*	sures analysis om Baseline
Time	Treatment	N	n (%)	LS-Mean (SE)	95% CI
OL Week 4	Pre: CR845	189	172 (91.0)	-0.1 (0.1)	(-0.3, -0.0)
ol week i	Pre: Placebo	210	200 (95.2)	,	(-0.8, -0.5)
OL Week 8	Pre: CR845	189	140 (74.1)	-0.1 (0.1)	(-0.3, 0.1)
	Pre: Placebo	210	162 (77.1)	-0.7 (0.1)	(-0.8, -0.6)
OL Week 12	Pre: CR845	189	137 (72.5)	-0.1 (0.1)	(-0.3, 0.1)
	Pre: Placebo	210	158 (75.2)	-0.7 (0.1)	(-0.8, -0.5)
OL Week 24	Pre: CR845	189	71 (37.6)	-0.2 (0.1)	(-0.4, -0.1)
	Pre: Placebo	210	76 (36.2)	-0.6 (0.1)	(-0.8, -0.4)
OL Week 36	Pre: CR845	189	23 (12.2)	0.1 (0.2)	(-0.3, 0.5)
	Pre: Placebo	210	30 (14.3)	-0.7 (0.2)	(-1.0, -0.3)

Note: SAF-L = Week 52 Safety set.

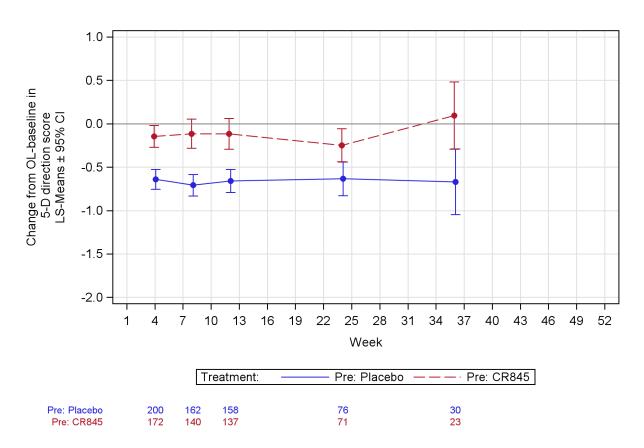
N = total number of patients in analysis set. n = number of non-missing values. MMRM = mixed repeated measures model. NE = not evaluable.

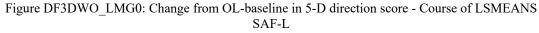
LS-Mean = Least square mean. SE = Standard error. 95% CI = 95% confidence interval.

For each treatment, a separate MMRM was applied with fixed factor time and baseline as covariate.

Due to the low number of patients with values at OL-Week 52, data from this time point were omitted from the analysis to enable convergence of the MMRM.

Page 1 of 1 Program Name: DF3DWO_MG0.sas Run Date: 11MAR2022:11:25:49





Note: SAF-L = Week 52 Safety set.

Symbols present least square mean (LS-Mean), bars present 95% confidence intervals (CI). CR845 = Difelikefalin.

OL - baseline = Baseline of open label period. No display of Week 52 due to the low patient numbers.

Source Table: DT3DWO LMD0

Table DT3DNO_LMHO: Change from OL-baseline in 5-D disability score SAF-L

		Treatment	Ν	n (%)	Mean (SD)	Min	Q50	Max
5-D disability score	OL Baseline	Pre: CR845	189	189 (100.0)	2.4 (1.3)	1	2.0	5
5-D disability score	OL Baseline	Pre: CR045 Pre: Placebo	210	210 (100.0)	2.4(1.3) 2.5(1.2)	1	2.0	5
	OL Week 4	Pre: CR845	189	173 (91.5)	2.3(1.2) 2.3(1.2)	1	2.0	5
	OL WEEK 4	Pre: Placebo	210	200 (95.2)	2.3 (1.2) 2.1 (1.1)	1	2.0	5
	OL Week 8	Pre: CR845	189	140 (74.1)	2.0 (1.2)	1	2.0	5
	OI WEEK 0	Pre: Placebo	210	162 (77.1)	2.0 (1.2) 2.1 (1.1)	1	2.0	5
	OL Week 12	Pre: CR845	189	137 (72.5)	2.0 (1.2)	1	2.0	5
	OH WEEK IL	Pre: Placebo	210	158 (75.2)	2.0 (1.0)	1	2.0	5
	OL Week 24	Pre: CR845	189	71 (37.6)	1.9(1.1)	1	2.0	5
	OL WEEK 24	Pre: Placebo	210	76 (36.2)	2.0 (1.2)	1	2.0	5
	OL Week 36	Pre: CR845	189	23 (12.2)	1.7 (1.1)	1	1.0	5
	of week so	Pre: Placebo	210	30 (14.3)	2.1 (1.1)	1	2.0	5
	OL Week 52	Pre: CR845	189	2 (1.1)	1.5 (0.7)	1	1.5	2
	of week of	Pre: Placebo	210	3 (1.4)	2.7 (0.6)	2	3.0	3
Change from OL-baseline in 5-D disability score	OL Week 4	Pre: CR845	189	173 (91.5)	-0.1 (1.1)	-4	0.0	4
-		Pre: Placebo	210	200 (95.2)	-0.5(1.1)	-4	0.0	2
	OL Week 8	Pre: CR845	189	140 (74.1)	-0.2 (1.1)	-4	0.0	4
		Pre: Placebo	210	162 (77.1)	-0.6(1.1)	-4	0.0	2
	OL Week 12	Pre: CR845	189	137 (72.5)	-0.2 (1.1)	-4	0.0	4
		Pre: Placebo	210	158 (75.2)	-0.6(1.1)	-4	-1.0	3
	OL Week 24	Pre: CR845	189	71 (37.6)	-0.2(1.4)	-4	0.0	4
		Pre: Placebo	210	76 (36.2)	-0.6(1.3)	-3	-1.0	3
	OL Week 36	Pre: CR845	189	23 (12.2)	-0.2(1.0)	-2	0.0	1
		Pre: Placebo	210	30 (14.3)	-0.5 (1.1)	-3	0.0	1
	OL Week 52	Pre: CR845	189	2 (1.1)	-0.5 (0.7)	-1	-0.5	0
		Pre: Placebo	210	3 (1.4)	-0.7 (0.6)	-1	-1.0	0

Note: SAF-L = Week 52 Safety set.

Table DT3DNO_LMD0:	Change from	OL-baseline i	in 5-D	disability	score	- LSMEANS	confidence	intervals
			SAF-					

Change from C disability sc	DL-baseline in 5-D core			Change from Baseline					
Time	Treatment	Ν	n (%)	LS-Mean (SE)	95% CI				
OL Week 4	Pre: CR845	189	173 (91.5)	-0.0 (0.1)	(-0.2, 0.1)				
	Pre: Placebo	210	200 (95.2)	-0.5 (0.1)	(-0.6, -0.4)				
OL Week 8	Pre: CR845	189	140 (74.1)	-0.2 (0.1)	(-0.4, -0.1)				
	Pre: Placebo	210	162 (77.1)	-0.5 (0.1)	(-0.6, -0.4)				
OL Week 12	Pre: CR845	189	137 (72.5)	-0.2 (0.1)	(-0.4, -0.0)				
	Pre: Placebo	210	158 (75.2)	-0.6 (0.1)	(-0.7, -0.4)				
OL Week 24	Pre: CR845	189	71 (37.6)	-0.2 (0.1)	(-0.4, 0.1)				
	Pre: Placebo	210	76 (36.2)	-0.6 (0.1)	(-0.8, -0.4)				
OL Week 36	Pre: CR845	189	23 (12.2)	-0.2 (0.2)	(-0.7, 0.2)				
	Pre: Placebo	210	30 (14.3)	-0.4 (0.2)	(-0.8, -0.1)				

Note: SAF-L = Week 52 Safety set.

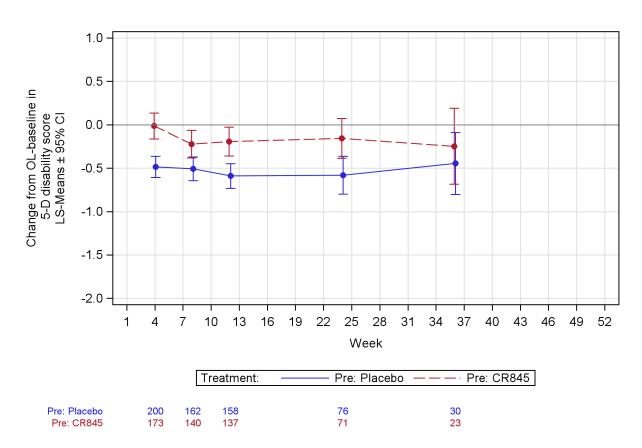
N = total number of patients in analysis set. n = number of non-missing values. MMRM = mixed repeated measures model. NE = not evaluable.

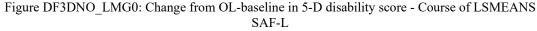
LS-Mean = Least square mean. SE = Standard error. 95% CI = 95% confidence interval.

For each treatment, a separate MMRM was applied with fixed factor time and baseline as covariate.

Due to the low number of patients with values at OL-Week 52, data from this time point were omitted from the analysis to enable convergence of the MMRM.

Page 1 of 1 Program Name: DF3DNO_MG0.sas Run Date: 11MAR2022:11:26:03





Note: SAF-L = Week 52 Safety set.

Symbols present least square mean (LS-Mean), bars present 95% confidence intervals (CI). CR845 = Difelikefalin.

OL - baseline = Baseline of open label period. No display of Week 52 due to the low patient numbers.

Source Table: DT3DNO LMD0

Table DT3DVO_LMHO: Change from OL-baseline in 5-D distribution score SAF-L

		Treatment	Ν	n (%)	Mean (SD)	Min	Q50	Max
5-D distribution score	OL Baseline	Pre: CR845	189	189 (100.0)	2.4 (1.3)	1	2.0	5
	ol papolino	Pre: Placebo	210	210 (100.0)	2.6 (1.1)	1	2.5	5
	OL Week 4	Pre: CR845	189	173 (91.5)	2.2 (1.2)	1	2.0	5
		Pre: Placebo	210	200 (95.2)	2.1 (1.1)	1	2.0	5
	OL Week 8	Pre: CR845	189	140 (74.1)	2.1 (1.2)	1	2.0	5
		Pre: Placebo	210	162 (77.1)	2.2 (1.1)	1	2.0	5
	OL Week 12	Pre: CR845	189	137 (72.5)	2.2 (1.2)	1	2.0	5
		Pre: Placebo	210	158 (75.2)	2.1 (1.0)	1	2.0	5
	OL Week 24	Pre: CR845	189	71 (37.6)	2.0 (1.2)	1	2.0	5
		Pre: Placebo	210	76 (36.2)	2.1 (1.2)	1	2.0	5
	OL Week 36	Pre: CR845	189	24 (12.7)	1.5 (0.9)	1	1.0	4
		Pre: Placebo	210	31 (14.8)	2.0 (1.2)	1	2.0	5
	OL Week 52	Pre: CR845	189	2 (1.1)	1.0 (0.0)	1	1.0	1
		Pre: Placebo	210	3 (1.4)	2.0 (0.0)	2	2.0	2
Change from OL-baseline in 5-D distribution score	OL Week 4	Pre: CR845	189	173 (91.5)	-0.2 (0.8)	-4	0.0	2
		Pre: Placebo	210	200 (95.2)	-0.5(1.0)	-4	0.0	3
	OL Week 8	Pre: CR845	189	140 (74.1)	-0.2 (0.7)	-2	0.0	1
		Pre: Placebo	210	162 (77.1)	-0.5 (1.0)	-4	-0.5	2
	OL Week 12	Pre: CR845	189	137 (72.5)	-0.2 (0.9)	-4	0.0	3
		Pre: Placebo	210	158 (75.2)	-0.6 (1.0)	-4	-1.0	3
	OL Week 24	Pre: CR845	189	71 (37.6)	-0.3 (0.8)	-3	0.0	1
		Pre: Placebo	210	76 (36.2)	-0.6 (1.0)	-4	-1.0	2
	OL Week 36	Pre: CR845	189	24 (12.7)	-0.5 (1.0)	-3	0.0	1
		Pre: Placebo	210	31 (14.8)	-0.6 (1.2)	-3	0.0	1
	OL Week 52	Pre: CR845	189	2 (1.1)	0.0 (0.0)	0	0.0	0
		Pre: Placebo	210	3 (1.4)	0.3 (1.2)	-1	1.0	1

Note: SAF-L = Week 52 Safety set.

Table DT3DVO_LMD0:	Change f	from	OL-baseline	in	5-D	distribution	score	_	LSMEANS	confidence	intervals
					SAI	F-L					

Change from C distribution	DL-baseline in 5-D			Change fr	om Baseline
Time	Treatment	Ν	n (%)	LS-Mean (SE)	95% CI
OL Week 4	Pre: CR845	189	173 (91.5)	-0.2 (0.1)	(-0.3, -0.0)
	Pre: Placebo	210	200 (95.2)	· · ·	(-0.6, -0.4)
OL Week 8	Pre: CR845	189	140 (74.1)	-0.2 (0.1)	(-0.3, -0.1)
	Pre: Placebo	210	162 (77.1)	-0.5 (0.1)	(-0.7, -0.4)
OL Week 12	Pre: CR845	189	137 (72.5)	-0.2 (0.1)	(-0.3, -0.0)
	Pre: Placebo	210	158 (75.2)	-0.6 (0.1)	(-0.7, -0.4)
OL Week 24	Pre: CR845	189	71 (37.6)	-0.2 (0.1)	(-0.4, -0.0)
	Pre: Placebo	210	76 (36.2)	-0.5 (0.1)	(-0.7, -0.3)
OL Week 36	Pre: CR845	189	24 (12.7)	-0.5 (0.1)	(-0.7, -0.2)
	Pre: Placebo	210	31 (14.8)	-0.6 (0.2)	(-1.0, -0.3)

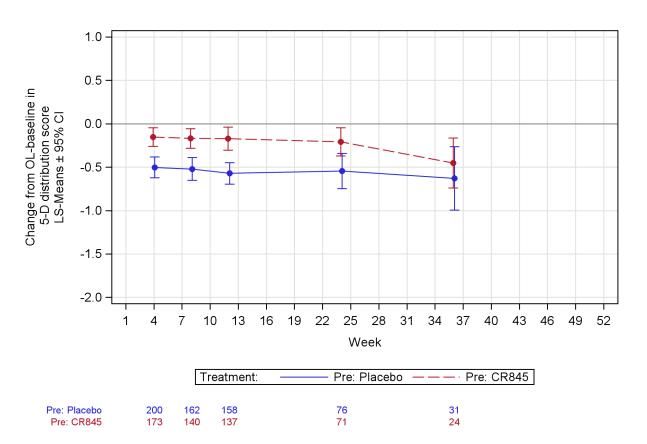
Note: SAF-L = Week 52 Safety set.

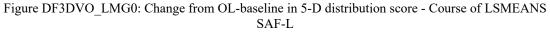
N = total number of patients in analysis set. n = number of non-missing values. MMRM = mixed repeated measures model.

- LS-Mean = Least square mean. SE = Standard error. 95% CI = 95% confidence interval.
- For each treatment, a separate MMRM was applied with fixed factor time and baseline as covariate.

Due to the low number of patients with values at OL-Week 52, data from this time point were omitted from the analysis to enable convergence of the MMRM.

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Note: SAF-L = Week 52 Safety set.

Symbols present least square mean (LS-Mean), bars present 95% confidence intervals (CI). CR845 = Difelikefalin.

OL - baseline = Baseline of open label period. No display of Week 52 due to the low patient numbers.

Source Table: DT3DVO LMD0

Table DT3DDO_CMHO: Change from OL-baseline in 5-D degree score SAF-C

		Treatment	N	n (%)	Mean (SD)	Min	Q50	Max
								_
5-D degree score	OL Baseline	Pre: CR845	14	14 (100.0)	2.2 (1.3)	1	2.0	5
		Pre: Placebo	21	21 (100.0)	2.9 (0.7)	2	3.0	4
	OL Week 4	Pre: CR845	14	14 (100.0)	2.1 (1.1)	1	2.0	5
		Pre: Placebo	21	21 (100.0)	2.2 (0.6)	1	2.0	3
	OL Week 8	Pre: CR845	14	14 (100.0)	1.8 (1.0)	1	1.5	4
		Pre: Placebo	21	21 (100.0)	2.2 (0.7)	1	2.0	4
	OL Week 12	Pre: CR845	14	14 (100.0)	1.7 (0.6)	1	2.0	3
		Pre: Placebo	21	21 (100.0)	2.1 (0.8)	1	2.0	4
	OL Week 24	Pre: CR845	14	14 (100.0)	2.0 (0.9)	1	2.0	4
		Pre: Placebo	21	21 (100.0)	1.9 (0.6)	1	2.0	3
	OL Week 36	Pre: CR845	14	13 (92.9)	2.3 (0.6)	2	2.0	4
		Pre: Placebo	21	20 (95.2)	2.4 (0.8)	1	2.0	4
	OL Week 52	Pre: CR845	14	2 (14.3)	2.0 (0.0)	2	2.0	2
		Pre: Placebo	21	3 (14.3)	2.3 (0.6)	2	2.0	3
Change from OL-baseline in 5-D degree score	OL Week 4	Pre: CR845	14	14 (100.0)	-0.1 (0.9)	-2	0.0	1
		Pre: Placebo	21	21 (100.0)	-0.6 (0.6)	-2	-1.0	0
	OL Week 8	Pre: CR845	14	14 (100.0)	-0.4 (0.9)	-3	0.0	0
		Pre: Placebo	21	21 (100.0)	-0.7(0.8)	-2	-1.0	1
	OL Week 12	Pre: CR845	14	14 (100.0)	-0.5 (1.2)	-3	0.0	1
		Pre: Placebo	21	21 (100.0)	-0.7 (1.0)	-2	-1.0	1
	OL Week 24	Pre: CR845	14	14 (100.0)	-0.2(1.2)	-3	0.0	2
		Pre: Placebo	21	21 (100.0)	-1.0(0.8)	-2	-1.0	0
	OL Week 36	Pre: CR845	14	13 (92.9)	0.0 (1.0)	-2	0.0	1
		Pre: Placebo	21	20 (95.2)	-0.5 (0.8)	-2	-0.5	1
	OL Week 52	Pre: CR845	14	2 (14.3)	-0.5 (0.7)	-1	-0.5	0
		Pre: Placebo	21	3 (14.3)	-1.0 (0.0)	-1	-1.0	-1
				/				

Note: SAF-C = Week 52 Study Completer Set.

Table DT3DDO_CMD0:	Change from	OL-baseline	in 5-D	degree	score	- LSMEANS	confidence	intervals
			SAF-C					

Change from C degree score	DL-baseline in 5-D			Change from Baseline				
Time	Treatment	Ν	n (%)	LS-Mean (SE)	95% CI			
OL Week 4	Pre: CR845	14	14 (100.0)	-0.2 (0.3)	(-0.8, 0.4)			
	Pre: Placebo	21	21 (100.0)	-0.6 (0.1)	(-0.9, -0.4)			
OL Week 8	Pre: CR845	14	14 (100.0)	-0.4 (0.2)	(-1.0, 0.1)			
	Pre: Placebo	21	21 (100.0)	-0.7 (0.1)	(-1.0, -0.4)			
OL Week 12	Pre: CR845	14	14 (100.0)	-0.5 (0.2)	(-0.9, -0.2)			
	Pre: Placebo	21	21 (100.0)	-0.7 (0.2)	(-1.1, -0.3)			
OL Week 24	Pre: CR845	14	14 (100.0)	-0.2 (0.2)	(-0.7, 0.2)			
	Pre: Placebo	21	21 (100.0)	-1.0 (0.1)	(-1.3, -0.7)			
OL Week 36	Pre: CR845	14	13 (92.9)	0.0 (0.1)	(-0.3, 0.4)			
	Pre: Placebo	21	20 (95.2)	-0.5 (0.2)	(-0.9, -0.2)			

Note: SAF-C = Week 52 Study Completer Set.

N = total number of patients in analysis set. n = number of non-missing values. MMRM = mixed repeated measures model.

LS-Mean = Least square mean. SE = Standard error. 95% CI = 95% confidence interval.

For each treatment, a separate MMRM was applied with fixed factor time and baseline as covariate.

Due to the low number of patients with values at OL-Week 52, data from this time point were omitted from the analysis to enable convergence of the MMRM.

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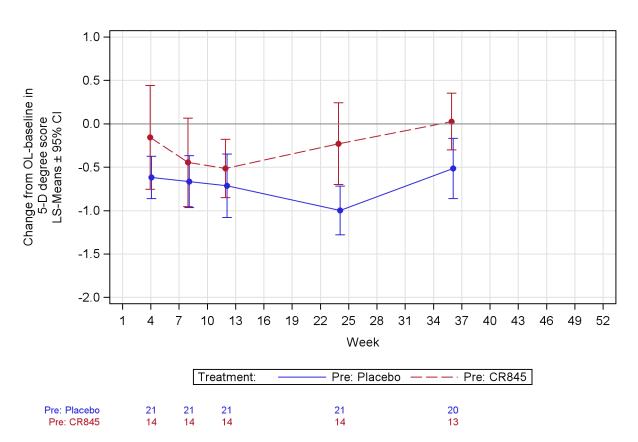


Figure DF3DDO_CMG0: Change from OL-baseline in 5-D degree score - Course of LSMEANS SAF-C

Note: SAF-C = Week 52 Study Completer Set.

Symbols present least square mean (LS-Mean), bars present 95% confidence intervals (CI). CR845 = Difelikefalin.

OL - baseline = Baseline of open label period. No display of Week 52 due to the low patient numbers.

Source Table: DT3DDO CMD0

Table DT3DLO_CMHO:	Change	from	OL-baseline	in	5-D	duration	score	
SAF-C								

		Treatment	N	n (%)	Mean (SD)	Min	Q50	Max
								_
5-D duration score	OL Baseline	Pre: CR845	14	14 (100.0)	1.6 (1.3)	1	1.0	5
		Pre: Placebo	21	21 (100.0)	2.0 (1.3)	1	2.0	5
	OL Week 4	Pre: CR845	14	14 (100.0)	1.4 (0.9)	1	1.0	4
		Pre: Placebo	21	21 (100.0)	1.4 (0.5)	1	1.0	2
	OL Week 8	Pre: CR845	14	14 (100.0)	1.4 (0.7)	1	1.0	3
		Pre: Placebo	21	21 (100.0)	1.3 (0.6)	1	1.0	3
	OL Week 12	Pre: CR845	14	14 (100.0)	1.4 (0.6)	1	1.0	3
		Pre: Placebo	21	21 (100.0)	1.5 (0.7)	1	1.0	3
	OL Week 24	Pre: CR845	14	14 (100.0)	1.3 (0.6)	1	1.0	3
		Pre: Placebo	21	21 (100.0)	1.1 (0.4)	1	1.0	2
	OL Week 36	Pre: CR845	14	14 (100.0)	1.1 (0.4)	1	1.0	2
		Pre: Placebo	21	21 (100.0)	1.2 (0.4)	1	1.0	2
	OL Week 52	Pre: CR845	14	2 (14.3)	1.0 (0.0)	1	1.0	1
		Pre: Placebo	21	3 (14.3)	2.0 (0.0)	2	2.0	2
Change from OL-baseline in 5-D duration score	OL Week 4	Pre: CR845	14	14 (100.0)	-0.1 (0.4)	-1	0.0	0
		Pre: Placebo	21	21 (100.0)	-0.6 (1.3)	-4	0.0	1
	OL Week 8	Pre: CR845	14	14 (100.0)	-0.2 (0.6)	-2	0.0	0
		Pre: Placebo	21	21 (100.0)	-0.7 (1.3)	-4	0.0	1
	OL Week 12	Pre: CR845	14	14 (100.0)	-0.2 (0.9)	-3	0.0	1
		Pre: Placebo	21	21 (100.0)	-0.5 (1.2)	-4	0.0	1
	OL Week 24	Pre: CR845	14	14 (100.0)	-0.3 (0.9)	-3	0.0	1
		Pre: Placebo	21	21 (100.0)	-0.9(1.4)	-4	0.0	1
	OL Week 36	Pre: CR845	14	14 (100.0)	-0.4(0.9)	-3	0.0	0
		Pre: Placebo	21	21 (100.0)	-0.8 (1.3)	-4	0.0	1
	OL Week 52	Pre: CR845	14	2 (14.3)	-0.5(0.7)	-1	-0.5	0
		Pre: Placebo	21	3 (14.3)	0.0 (0.0)	0	0.0	0

Note: SAF-C = Week 52 Study Completer Set.

Table DT3DLO_CMD0:	Change from	OL-baseline	in	5-D	duration	score	- LSMEANS	confidence	intervals
			S	SAF-0	5				

duration scor	L-baseline in 5-D e			Change fr	om Baseline
Time	Treatment	Ν	n (%)	LS-Mean (SE)	95% CI
OL Week 4	Pre: CR845	14	14 (100.0)	-0.1 (0.1)	(-0.3, 0.0)
	Pre: Placebo	21	21 (100.0)	-0.6 (0.1)	(-0.8, -0.4)
DL Week 8	Pre: CR845	14	14 (100.0)	-0.2 (0.1)	(-0.4, -0.0)
	Pre: Placebo	21	21 (100.0)	-0.7 (0.1)	(-0.9, -0.4)
DL Week 12	Pre: CR845	14	14 (100.0)	-0.2 (0.1)	(-0.4, -0.0)
	Pre: Placebo	21	21 (100.0)	-0.5 (0.1)	(-0.7, -0.3)
OL Week 24	Pre: CR845	14	14 (100.0)	-0.3 (0.1)	(-0.5, -0.1)
	Pre: Placebo	21	21 (100.0)	-0.9 (0.1)	(-1.1, -0.6)
OL Week 36	Pre: CR845	14	14 (100.0)	-0.4 (0.1)	(-0.6, -0.2)
	Pre: Placebo	21	21 (100.0)	-0.8 (0.1)	(-1.0, -0.6)

Note: SAF-C = Week 52 Study Completer Set.

N = total number of patients in analysis set. n = number of non-missing values. MMRM = mixed repeated measures model.

LS-Mean = Least square mean. SE = Standard error. 95% CI = 95% confidence interval.

For each treatment, a separate MMRM was applied with fixed factor time and baseline as covariate.

Due to the low number of patients with values at OL-Week 52, data from this time point were omitted from the analysis to enable convergence of the MMRM. In addition, a first order autoregressive instead of an unstructured covariance structure was established. Source Data: afived, created on: 07MAR2022

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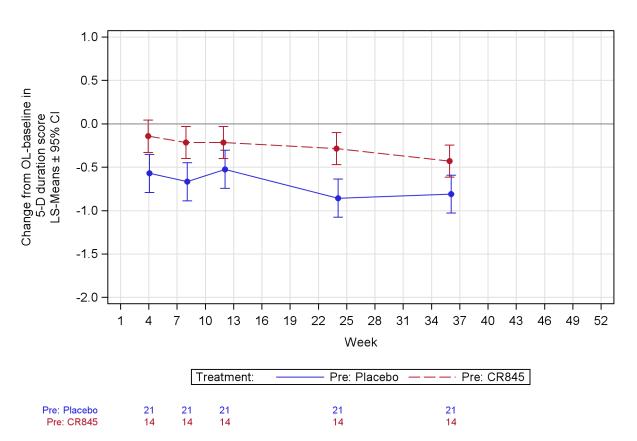


Figure DF3DLO_CMG0: Change from OL-baseline in 5-D duration score - Course of LSMEANS SAF-C

Note: SAF-C = Week 52 Study Completer Set.

Symbols present least square mean (LS-Mean), bars present 95% confidence intervals (CI). CR845 = Difelikefalin.

OL - baseline = Baseline of open label period. No display of Week 52 due to the low patient numbers.

Source Table: DT3DLO CMD0

Table DT3DWO_CMHO: Change from OL-baseline in 5-D direction score SAF-C

		Treatment	Ν	n (%)	Mean (SD)	Min	Q50	Max
5-D direction score	OL Baseline	Pre: CR845	1.4	14 (100 0)	24(12)	1	2.0	F
S-D direction score	OL Baseline	Pre: CR845 Pre: Placebo	14 21	14 (100.0) 21 (100.0)	2.4 (1.2) 3.0 (0.7)	1 2	2.0 3.0	5 4
	OL Week 4	Pre: CR845	21 14	14 (100.0)	2.0 (1.0)	2	2.0	4
	OL Week 4	Pre: CR045 Pre: Placebo	21	14 (100.0) 21 (100.0)	2.3 (0.7)	1	2.0	4 4
	OL Week 8	Pre: CR845	21 14	14 (100.0)	1.9 (0.9)	1	2.0	4
	OL WEEK 8	Pre: Placebo	21	21 (100.0)	2.1 (0.7)	1	2.0	3
	OL Week 12	Pre: CR845	21 14	14 (100.0)	1.9(1.0)	1	2.0	3 4
	OL Week 12	Pre: CR045 Pre: Placebo	21	, ,	2.1 (0.7)	1	2.0	
	OL Week 24	Pre: CR845	21 14	21 (100.0) 14 (100.0)			2.0	4
	OL Week 24	Pre: CR845 Pre: Placebo		. ,	2.1(1.1)	1		4 5
	OT Usels 20		21 14	21 (100.0)	2.0 (0.9)	1	2.0	
	OL Week 36	Pre: CR845 Pre: Placebo		13 (92.9)	2.5 (0.9)	2	2.0 2.0	4
			21	20 (95.2)	2.3 (0.7)	1		4
	OL Week 52	Pre: CR845	14	2 (14.3)	2.0 (0.0)	2	2.0	2
		Pre: Placebo	21	3 (14.3)	2.3 (0.6)	2	2.0	3
Change from OL-baseline in 5-D direction score	OL Week 4	Pre: CR845	14	14 (100.0)	-0.4 (1.0)	-3	0.0	1
		Pre: Placebo	21	21 (100.0)	-0.7(0.8)	-3	-1.0	0
	OL Week 8	Pre: CR845	14	14 (100.0)	-0.5(1.0)	-2	-0.5	2
		Pre: Placebo	21	21 (100.0)	-0.9(0.8)	-3	-1.0	0
	OL Week 12	Pre: CR845	14	14 (100.0)	-0.5(1.2)	-3	-0.5	2
		Pre: Placebo	21	21 (100.0)	-1.0(1.0)	-3	-1.0	1
	OL Week 24	Pre: CR845	14	14 (100.0)	-0.3 (1.5)	-3	0.0	2
		Pre: Placebo	21	21 (100.0)	-1.0 (1.2)	-3	-1.0	3
	OL Week 36	Pre: CR845	14	13 (92.9)	-0.1 (1.3)	-3	0.0	2
		Pre: Placebo	21	20 (95.2)	-0.8 (0.9)	-3	-1.0	0
	OL Week 52	Pre: CR845	14	2 (14.3)	-0.5 (0.7)	-1	-0.5	0
		Pre: Placebo	21	3 (14.3)	-1.3 (0.6)	-2	-1.0	-1
					= (-		-

Note: SAF-C = Week 52 Study Completer Set.

Table DT3DWO_CMD0:	Change from	0L-baseline	in 5-1	direction	score -	- LSMEANS	confidence in	itervals
			SAF	-C				

Change from C direction sco	DL-baseline in 5-D			Change fr	om Baseline
Time	Treatment	Ν	n (%)	LS-Mean (SE)	95% CI
OL Week 4	Pre: CR845	14	14 (100.0)	-0.4 (0.2)	(-0.9, 0.0)
	Pre: Placebo	21	21 (100.0)	-0.7 (0.1)	(-1.0, -0.4)
OL Week 8	Pre: CR845	14	14 (100.0)	-0.5 (0.2)	(-1.0, -0.1)
	Pre: Placebo	21	21 (100.0)	-0.9 (0.1)	(-1.2, -0.6)
OL Week 12	Pre: CR845	14	14 (100.0)	-0.5 (0.3)	(-1.1, 0.0)
	Pre: Placebo	21	21 (100.0)	-1.0 (0.2)	(-1.3, -0.6)
OL Week 24	Pre: CR845	14	14 (100.0)	-0.3 (0.3)	(-1.0, 0.4)
	Pre: Placebo	21	21 (100.0)	-1.0 (0.2)	(-1.5, -0.6)
OL Week 36	Pre: CR845	14	13 (92.9)	-0.0 (0.2)	(-0.6, 0.5)
	Pre: Placebo	21	20 (95.2)	-0.8 (0.2)	(-1.1, -0.4)

Note: SAF-C = Week 52 Study Completer Set.

N = total number of patients in analysis set. n = number of non-missing values. MMRM = mixed repeated measures model. NE = not evaluable.

LS-Mean = Least square mean. SE = Standard error. 95% CI = 95% confidence interval.

For each treatment, a separate MMRM was applied with fixed factor time and baseline as covariate.

Due to the low number of patients with values at OL-Week 52, data from this time point were omitted from the analysis to enable convergence of the MMRM.

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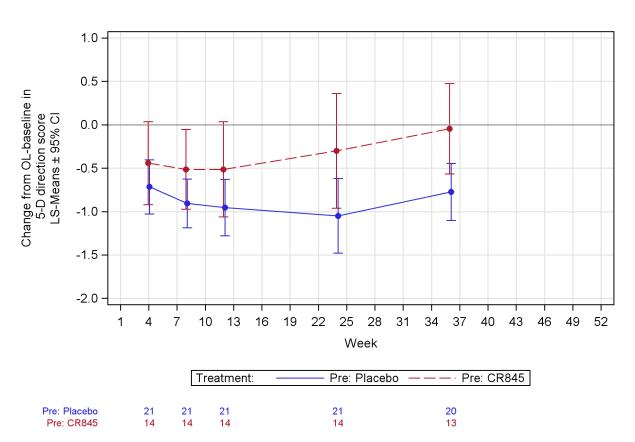


Figure DF3DWO_CMG0: Change from OL-baseline in 5-D direction score - Course of LSMEANS SAF-C

Note: SAF-C = Week 52 Study Completer Set.

Symbols present least square mean (LS-Mean), bars present 95% confidence intervals (CI). CR845 = Difelikefalin.

OL - baseline = Baseline of open label period. No display of Week 52 due to the low patient numbers.

Source Table: DT3DWO CMD0

Table DT3DNO_CMHO: Change from OL-baseline in 5-D disability score SAF-C

		Treatment	Ν	n (%)	Mean (SD)	Min	Q50	Max
5-D disability score	OL Baseline	Pre: CR845	14	14 (100.0)	1.6 (1.3)	1	1.0	5
J-D disability score	OL DASEIINE	Pre: Placebo	21	21 (100.0)	2.6 (1.2)	1	3.0	5
	OL Week 4	Pre: CR845	14	14 (100.0)	1.8(1.3)	1	1.0	5
	OL WEEK 4	Pre: Placebo	21	14 (100.0) 21 (100.0)	2.0 (0.9)	1	2.0	4
	OL Week 8	Pre: CR845	14	14 (100.0)	1.6 (1.2)	1	1.0	4 5
	OL WEEK 0	Pre: Placebo	21	14 (100.0) 21 (100.0)	2.0 (0.9)	1	2.0	4
	OL Week 12	Pre: CR845	14	14 (100.0)	1.4(1.1)	1	1.0	5
	OF MEEK IN	Pre: Placebo	21	14 (100.0) 21 (100.0)	2.0 (0.9)	1	2.0	4
	OL Week 24	Pre: CR845	21 14	14 (100.0)	1.9(1.5)	1	2.0	4 5
	OL Week 24	Pre: Placebo	14 21	14 (100.0) 21 (100.0)	2.0 (1.0)	1	2.0	4
	OL Week 36	Pre: CR845	14	13 (92.9)	1.6(1.0)	1	1.0	
	OL WEEK 30	Pre: Placebo	14 21	20 (95.2)	2.3(1.0)	1	2.0	5 5
	OL Week 52	Pre: CR845	21 14	20 (95.2) 2 (14.3)	1.5(0.7)	1	1.5	
	OL Week 52			· · · ·	. ,	1		2
		Pre: Placebo	21	3 (14.3)	2.7 (0.6)	2	3.0	3
Change from OL-baseline in 5-D disability score	OL Week 4	Pre: CR845	14	14 (100.0)	0.1 (0.5)	-1	0.0	1
		Pre: Placebo	21	21 (100.0)	-0.6(1.1)	-3	0.0	2
	OL Week 8	Pre: CR845	14	14 (100.0)	-0.1(0.5)	-1	0.0	1
		Pre: Placebo	21	21 (100.0)	-0.6(1.3)	-3	0.0	2
	OL Week 12	Pre: CR845	14	14 (100.0)	-0.3 (0.6)	-2	0.0	0
		Pre: Placebo	21	21 (100.0)	-0.6(1.3)	-3	-1.0	2
	OL Week 24	Pre: CR845	14	14 (100.0)	0.2 (1.3)	-1	0.0	4
		Pre: Placebo	21	21 (100.0)	-0.6 (1.4)	-3	0.0	2
	OL Week 36	Pre: CR845	14	13 (92.9)	-0.1(0.9)	-2	0.0	1
		Pre: Placebo	21	20 (95.2)	-0.4(1.0)	-2	0.0	1
	OL Week 52	Pre: CR845	14	2 (14.3)	-0.5(0.7)	-1	-0.5	0
		Pre: Placebo	21	3 (14.3)	-0.7 (0.6)	-1	-1.0	0
		TIC. TIACEDO	2 I	5 (14.5)	0.7 (0.0)	1	1.0	0

Note: SAF-C = Week 52 Study Completer Set.

Table DT3DNO_CMD0:	Change	from (OL-baseline	in	5-D	disability	score	-	LSMEANS	confidence	intervals
					SAF	-C					

Change from C disability sc	DL-baseline in 5-D core			Change fr	om Baseline
Time	Treatment	Ν	n (%)	LS-Mean (SE)	95% CI
OL Week 4	Pre: CR845	14	14 (100.0)	0.1 (0.1)	(-0.2, 0.4)
	Pre: Placebo	21	21 (100.0)	-0.6 (0.2)	(-0.9, -0.2)
OL Week 8	Pre: CR845	14	14 (100.0)	-0.1 (0.1)	(-0.3, 0.2)
	Pre: Placebo	21	21 (100.0)	-0.6 (0.2)	(-1.0, -0.2)
DL Week 12	Pre: CR845	14	14 (100.0)	-0.3 (0.1)	(-0.6, 0.0)
	Pre: Placebo	21	21 (100.0)	-0.6 (0.2)	(-1.0, -0.2)
DL Week 24	Pre: CR845	14	14 (100.0)	0.2 (0.3)	(-0.5, 1.0)
	Pre: Placebo	21	21 (100.0)	-0.6 (0.2)	(-1.1, -0.2)
OL Week 36	Pre: CR845	14	13 (92.9)	-0.1 (0.2)	(-0.5, 0.4)
	Pre: Placebo	21	20 (95.2)	-0.3 (0.2)	(-0.7, 0.1)

Note: SAF-C = Week 52 Study Completer Set.

N = total number of patients in analysis set. n = number of non-missing values. MMRM = mixed repeated measures model. NE = not evaluable.

LS-Mean = Least square mean. SE = Standard error. 95% CI = 95% confidence interval.

For each treatment, a separate MMRM was applied with fixed factor time and baseline as covariate.

Due to the low number of patients with values at OL-Week 52, data from this time point were omitted from the analysis to enable convergence of the MMRM.

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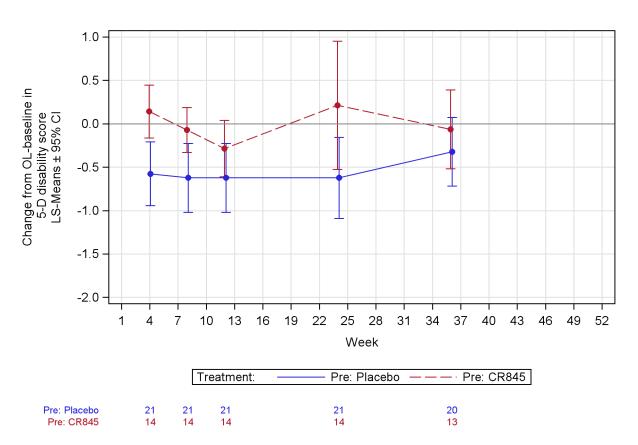


Figure DF3DNO_CMG0: Change from OL-baseline in 5-D disability score - Course of LSMEANS SAF-C

Note: SAF-C = Week 52 Study Completer Set.

Symbols present least square mean (LS-Mean), bars present 95% confidence intervals (CI). CR845 = Difelikefalin.

OL - baseline = Baseline of open label period. No display of Week 52 due to the low patient numbers.

Source Table: DT3DNO CMD0

Source Data: afived, created on: 07MAR2022

Table DT3DVO_CMHO: Change from OL-baseline in 5-D distribution score SAF-C

		Treatment	Ν	n (%)	Mean (SD)	Min	Q50	Max
5-D distribution score	OL Baseline	Pre: CR845	14	14 (100.0)	1.4 (0.9)	1	1.0	4
		Pre: Placebo	21	21 (100.0)	2.5 (1.2)	1	2.0	5
	OL Week 4	Pre: CR845	14	14 (100.0)	1.3 (0.8)	1	1.0	4
		Pre: Placebo	21	21 (100.0)	2.0 (1.1)	1	2.0	5
	OL Week 8	Pre: CR845	14	14 (100.0)	1.3 (0.8)	1	1.0	4
		Pre: Placebo	21	21 (100.0)	2.0 (1.0)	1	2.0	5
	OL Week 12	Pre: CR845	14	14 (100.0)	1.2 (0.4)	1	1.0	2
		Pre: Placebo	21	21 (100.0)	1.7 (0.8)	1	2.0	3
	OL Week 24	Pre: CR845	14	14 (100.0)	1.2 (0.4)	1	1.0	2
		Pre: Placebo	21	21 (100.0)	1.9 (1.1)	1	2.0	5
	OL Week 36	Pre: CR845	14	14 (100.0)	1.1 (0.5)	1	1.0	3
		Pre: Placebo	21	21 (100.0)	2.1 (1.2)	1	2.0	5
	OL Week 52	Pre: CR845	14	2 (14.3)	1.0 (0.0)	1	1.0	1
		Pre: Placebo	21	3 (14.3)	2.0 (0.0)	2	2.0	2
Change from OL-baseline in 5-D distribution score	OL Week 4	Pre: CR845	14	14 (100.0)	-0.1 (0.4)	-1	0.0	0
		Pre: Placebo	21	21 (100.0)	-0.4 (1.0)	-3	0.0	1
	OL Week 8	Pre: CR845	14	14 (100.0)	-0.1(0.4)	-1	0.0	0
		Pre: Placebo	21	21 (100.0)	-0.5 (0.8)	-3	0.0	0
	OL Week 12	Pre: CR845	14	14 (100.0)	-0.2 (0.6)	-2	0.0	0
		Pre: Placebo	21	21 (100.0)	-0.8(0.8)	-2	-1.0	0
	OL Week 24	Pre: CR845	14	14 (100.0)	-0.2(0.9)	-3	0.0	1
		Pre: Placebo	21	21 (100.0)	-0.6 (1.2)	-4	0.0	1
	OL Week 36	Pre: CR845	14	14 (100.0)	-0.3 (0.9)	-3	0.0	1
		Pre: Placebo	21	21 (100.0)	-0.4 (1.2)	-3	0.0	1
	OL Week 52	Pre: CR845	14	2 (14.3)	0.0 (0.0)	0	0.0	0
		Pre: Placebo	21	3 (14.3)	0.3 (1.2)	-1	1.0	1

Note: SAF-C = Week 52 Study Completer Set.

Table DT3DVO_CMD0:	Change fr	om OL-baseline	in	5-D	distribution	score	-	LSMEANS	confidence	intervals
				SAI	F-C					

5	L-baseline in 5-D			±	sures analysis
listribution Fime	Treatment	N	n (%)	LS-Mean (SE)	om Baseline 95% CI
	Data (DO 45	4.4	14 (100 0)		
DL Week 4	Pre: CR845	14	14 (100.0)	-0.1(0.1)	(-0.4, 0.1)
	Pre: Placebo	21	21 (100.0)	-0.4 (0.2)	(-0.8, -0.1)
DL Week 8	Pre: CR845	14	14 (100.0)	-0.1 (0.1)	(-0.4, 0.1)
	Pre: Placebo	21	21 (100.0)	-0.5 (0.2)	(-0.8, -0.1)
DL Week 12	Pre: CR845	14	14 (100.0)	-0.2 (0.1)	(-0.5, 0.1)
	Pre: Placebo	21	21 (100.0)	-0.8 (0.2)	(-1.1, -0.4)
DL Week 24	Pre: CR845	14	14 (100.0)	-0.2 (0.1)	(-0.5, 0.1)
	Pre: Placebo	21	21 (100.0)	-0.6 (0.2)	(-0.9, -0.2)
DL Week 36	Pre: CR845	14	14 (100.0)	-0.3 (0.1)	(-0.6, -0.0)
	Pre: Placebo	21	21 (100.0)	-0.4 (0.2)	(-0.7, -0.0)

Note: SAF-C = Week 52 Study Completer Set.

N = total number of patients in analysis set. n = number of non-missing values. MMRM = mixed repeated measures model.

LS-Mean = Least square mean. SE = Standard error. 95% CI = 95% confidence interval.

For each treatment, a separate MMRM was applied with fixed factor time and baseline as covariate.

Due to the low number of patients with values at OL-Week 52, data from this time point were omitted from the analysis to enable convergence of the MMRM. In addition, a first order autoregressive instead of an unstructured covariance structure was established. Source Data: afived, created on: 07MAR2022

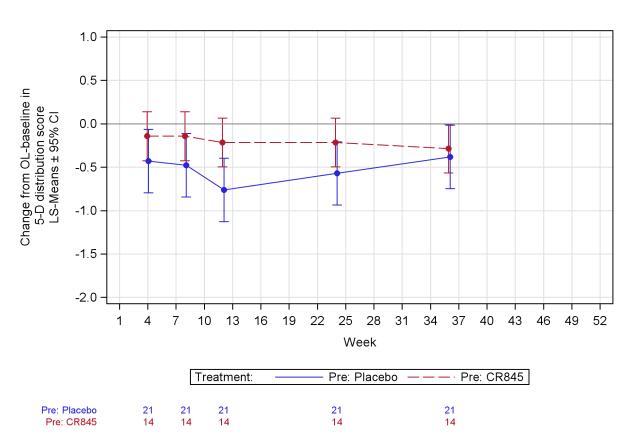


Figure DF3DVO_CMG0: Change from OL-baseline in 5-D distribution score - Course of LSMEANS SAF-C

Note: SAF-C = Week 52 Study Completer Set.

Symbols present least square mean (LS-Mean), bars present 95% confidence intervals (CI). CR845 = Difelikefalin.

OL - baseline = Baseline of open label period. No display of Week 52 due to the low patient numbers.

Source Table: DT3DVO CMD0

	Pre: CR845		Pre: Placebo		
TEAEs during OLP	N	n (%) [95 % CI]	N	n (%) [95 % CI]	
SOC: Cardiac disorders	189	7 (3.7) [1.5, 7.5]	210	11 (5.2) [2.6, 9.2]	
SOC: Gastrointestinal disorders	189	26 (13.8) [9.2, 19.5]	210	34 (16.2) [11.5, 21.9]	
Diarrhoea	189	[9.2, 19.3] 8 (4.2) [1.8, 8.2]	210	[11.3, 21.9] 11 (5.2) [2.6, 9.2]	
SOC: General disorders and administration site conditions	189	18 (9.5) [5.7, 14.6]	210	17 (8.1) [4.8, 12.6]	
SOC: Infections and infestations	189	27 (14.3) [9.6, 20.1]	210	38 (18.1) [13.1, 24.0]	
SOC: Injury, poisoning and procedural complications	189	34 (18.0) [12.8, 24.2]	210	35 (16.7) [11.9, 22.4]	
Fall	189	11 (5.8) [2.9, 10.2]	210	11 (5.2) [2.6, 9.2]	
SOC: Metabolism and nutrition disorders	189	17 (9.0) [5.3, 14.0]	210	14 (6.7) [3.7, 10.9]	
SOC: Musculoskeletal and connective tissue disorders	189	19 (10.1) [6.2, 15.3]	210	19 (9.0) [5.5, 13.8]	
SOC: Nervous system disorders	189	8 (4.2) [1.8, 8.2]	210	24 (11.4) [7.5, 16.5]	
SOC: Psychiatric disorders	189	11 (5.8) [2.9, 10.2]	210	12 (5.7) [3.0, 9.8]	
SOC: Respiratory, thoracic and mediastinal disorders	189	13 (6.9) [3.7, 11.5]	210	13 (6.2) [3.3, 10.4]	
SOC: Skin and subcutaneous tissue disorders	189	10 (5.3) [2.6, 9.5]	210	10 (4.8) [2.3, 8.6]	

Table DT3LA_LMS1: TEAEs during first quarter of OLP by SOC and PT SAF-L

Note: SAF-L = Week 52 Safety set. Only events are displayed with an incidence of at least 10 percent in a treatment group or 10 patients with an incidence of at least 1 percent in a treatment group.

N = total number of patients in analysis set. n = number of patients with events during OLP. OLP = open label period.

95% CI = 95% confidence interval according to Clopper Pearson. TEAE = treatment emergent adverse event. SOC = system organ class. PT = preferred term.

Source Data: aae, created on: 03MAR2022

Table DT3LA_LMS1: TEAEs during first quarter of OLP by SOC and PT $$\rm SAF-L$$

	I	Pre: CR845	Pı	re: Placebo
		n (%)		n (%)
TEAEs during OLP	N	[95 % CI]	N	[95 % CI]
SOC: Vascular disorders	189	15 (7.9)	210	21 (10.0)
		[4.5, 12.8]		[6.3, 14.9]

Note: SAF-L = Week 52 Safety set. Only events are displayed with an incidence of at least 10 percent in a treatment group or 10 patients with an incidence of at least 1 percent in a treatment group.

N = total number of patients in analysis set. n = number of patients with events during OLP. OLP = open label period.

95% CI = 95% confidence interval according to Clopper Pearson. TEAE = treatment emergent adverse event. SOC = system organ class. PT = preferred term.

Source Data: aae, created on: 03MAR2022

		Pre: CR845	Pre: Placebo		
TEAEs during OLP	N	n (%) [95 % CI]	N	n (%) [95 % CI]	
SOC: Cardiac disorders	189	12 (6.3) [3.3, 10.8]	210	16 (7.6) [4.4, 12.1]	
SOC: Gastrointestinal disorders	189	39 (20.6) [15.1, 27.1]	210	51 (24.3) [18.6, 30.7]	
Abdominal pain	189	10 (5.3) [2.6, 9.5]	210	5 (2.4) [0.8, 5.5]	
Diarrhoea	189	10 (5.3) [2.6, 9.5]	210	15 (7.1) [4.1, 11.5]	
SOC: General disorders and administration site conditions	189	23 (12.2) [7.9, 17.7]	210	28 (13.3) [9.0, 18.7]	
SOC: Infections and infestations	189	50 (26.5) [20.3, 33.3]	210	66 (31.4) [25.2, 38.2]	
Bronchitis	189	6 (3.2) [1.2, 6.8]	210	12 (5.7) [3.0, 9.8]	
Pneumonia	189	13 (6.9) [3.7, 11.5]	210	13 (6.2) [3.3, 10.4]	
SOC: Injury, poisoning and procedural complications	189	48 (25.4) [19.4, 32.2]	210	49 (23.3) [17.8, 29.6]	
Fall	189	17 (9.0) [5.3, 14.0]	210	16 (7.6) [4.4, 12.1]	
SOC: Investigations	189	7 (3.7) [1.5, 7.5]	210	12 (5.7) [3.0, 9.8]	
SOC: Metabolism and nutrition disorders	189	30 (15.9) [11.0, 21.9]	210	24 (11.4) [7.5, 16.5]	
Hyperkalaemia	189	10 (5.3) [2.6, 9.5]	210	[7.3, 10.3] 7 (3.3) [1.4, 6.7]	
SOC: Musculoskeletal and connective	189	25 (13.2)	210	29 (13.8)	

Table DT3LA_LMSO: TEAEs during OLP by SOC and PT $_{\rm SAF-L}$

Note: SAF-L = Week 52 Safety set. Only events are displayed with an incidence of at least 10 percent in a treatment group or 10 patients with an incidence of at least 1 percent in a treatment group.

[8.7, 18.9] [9.4, 19.2]

N = total number of patients in analysis set. n = number of patients with events during OLP. OLP = open label period.

tissue disorders

- 95% CI = 95% confidence interval according to Clopper Pearson. TEAE = treatment emergent adverse event. SOC = system organ class. PT = preferred term.
- Source Data: aae, created on: 03MAR2022

Table	dt3la_	_LMSO:	TEAEs	during	OLP	by	SOC	and	PT	
			SA	F-L						

	I	Pre: CR845	Pre: Placebo		
TEAEs during OLP	N	n (%) [95 % CI]	N	n (%) [95 % CI]	
SOC: Nervous system disorders	189	16 (8.5) [4.9. 13.4]		36 (17.1) [12.3, 22.9]	
Dizziness	189	4 (2.1)	210		
SOC: Psychiatric disorders	189	14 (7.4) [4.1, 12.1]			
SOC: Renal and urinary disorders	189	2 (1.1) [0.1, 3.8]		. ,	
SOC: Respiratory, thoracic and mediastinal disorders	189	25 (13.2) [8.7, 18.9]		. ,	
SOC: Skin and subcutaneous tissue disorders	189	15 (7.9) [4.5, 12.8]			
SOC: Vascular disorders	189	26 (13.8) [9.2, 19.5]			
Hypotension	189	10 (5.3) [2.6, 9.5]		12 (5.7) [3.0, 9.8]	

Note: SAF-L = Week 52 Safety set. Only events are displayed with an incidence of at least 10 percent in a treatment group or 10 patients with an incidence of at least 1 percent in a treatment group.

N = total number of patients in analysis set. n = number of patients with events during OLP. OLP = open label period.

95% CI = 95% confidence interval according to Clopper Pearson. TEAE = treatment emergent adverse event. SOC = system organ class. PT = preferred term.

Source Data: aae, created on: 03MAR2022

		Pre: CR845	Pre: Placebo		
TEAEs during OLP	N	n (%) [95 % CI]	N	n (%) [95 % CI]	
SOC: Cardiac disorders	14	0 (0.0) [0.0, 23.2]	21	4 (19.0) [5.4, 41.9]	
SOC: Gastrointestinal disorders	14	2 (14.3) [1.8, 42.8]	21	8 (38.1) [18.1, 61.6]	
Diarrhoea	14	1 (7.1) [0.2, 33.9]	21	3 (14.3) [3.0, 36.3]	
Nausea	14	0 (0.0) [0.0, 23.2]	21	3 (14.3) [3.0, 36.3]	
SOC: General disorders and administration site conditions	14	1 (7.1) [0.2, 33.9]	21	6 (28.6) [11.3, 52.2]	
SOC: Infections and infestations	14	6 (42.9) [17.7, 71.1]	21	11 (52.4) [29.8, 74.3]	
Bronchitis	14	2 (14.3) [1.8, 42.8]	21	3 (14.3) [3.0, 36.3]	
Nasopharyngitis	14	0 (0.0) [0.0, 23.2]	21	3 (14.3) [3.0, 36.3]	
Pneumonia	14	2 (14.3) [1.8, 42.8]	21	4 (19.0) [5.4, 41.9]	
SOC: Injury, poisoning and procedural complications	14	4 (28.6) [8.4, 58.1]	21	10 (47.6) [25.7, 70.2]	
Arteriovenous fistula thrombosis	14	0 (0.0)	21	4 (19.0) [5.4, 41.9]	
Fall	14	1 (7.1) [0.2, 33.9]	21	4 (19.0) [5.4, 41.9]	
Head injury	14	2 (14.3) [1.8, 42.8]	21	0 (0.0) [0.0, 16.1]	
SOC: Metabolism and nutrition disorders	14	6 (42.9) [17.7, 71.1]	21	7 (33.3) [14.6, 57.0]	
Fluid overload	14	2 (14.3)	21	3 (14.3)	

Table DT3LA_CMSO: TEAEs during OLP by SOC and PT $${\rm SAF-C}$$

Note: SAF-C = Week 52 Study Completer Set. Only events are displayed with an incidence of at least 10 percent in a treatment group or 10 patients with an incidence of at least 1 percent in a treatment group.

[1.8, 42.8] [3.0, 36.3]

N = total number of patients in analysis set. n = number of patients with events during OLP. OLP = open label period.

- 95% CI = 95% confidence interval according to Clopper Pearson. TEAE = treatment emergent adverse event. SOC = system organ class. PT = preferred term.
- Source Data: aae, created on: 03MAR2022

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		Pre: CR845	Pre: Placebo		
TEAEs during OLP	N	n (%) [95 % CI]	N	n (%) [95 % CI]	
Hyperkalaemia	14	2 (14.3) [1.8, 42.8]		3 (14.3) [3.0, 36.3]	
SOC: Musculoskeletal and connective tissue disorders	14	1 (7.1) [0.2, 33.9]		4 (19.0) [5.4, 41.9]	
SOC: Nervous system disorders	14	3 (21.4) [4.7, 50.8]		3 (14.3) [3.0, 36.3]	
SOC: Respiratory, thoracic and mediastinal disorders	14	3 (21.4) [4.7, 50.8]		4 (19.0) [5.4, 41.9]	
SOC: Vascular disorders	14	3 (21.4) [4.7.50.8]		6 (28.6) [11.3, 52.2]	
Hypotension	14	1 (7.1) [0.2, 33.9]	21	4 (19.0) [5.4, 41.9]	

Table DT3LA_CMSO: TEAEs during OLP by SOC and PT $${\rm SAF-C}$$

Note: SAF-C = Week 52 Study Completer Set. Only events are displayed with an incidence of at least 10 percent in a treatment group or 10 patients with an incidence of at least 1 percent in a treatment group.

N = total number of patients in analysis set. n = number of patients with events during OLP. OLP = open label period.

95% CI = 95% confidence interval according to Clopper Pearson. TEAE = treatment emergent adverse event. SOC = system organ class. PT = preferred term.

Source Data: aae, created on: 03MAR2022

Table DT3LAEGN_LMI1: AESI gait disturbance - non-severe during first quarter of OLP SAF-L

	Pre: CR845		Pre: Placebo	
	N	n (%) [95 % CI]	N	n (%) [95 % CI]
AESI gait disturbance - non-severe during OLP	189	0 (0.0)	210	0 (0.0)

Table DT3LAEFN_LMI1: AESI falls/injuries - non-severe during first quarter of OLP SAF-L

	1	Pre: CR845	Pre: Placebo		
		n (%)		n (%)	
	N	[95 % CI]	N	[95 % CI]	
AESI falls/injuries - non-severe during OLP	189	15 (7.9) [4.5, 12.8]	210	12 (5.7) [3.0, 9.8]	

Table DT3LAEVN_LMI1: AESI dizziness - non-severe during first quarter of OLP SAF-L

	F	Pre: CR845		e: Placebo
	N	n (%) [95 % CI]	N	n (%) [95 % CI]
AESI dizziness - non-severe during OLP	189	4 (2.1) [0.6, 5.3]	210	7 (3.3)

Table DT3LAEYN_LMI1: AESI syncope - non-severe during first quarter of OLP SAF-L

	I	Pre: CR845		e: Placebo
	N	n (%) [95 % CI]	N	n (%) [95 % CI]
AESI syncope - non-severe during OLP	189	0 (0.0)	210	4 (1.9) [0.5, 4.8]

Table DT3LAEON_LMI1: AESI somnolence - non-severe during first quarter of OLP SAF-L

	Pre: CR845		Pre: Placebo	
_	N	n (%) [95 % CI]	N	n (%) [95 % CI]
AESI somnolence - non-severe during OLP	189	1 (0.5) [0.0, 2.9]	210	1 (0.5) [0.0, 2.6]

Table DT3LAEKN_LMI1: AESI seizures - non-severe during first quarter of OLP SAF-L

	Pre: CR845		Pre: Placebo	
	N	n (%) [95 % CI]	N	n (%) [95 % CI]
AESI seizures - non-severe during OLP	189	0 (0.0) [0.0, 1.9]	210	1 (0.5) [0.0, 2.6]

Table DT3LAEMN_LMI1: AESI mental status change - non-severe during first quarter of OLP SAF-L

	Pre: CR845		Pre: Placebo	
		n (%)	-	n (%)
	N	[95 % CI]	N	[95 % CI]
AESI mental status change - non-severe during OLP	189	2 (1.1) [0.1, 3.8]	210	7 (3.3) [1.4, 6.7]

Table DT3LAEEN_LMI1: AESI mood change - non-severe during first quarter of OLP SAF-L

	Pre: CR845		Pre: Placebo	
	N	n (%) [95 % CI]	N	n (%) [95 % CI]
AESI mood change - non-severe	189	3 (1.6)	210	1 (0.5)
during OLP		[0.3, 4.6]		[0.0, 2.6]

Table DT3LAEUN_LMI1: AESI unusual feeling/sensation - non-severe during first quarter of OLP SAF-L

	Pre: CR845		Pre: Placebo	
	N	n (%) [95 % CI]	N	n (%) [95 % CI]
	1	[95 % C1]	IN	[95 % CI]
AESI unusual feeling/sensation - non-severe during OLP	189	7 (3.7) [1.5, 7.5]	210	4 (1.9) [0.5, 4.8]

Table DT3LAERN_LMI1: AESI tachycardia/palpitation - non-severe during first quarter of OLP SAF-L

	Pre: CR845		Pre: Placebo	
	N	n (%) [95 % CI]	N	n (%) [95 % CI]
AESI tachycardia/palpitation - non-severe during OLP	189	2 (1.1) [0.1, 3.8]	210	1 (0.5) [0.0, 2.6]

Table DT3LAEGN_LMIO: AESI gait disturbance - non-severe during OLP SAF-L

	Pre: CR845		Pre: Placebo	
	N	n (%) [95 % CI]	N	n (%) [95 % CI]
AESI gait disturbance - non-severe during OLP	189	0 (0.0)	210	1 (0.5) [0.0, 2.6]

Table DT3LAEFN_LMIO: AESI falls/injuries - non-severe during OLP SAF-L

	Pre: CR845		Pre: Placebo	
	N	n (%)	N	n (%)
	N	[95 % CI]	N	[95 % CI]
AESI falls/injuries - non-severe during OLP	189	22 (11.6) [7.4, 17.1]	210	18 (8.6) [5.2, 13.2]

Table DT3LAEVN_LMIO: AESI dizziness - non-severe during OLP SAF-L

	Pre: CR845		Pre: Placebo	
	N	n (%) [95 % CI]	N	n (%) [95 % CI]
AESI dizziness - non-severe during OLP	189	6 (3.2) [1.2, 6.8]	210	10 (4.8) [2.3, 8.6]

Table DT3LAEYN_LMIO: AESI syncope - non-severe during OLP SAF-L

	Pre: CR845		Pre: Placebo	
	N	n (%) [95 % CI]	N	n (%) [95 % CI]
AESI syncope - non-severe during OLP	189	2(1.1) [0.1, 3.8]	210	4 (1.9) [0.5, 4.8]

Table DT3LAEON_LMIO: AESI somnolence - non-severe during OLP SAF-L

	Pre: CR845		Pre: Placebo	
	N	n (%) [95 % CI]	N	n (%) [95 % CI]
AESI somnolence - non-severe during OLP	189	1 (0.5) [0.0, 2.9]	210	1 (0.5) [0.0, 2.6]

Table DT3LAEKN_LMIO: AESI seizures - non-severe during OLP SAF-L

	Pre: CR845		Pre: Placebo		_
	N	n (%) [95 % CI]	N	n (%) [95 % CI]	-
AESI seizures - non-severe during OLP	189	0 (0.0) [0.0, 1.9]	210	2 (1.0) [0.1, 3.4]	-

Table DT3LAEMN_LMIO: AESI mental status change - non-severe during OLP SAF-L

	Pre: CR845		Pr	e: Placebo
		n (%)		n (%)
	N	[95 % CI]	N	[95 % CI]
AESI mental status change - non-severe during OLP	189	2 (1.1) [0.1, 3.8]	210	10 (4.8) [2.3, 8.6]

Table DT3LAEEN_LMIO: AESI mood change - non-severe during OLP SAF-L

	F	re: CR845	Pr	ce: Placebo
	N	n (%) [95 % CI]	N	n (%) [95 % CI]
AESI mood change - non-severe	189	3 (1.6)	210	3 (1.4)
during OLP		[0.3, 4.6]		[0.3, 4.1]

Table DT3LAEUN_LMIO: AESI unusual feeling/sensation - non-severe during OLP SAF-L

	Pre: CR845		Pr	Pre: Placebo	
	N	n (%) [95 % CI]	N	n (%) [95 % CI]	
AESI unusual feeling/sensation - non-severe during OLP	189	7 (3.7) [1.5, 7.5]	210	7 (3.3) [1.4, 6.7]	

Table DT3LAERN_LMIO: AESI tachycardia/palpitation - non-severe during OLP SAF-L

	Pre: CR845		Pr	Pre: Placebo	
	N	n (%) [95 % CI]	N	n (%) [95 % CI]	
AESI tachycardia/palpitation - non-severe during OLP	189	2 (1.1) [0.1, 3.8]	210	2 (1.0) [0.1, 3.4]	

Table DT3LAEGN_CMIO: AESI gait disturbance - non-severe during OLP SAF-C

(%)	n (%)
% CI] N	[95 % CI]
. ,	0 (0.0)
	(0.0) 21

Table DT3LAEFN_CMIO: AESI falls/injuries - non-severe during OLP SAF-C

		Pre: CR845	P	re: Placebo
	N	n (%) [95 % CI]	N	n (%) [95 % CI]
	IN	[93 % C1]	IN	[93 % CI]
AESI falls/injuries - non-severe during OLP	14	2 (14.3) [1.8, 42.8]	21	4 (19.0) [5.4, 41.9]

Table DT3LAEVN_CMIO: AESI dizziness - non-severe during OLP SAF-C

		Pre: CR845	P	re: Placebo
	N	n (%) [95 % CI]	N	n (%) [95 % CI]
AESI dizziness - non-severe during OLP	14	1 (7.1) [0.2, 33.9]	21	1 (4.8) [0.1, 23.8]

Table DT3LAEYN_CMIO: AESI syncope - non-severe during OLP SAF-C

		Pre: CR845	P	re: Placebo	_
	N	n (%) [95 % CI]	N	n (%) [95 % CI]	
AESI syncope - non-severe during OLP	14	1 (7.1) [0.2, 33.9]	21	0 (0.0) [0.0, 16.1]	•

Table DT3LAEON_CMIO: AESI somnolence - non-severe during OLP SAF-C

	j	Pre: CR845	P	re: Placebo	_
	N	n (%) [95 % CI]	N	n (%) [95 % CI]	
AESI somnolence - non-severe during OLP	14	0 (0.0) [0.0, 23.2]	21	0 (0.0) [0.0, 16.1]	•

Table DT3LAEKN_CMIO: AESI seizures - non-severe during OLP SAF-C

		Pre: CR845	P	re: Placebo	_
	N	n (%) [95 % CI]	N	n (%) [95 % CI]	-
AESI seizures - non-severe during OLP	14	0 (0.0)	21	1 (4.8) [0.1, 23.8]	-

Table DT3LAEMN_CMIO: AESI mental status change - non-severe during OLP SAF-C

	1	Pre: CR845	P	re: Placebo
	NT	n (%)	NT	n (%)
	N	[95 % CI]	N	[95 % CI]
AESI mental status change - non-severe during OLP	14	0 (0.0) [0.0, 23.2]	21	1 (4.8) [0.1, 23.8]

Table DT3LAEEN_CMIO: AESI mood change - non-severe during OLP SAF-C

	1	Pre: CR845	P	re: Placebo	_
	N	n (%) [95 % CI]	N	n (%) [95 % CI]	-
	11	[95 % CI]	IN	[95 % CI]	-
AESI mood change - non-severe during OLP	14	0 (0.0) [0.0, 23.2]	21	0 (0.0) [0.0, 16.1]	

Table DT3LAEUN_CMIO: AESI unusual feeling/sensation - non-severe during OLP SAF-C

]	Pre: CR845		Pre: Placebo	
		n (%)		n (%)	
	N	[95 % CI]	N	[95 % CI]	
AESI unusual feeling/sensation - non-severe during OLP	14	1 (7.1) [0.2, 33.9]	21	3 (14.3) [3.0, 36.3]	

Table DT3LAERN_CMIO: AESI tachycardia/palpitation - non-severe during OLP SAF-C

	Pre: CR845		Pre: Placebo	
	N	n (%) [95 % CI]	N	n (%) [95 % CI]
AESI tachycardia/palpitation - non-severe during OLP	14	0 (0.0) [0.0, 23.2]	21	1 (4.8) [0.1, 23.8]

Anhang 4-I-3: Zusatzauswertungen der gepoolten Analyse

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Table PT3DDO_LMHO: Change from OL-baseline in 5-D degree score SAF-L

		Treatment	Ν	n (%)	Mean (SD)	Min	Q50	Max
		Pre: CR845	240	240 (100 0)		1	2.0	F
5-D degree score	OL Baseline	Pre: CR845 Pre: Placebo	340 372	340 (100.0) 372 (100.0)	2.6 (0.8) 2.8 (0.9)	1 1	2.0 3.0	5 5
	OL Week 4	Pre: CR845	340			1	2.0	5
	OL Week 4	Pre: CR045 Pre: Placebo	340 372	319 (93.8) 352 (94.6)	2.4 (0.8) 2.4 (0.8)	1	2.0	5
	OL Week 8	Pre: CR845	340	281 (82.6)	2.3 (0.8)	1	2.0	5
	OL WEEK O	Pre: Placebo	340	312 (83.9)	2.3 (0.8)	1	2.0	5
	OL Week 12	Pre: CR845	340	271 (79.7)	2.3 (0.9)	1	2.0	5
	OL WEEK 12	Pre: CR045 Pre: Placebo	340 372	300 (80.6)	2.3 (0.9)	1	2.0	5
	OL Week 24	Pre: CR845		, ,	2.2 (0.8)	1	2.0	
	OL Week 24		340	197 (57.9)	()			5 5
	OT Usels 20	Pre: Placebo	372	206 (55.4)	2.3 (0.9)	1	2.0 2.0	
	OL Week 36	Pre: CR845	340	144 (42.4)	2.2 (0.8)	1 1	2.0	5 5
		Pre: Placebo	372	153 (41.1)	2.3 (0.8)			
	OL Week 52	Pre: CR845	340	94 (27.6)	2.1 (0.9)	1	2.0	4
		Pre: Placebo	372	97 (26.1)	2.3 (0.9)	1	2.0	5
Change from OL-baseline in 5-D degree score	OL Week 4	Pre: CR845	340	319 (93.8)	-0.1 (0.8)	-3	0.0	2
		Pre: Placebo	372	352 (94.6)	-0.4(0.9)	-4	0.0	2
	OL Week 8	Pre: CR845	340	281 (82.6)	-0.2 (0.8)	-3	0.0	3
		Pre: Placebo	372	312 (83.9)	-0.5(0.9)	-4	0.0	3
	OL Week 12	Pre: CR845	340	271 (79.7)	-0.2 (0.9)	-3	0.0	2
		Pre: Placebo	372	300 (80.6)	-0.5 (1.0)	-4	-1.0	2
	OL Week 24	Pre: CR845	340	197 (57.9)	-0.3 (0.9)	-4	0.0	2
		Pre: Placebo	372	206 (55.4)	-0.6 (1.1)	-4	-1.0	3
	OL Week 36	Pre: CR845	340	144 (42.4)	-0.3 (0.9)	-3	0.0	2
		Pre: Placebo	372	153 (41.1)	-0.6 (1.1)	-3	-1.0	3
	OL Week 52	Pre: CR845	340	94 (27.6)	-0.4(1.0)	-4	0.0	2
		Pre: Placebo	372	97 (26.1)	-0.6(1.1)	-3	-1.0	3
					()	-		-

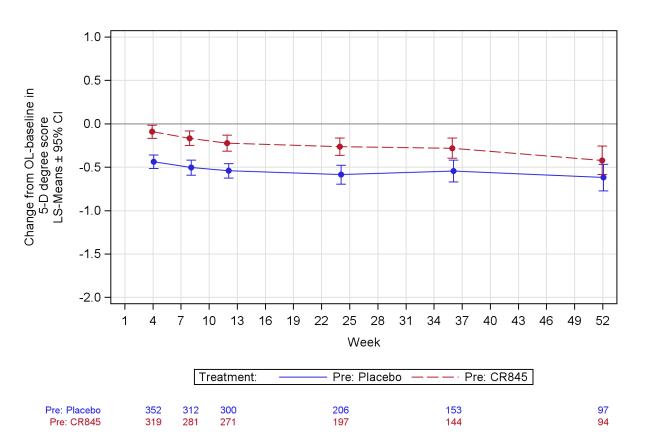
Note: SAF-L = Week 52 Safety set.

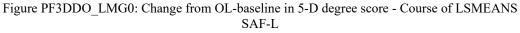
Table PT3DDO_LMD0:	Change from OL-basel	ine in 5-D degree	score - LSMEANS	confidence intervals
		SAF-L		

				Repeated mea	sures analysis
degree score	DL-baseline in 5-D			Change fr	om Baseline
Time	Treatment	Ν	n (%)	LS-Mean (SE)	95% CI
OL Week 4	Pre: CR845	340	319 (93.8)	-0.1 (0.0)	(-0.2, -0.0)
	Pre: Placebo	372	352 (94.6)	-0.4 (0.0)	(-0.5, -0.4)
OL Week 8	Pre: CR845	340	281 (82.6)	-0.2 (0.0)	(-0.2, -0.1)
	Pre: Placebo	372	312 (83.9)	-0.5 (0.0)	(-0.6, -0.4)
OL Week 12	Pre: CR845	340	271 (79.7)	-0.2 (0.0)	(-0.3, -0.1)
	Pre: Placebo	372	300 (80.6)	-0.5 (0.0)	(-0.6, -0.5)
OL Week 24	Pre: CR845	340	197 (57.9)	-0.3 (0.1)	(-0.4, -0.2)
	Pre: Placebo	372	206 (55.4)	-0.6 (0.1)	(-0.7, -0.5)
OL Week 36	Pre: CR845	340	144 (42.4)	-0.3 (0.1)	(-0.4, -0.2)
	Pre: Placebo	372	153 (41.1)	-0.5 (0.1)	(-0.7, -0.4)
OL Week 52	Pre: CR845	340	94 (27.6)	-0.4 (0.1)	(-0.6, -0.3)
	Pre: Placebo	372	97 (26.1)	-0.6 (0.1)	(-0.8, -0.5)

Note: SAF-L = Week 52 Safety set.

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Note: SAF-L = Week 52 Safety set.

Symbols present least square mean (LS-Mean), bars present 95% confidence intervals (CI).

CR845 = Difelikefalin, OL - baseline = Baseline of open label period.

Source Table: PT3DDO LMD0

Table	PT3DLO_LMHO:	Change	from	OL-baseline	in	5-D	duration	score	
			S	AF-L					

		Treatment	Ν	n (%)	Mean (SD)	Min	Q50	Max
5-D duration score	OL Baseline	Pre: CR845	340	340 (100.0)	1.8 (1.1)	1	1.0	5
o b daración booro	ol babolino	Pre: Placebo	372	372 (100.0)	2.1 (1.3)	1	2.0	5
	OL Week 4	Pre: CR845	340	316 (92.9)	1.6 (1.0)	1	1.0	5
		Pre: Placebo	372	352 (94.6)	1.7 (1.0)	1	1.0	5
	OL Week 8	Pre: CR845	340	281 (82.6)	1.5 (1.0)	1	1.0	5
		Pre: Placebo	372	312 (83.9)	1.5 (1.0)	1	1.0	5
	OL Week 12	Pre: CR845	340	271 (79.7)	1.5 (1.0)	1	1.0	5
		Pre: Placebo	372	300 (80.6)	1.6 (1.0)	1	1.0	5
	OL Week 24	Pre: CR845	340	195 (57.4)	1.5 (0.9)	1	1.0	5
		Pre: Placebo	372	206 (55.4)	1.6 (1.1)	1	1.0	5
	OL Week 36	Pre: CR845	340	144 (42.4)	1.3 (0.7)	1	1.0	5
		Pre: Placebo	372	154 (41.4)	1.6 (1.1)	1	1.0	5
	OL Week 52	Pre: CR845	340	94 (27.6)	1.3 (0.7)	1	1.0	5
		Pre: Placebo	372	97 (26.1)	1.5 (1.0)	1	1.0	5
Change from OL-baseline in 5-D duration score	OL Week 4	Pre: CR845	340	316 (92.9)	-0.1 (1.0)	-4	0.0	4
		Pre: Placebo	372	352 (94.6)	-0.4(1.3)	-4	0.0	4
	OL Week 8	Pre: CR845	340	281 (82.6)	-0.2 (1.0)	-4	0.0	4
		Pre: Placebo	372	312 (83.9)	-0.6 (1.3)	-4	0.0	4
	OL Week 12	Pre: CR845	340	271 (79.7)	-0.2 (1.0)	-4	0.0	4
		Pre: Placebo	372	300 (80.6)	-0.6 (1.2)	-4	0.0	4
	OL Week 24	Pre: CR845	340	195 (57.4)	-0.2 (1.0)	-4	0.0	4
		Pre: Placebo	372	206 (55.4)	-0.6 (1.2)	-4	0.0	2
	OL Week 36	Pre: CR845	340	144 (42.4)	-0.4 (0.9)	-4	0.0	2
		Pre: Placebo	372	154 (41.4)	-0.6 (1.4)	-4	0.0	3
	OL Week 52	Pre: CR845	340	94 (27.6)	-0.5 (1.0)	-4	0.0	3
		Pre: Placebo	372	97 (26.1)	-0.8(1.5)	-4	0.0	3

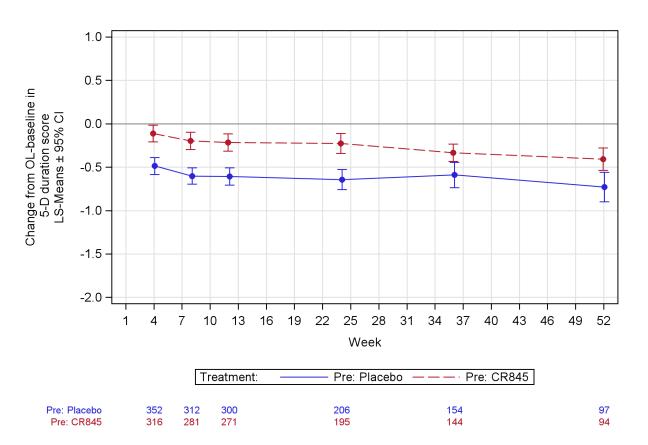
Note: SAF-L = Week 52 Safety set.

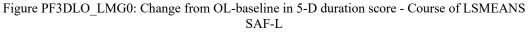
Table PT3DLO_LMD0:	Change	from	OL-baseline	in	5-D	duration	score	-	LSMEANS	confidence	intervals
				S	SAF-I	_					

Change from C duration scor	DL-baseline in 5-D			Change fr	om Baseline
Time	Treatment	N	n (%)	LS-Mean (SE)	95% CI
OL Week 4	Pre: CR845	340	316 (92.9)	-0.1 (0.0)	(-0.2, -0.0)
	Pre: Placebo	372	352 (94.6)	-0.5 (0.0)	(-0.6, -0.4)
OL Week 8	Pre: CR845	340	281 (82.6)	-0.2 (0.1)	(-0.3, -0.1)
	Pre: Placebo	372	312 (83.9)	-0.6 (0.0)	(-0.7, -0.5)
DL Week 12	Pre: CR845	340	271 (79.7)	-0.2 (0.1)	(-0.3, -0.1)
	Pre: Placebo	372	300 (80.6)	-0.6 (0.1)	(-0.7, -0.5)
DL Week 24	Pre: CR845	340	195 (57.4)	-0.2 (0.1)	(-0.3, -0.1)
	Pre: Placebo	372	206 (55.4)	-0.6 (0.1)	(-0.8, -0.5)
DL Week 36	Pre: CR845	340	144 (42.4)	-0.3 (0.0)	(-0.4, -0.2)
	Pre: Placebo	372	154 (41.4)	-0.6 (0.1)	(-0.7, -0.4)
DL Week 52	Pre: CR845	340	94 (27.6)	-0.4 (0.1)	(-0.5, -0.3)
	Pre: Placebo	372	97 (26.1)	-0.7(0.1)	(-0.9, -0.6)

Note: SAF-L = Week 52 Safety set.

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Note: SAF-L = Week 52 Safety set.

- Symbols present least square mean (LS-Mean), bars present 95% confidence intervals (CI).
- CR845 = Difelikefalin, OL baseline = Baseline of open label period.
- Source Table: PT3DLO LMD0

Source Data: afived_p, created on: 07MAR2022

Table PT3DWO_LMHO: Change from OL-baseline in 5-D direction score SAF-L

		Treatment	Ν	n (%)	Mean (SD)	Min	Q50	Max
5-D direction score	OL Baseline	Pre: CR845	340	340 (100.0)	2.6 (0.9)	1	2.0	5
5-D direction score	OL Baseline	Pre: CR045 Pre: Placebo	340 372	340 (100.0) 372 (100.0)	2.8 (0.9) 2.9 (1.0)	1	2.0	5
	OL Week 4	Pre: CR845	340	318 (93.5)	2.5 (0.9)	1	2.0	5
	OT WEEK 4	Pre: Placebo	372	352 (94.6)	2.3 (0.9) 2.4 (0.9)	1	2.0	5
	OL Week 8	Pre: CR845	340	280 (82.4)	2.4(0.9)	1	2.0	5
	01 10011 0	Pre: Placebo	372	312 (83.9)	2.4 (0.9)	1	2.0	5
	OL Week 12	Pre: CR845	340	272 (80.0)	2.4 (1.0)	1	2.0	5
		Pre: Placebo	372	300 (80.6)	2.4 (0.9)	1	2.0	5
	OL Week 24	Pre: CR845	340	197 (57.9)	2.4 (0.9)	1	2.0	5
		Pre: Placebo	372	206 (55.4)	2.4 (1.0)	1	2.0	5
	OL Week 36	Pre: CR845	340	144 (42.4)	2.3 (0.9)	1	2.0	5
		Pre: Placebo	372	153 (41.1)	2.3 (0.9)	1	2.0	5
	OL Week 52	Pre: CR845	340	94 (27.6)	2.0 (0.8)	1	2.0	4
		Pre: Placebo	372	97 (26.1)	2.3 (1.0)	1	2.0	5
Change from OL-baseline in 5-D direction score	OL Week 4	Pre: CR845	340	318 (93.5)	-0.1 (0.9)	-3	0.0	3
		Pre: Placebo	372	352 (94.6)	-0.6(1.1)	-4	0.0	2
	OL Week 8	Pre: CR845	340	280 (82.4)	-0.1 (1.1)	-3	0.0	4
		Pre: Placebo	372	312 (83.9)	-0.6 (1.1)	-4	-1.0	3
	OL Week 12	Pre: CR845	340	272 (80.0)	-0.1 (1.1)	-3	0.0	3
		Pre: Placebo	372	300 (80.6)	-0.6 (1.1)	-4	-1.0	3
	OL Week 24	Pre: CR845	340	197 (57.9)	-0.2 (1.0)	-3	0.0	3
		Pre: Placebo	372	206 (55.4)	-0.6 (1.1)	-3	0.0	4
	OL Week 36	Pre: CR845	340	144 (42.4)	-0.2 (1.0)	-3	0.0	2
		Pre: Placebo	372	153 (41.1)	-0.6 (1.0)	-3	-1.0	2
	OL Week 52	Pre: CR845	340	94 (27.6)	-0.4 (0.9)	-3	0.0	1
		Pre: Placebo	372	97 (26.1)	-0.7 (1.3)	-4	-1.0	3

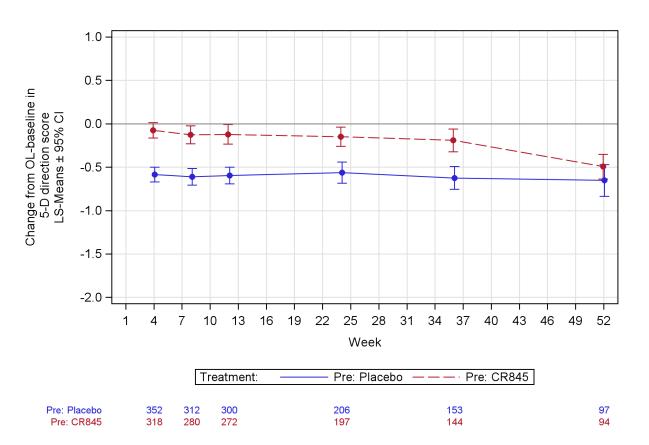
Note: SAF-L = Week 52 Safety set.

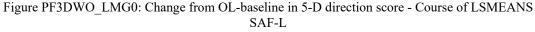
Table PT3DWO_LMD0: Change	from OL-baseline	e in 5-D direction	score - LSMEANS	confidence intervals
		SAF-L		

Channe Carro				Repeated mea	Repeated measures analysis				
direction sco	L-baseline in 5-D re	_		Change fr	om Baseline				
Time	Treatment	N	n (%)	LS-Mean (SE)	95% CI				
OL Week 4	Pre: CR845	340	318 (93.5)	-0.1 (0.0)	(-0.2, 0.0)				
	Pre: Placebo	372	352 (94.6)	-0.6 (0.0)	(-0.7, -0.5)				
OL Week 8	Pre: CR845	340	280 (82.4)	-0.1 (0.1)	(-0.2, -0.0)				
	Pre: Placebo	372	312 (83.9)	-0.6 (0.0)	(-0.7, -0.5)				
OL Week 12	Pre: CR845	340	272 (80.0)	-0.1 (0.1)	(-0.2, -0.0)				
	Pre: Placebo	372	300 (80.6)	-0.6 (0.0)	(-0.7, -0.5)				
OL Week 24	Pre: CR845	340	197 (57.9)	-0.1 (0.1)	(-0.3, -0.0)				
	Pre: Placebo	372	206 (55.4)	-0.6 (0.1)	(-0.7, -0.4)				
OL Week 36	Pre: CR845	340	144 (42.4)	-0.2 (0.1)	(-0.3, -0.1)				
	Pre: Placebo	372	153 (41.1)	-0.6 (0.1)	(-0.8, -0.5)				
OL Week 52	Pre: CR845	340	94 (27.6)	-0.5(0.1)	(-0.6, -0.4)				
	Pre: Placebo	372	97 (26.1)	-0.7 (0.1)					

Note: SAF-L = Week 52 Safety set.

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Note: SAF-L = Week 52 Safety set.

Symbols present least square mean (LS-Mean), bars present 95% confidence intervals (CI).

CR845 = Difelikefalin, OL - baseline = Baseline of open label period.

Source Table: PT3DWO LMD0

Table PT3DNO_LMHO: Change from OL-baseline in 5-D disability score SAF-L

		Treatment	N	n (%)	Mean (SD)	Min	Q50	Max
5-D disability score	OL Baseline	Pre: CR845	340	340 (100.0)	2.5 (1.2)	1	2.0	5
		Pre: Placebo	372	372 (100.0)	2.6 (1.2)	1	3.0	5
	OL Week 4	Pre: CR845	340	319 (93.8)	2.3 (1.2)	1	2.0	5
		Pre: Placebo	372	352 (94.6)	2.2 (1.1)	1	2.0	5
	OL Week 8	Pre: CR845	340	281 (82.6)	2.1 (1.2)	1	2.0	5
		Pre: Placebo	372	312 (83.9)	2.2 (1.1)	1	2.0	5
	OL Week 12	Pre: CR845	340	272 (80.0)	2.1 (1.2)	1	2.0	5
		Pre: Placebo	372	300 (80.6)	2.1 (1.1)	1	2.0	5
	OL Week 24	Pre: CR845	340	197 (57.9)	2.1 (1.1)	1	2.0	5
		Pre: Placebo	372	206 (55.4)	2.2 (1.2)	1	2.0	5
	OL Week 36	Pre: CR845	340	144 (42.4)	2.0 (1.1)	1	2.0	5
		Pre: Placebo	372	153 (41.1)	2.2 (1.2)	1	2.0	5
	OL Week 52	Pre: CR845	340	94 (27.6)	1.9 (1.1)	1	2.0	5
		Pre: Placebo	372	97 (26.1)	2.2 (1.2)	1	2.0	5
Change from OL-baseline in 5-D disability score	OL Week 4	Pre: CR845	340	319 (93.8)	-0.1 (1.1)	-4	0.0	4
		Pre: Placebo	372	352 (94.6)	-0.5(1.2)	-4	0.0	3
	OL Week 8	Pre: CR845	340	281 (82.6)	-0.2 (1.1)	-4	0.0	4
		Pre: Placebo	372	312 (83.9)	-0.5 (1.2)	-4	0.0	4
	OL Week 12	Pre: CR845	340	272 (80.0)	-0.2 (1.1)	-4	0.0	4
		Pre: Placebo	372	300 (80.6)	-0.6 (1.2)	-4	-1.0	3
	OL Week 24	Pre: CR845	340	197 (57.9)	-0.3 (1.2)	-4	0.0	4
		Pre: Placebo	372	206 (55.4)	-0.5 (1.3)	-4	0.0	3
	OL Week 36	Pre: CR845	340	144 (42.4)	-0.4 (1.1)	-3	0.0	3
		Pre: Placebo	372	153 (41.1)	-0.6 (1.4)	-4	0.0	3
	OL Week 52	Pre: CR845	340	94 (27.6)	-0.5 (1.3)	-4	0.0	4
		Pre: Placebo	372	97 (26.1)	-0.7 (1.4)	-4	-1.0	4

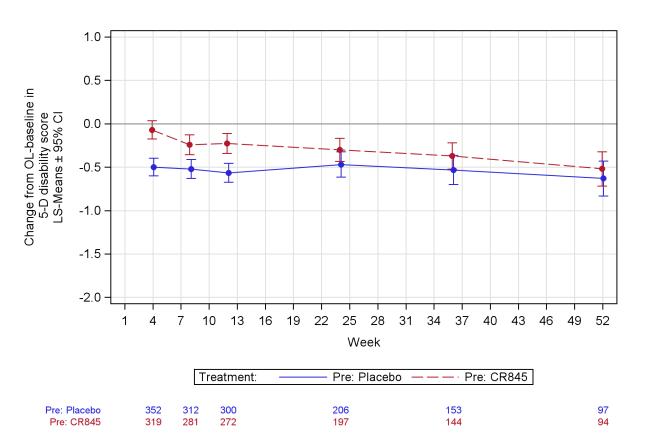
Note: SAF-L = Week 52 Safety set.

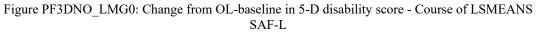
Table PT3DNO_LMD0:	Change	from OL-baseline	in	5-D	disability	score	- L	LSMEANS	confidence	intervals
				SAF	-L					

Change from O disability sc	L-baseline in 5-D ore			Change fr	om Baseline
Time	Treatment	N	n (%)	LS-Mean (SE)	95% CI
OL Week 4	Pre: CR845	340	319 (93.8)	-0.1(0.1)	(-0.2, 0.0)
	Pre: Placebo	372	352 (94.6)	. ,	. , ,
OL Week 8	Pre: CR845	340	281 (82.6)	-0.2 (0.1)	(-0.4, -0.1)
	Pre: Placebo	372	312 (83.9)	-0.5 (0.1)	(-0.6, -0.4)
OL Week 12	Pre: CR845	340	272 (80.0)	-0.2 (0.1)	(-0.3, -0.1)
	Pre: Placebo	372	300 (80.6)	-0.6 (0.1)	(-0.7, -0.5)
OL Week 24	Pre: CR845	340	197 (57.9)	-0.3 (0.1)	(-0.4, -0.2)
	Pre: Placebo	372	206 (55.4)	-0.5 (0.1)	(-0.6, -0.3)
OL Week 36	Pre: CR845	340	144 (42.4)	-0.4 (0.1)	(-0.5, -0.2)
	Pre: Placebo	372	153 (41.1)	-0.5 (0.1)	(-0.7, -0.4)
OL Week 52	Pre: CR845	340	94 (27.6)	-0.5 (0.1)	(-0.7, -0.3)
	Pre: Placebo	372	97 (26.1)	-0.6 (0.1)	(-0.8, -0.4)

Note: SAF-L = Week 52 Safety set.

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Note: SAF-L = Week 52 Safety set.

Symbols present least square mean (LS-Mean), bars present 95% confidence intervals (CI).

CR845 = Difelikefalin, OL - baseline = Baseline of open label period.

Source Table: PT3DNO LMD0

Table	PT3DVO_	LMHO:	Change	from	OL-baseline	in	5-D	distribution	score	
					SAF-L					

		Treatment	Ν	n (%)	Mean (SD)	Min	Q50	Max
5-D distribution score	OL Baseline	Pre: CR845	340	340 (100.0)	2.5 (1.2)	1	2.0	5
5-D distribution score	OL DASEIINE	Pre: Placebo	340	372 (100.0)	2.3 (1.2) 2.8 (1.2)	1	2.0	5
	OL Week 4	Pre: CR845	340	319 (93.8)	2.3 (1.2)	1	2.0	5
	OL WEEK 4	Pre: Placebo	372	352 (94.6)	2.3(1.2) 2.4(1.2)	1	2.0	5
	OL Week 8	Pre: CR845	340	281 (82.6)	2.2(1.2)	1	2.0	5
		Pre: Placebo	372	312 (83.9)	2.4 (1.2)	1	2.0	5
	OL Week 12	Pre: CR845	340	272 (80.0)	2.3 (1.3)	1	2.0	5
		Pre: Placebo	372	300 (80.6)	2.4 (1.1)	1	2.0	5
	OL Week 24	Pre: CR845	340	197 (57.9)	2.2 (1.2)	1	2.0	5
		Pre: Placebo	372	206 (55.4)	2.3 (1.2)	1	2.0	5
	OL Week 36	Pre: CR845	340	146 (42.9)	2.1 (1.2)	1	2.0	5
		Pre: Placebo	372	154 (41.4)	2.3 (1.2)	1	2.0	5
	OL Week 52	Pre: CR845	340	94 (27.6)	2.1 (1.1)	1	2.0	5
		Pre: Placebo	372	97 (26.1)	2.2 (1.2)	1	2.0	5
Change from OL-baseline in 5-D distribution score	OL Week 4	Pre: CR845	340	319 (93.8)	-0.2 (0.9)	-4	0.0	2
		Pre: Placebo	372	352 (94.6)	-0.4 (1.0)	-4	0.0	3
	OL Week 8	Pre: CR845	340	281 (82.6)	-0.3 (0.9)	-4	0.0	2
		Pre: Placebo	372	312 (83.9)	-0.5 (1.1)	-4	0.0	4
	OL Week 12	Pre: CR845	340	272 (80.0)	-0.3 (1.0)	-4	0.0	3
		Pre: Placebo	372	300 (80.6)	-0.5 (1.0)	-4	-1.0	4
	OL Week 24	Pre: CR845	340	197 (57.9)	-0.4 (0.9)	-4	0.0	2
		Pre: Placebo	372	206 (55.4)	-0.7 (1.2)	-4	-1.0	4
	OL Week 36	Pre: CR845	340	146 (42.9)	-0.6 (1.0)	-3	0.0	3
		Pre: Placebo	372	154 (41.4)	-0.8 (1.3)	-4	-1.0	4
	OL Week 52	Pre: CR845	340	94 (27.6)	-0.7 (1.1)	-4	-1.0	3
		Pre: Placebo	372	97 (26.1)	-1.0 (1.3)	-4	-1.0	2

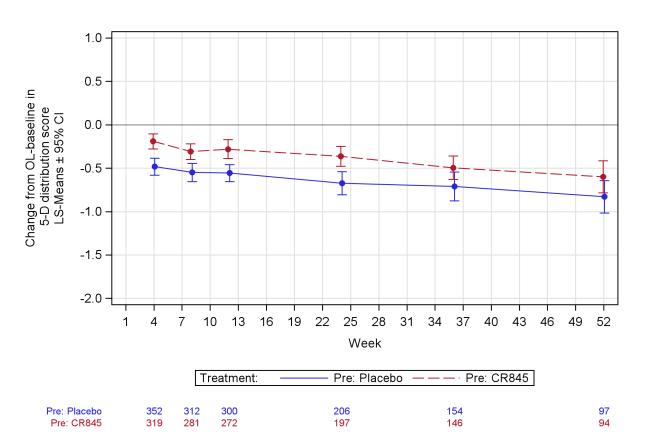
Note: SAF-L = Week 52 Safety set.

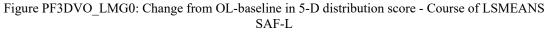
Table PT3DVO_LMD0:	Change f	Erom	OL-baseline	in	5-D	distribution	score	-	LSMEANS	confidence	intervals
					SAI	F-L					

~				Repeated mea	sures analysis		
Change from C distribution	DL-baseline in 5-D score			Change from Baseline			
Time	Treatment	Ν	n (%)	LS-Mean (SE)	95% CI		
OL Week 4	Pre: CR845	340	319 (93.8)	-0.2 (0.0)	(-0.3, -0.1)		
	Pre: Placebo	372	352 (94.6)	-0.5 (0.0)	(-0.6, -0.4)		
OL Week 8	Pre: CR845	340	281 (82.6)	-0.3 (0.0)	(-0.4, -0.2)		
	Pre: Placebo	372	312 (83.9)	-0.5 (0.1)	(-0.7, -0.4)		
OL Week 12	Pre: CR845	340	272 (80.0)	-0.3 (0.1)	(-0.4, -0.2)		
	Pre: Placebo	372	300 (80.6)	-0.6 (0.0)	(-0.7, -0.5)		
OL Week 24	Pre: CR845	340	197 (57.9)	-0.4 (0.1)	(-0.5, -0.2)		
	Pre: Placebo	372	206 (55.4)	-0.7 (0.1)	(-0.8, -0.5)		
OL Week 36	Pre: CR845	340	146 (42.9)	-0.5 (0.1)	(-0.6, -0.4)		
	Pre: Placebo	372	154 (41.4)	-0.7 (0.1)	(-0.9, -0.5)		
OL Week 52	Pre: CR845	340	94 (27.6)	-0.6 (0.1)	(-0.8, -0.4)		
	Pre: Placebo	372	97 (26.1)	-0.8 (0.1)	(-1.0, -0.6)		

Note: SAF-L = Week 52 Safety set.

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Note: SAF-L = Week 52 Safety set.

Symbols present least square mean (LS-Mean), bars present 95% confidence intervals (CI).

CR845 = Difelikefalin, OL - baseline = Baseline of open label period.

Source Table: PT3DVO LMD0

Table PT3DDO_CMHO: Change from OL-baseline in 5-D degree score SAF-C

		Treatment	Ν	n (%)	Mean (SD)	Min	Q50	Max
E D dograd gaara	OL Baseline	Pre: CR845	126	126 (100 0)	$2 \in (0, 0)$	1	2.0	F
5-D degree score	OL Baseline	Pre: CR845 Pre: Placebo	136 143	136 (100.0) 143 (100.0)	2.5 (0.9) 2.9 (0.9)	1	2.0 3.0	5 5
	OL Week 4	Pre: CR845	143	143 (100.0) 135 (99.3)	2.3 (0.8)	1	2.0	5
	OL Week 4	Pre: CR045 Pre: Placebo	143	133 (99.3)	2.5 (0.8)	1	2.0	5
	OL Week 8	Pre: CR845	143	133 (97.8)	2.2 (0.8)	1	2.0	5
	OL WEEK 0	Pre: Placebo	143	140 (97.9)	2.2 (0.8)	1	2.0	5
	OL Week 12	Pre: CR845	143	133 (97.8)	2.2 (0.8)	1	2.0	5
	OF MEEK IN	Pre: Placebo	143	137 (95.8)	2.2 (0.8)	1	2.0	4
	OL Week 24	Pre: CR845	136	137 (95.8)	, ,		2.0	
	OL week 24	Pre: CR845 Pre: Placebo	136	, ,	2.2 (0.8) 2.3 (0.9)	1 1	2.0	5 5
	OL Week 36	Pre: CR845	143	143 (100.0) 132 (97.1)	2.2 (0.8)	1	2.0	
	OL week 36	Pre: CR845 Pre: Placebo		· ,	· · ·	1	2.0	5
			143	141 (98.6)	2.3 (0.8)			5
	OL Week 52	Pre: CR845	136	94 (69.1)	2.1 (0.9)	1	2.0	4
		Pre: Placebo	143	97 (67.8)	2.3 (0.9)	1	2.0	5
Change from OL-baseline in 5-D degree score	OL Week 4	Pre: CR845	136	135 (99.3)	-0.2 (0.8)	-3	0.0	2
		Pre: Placebo	143	138 (96.5)	-0.4 (1.0)	-3	0.0	2
	OL Week 8	Pre: CR845	136	133 (97.8)	-0.2 (0.8)	-3	0.0	2
		Pre: Placebo	143	140 (97.9)	-0.5 (0.9)	-3	0.0	2
	OL Week 12	Pre: CR845	136	133 (97.8)	-0.3 (0.9)	-3	0.0	2
		Pre: Placebo	143	137 (95.8)	-0.6(1.0)	-3	-1.0	2
	OL Week 24	Pre: CR845	136	133 (97.8)	-0.3 (1.0)	-4	0.0	2
		Pre: Placebo	143	143 (100.0)	-0.6(1.1)	-3	-1.0	3
	OL Week 36	Pre: CR845	136	132 (97.1)	-0.3 (0.8)	-3	0.0	2
		Pre: Placebo	143	141 (98.6)	-0.6 (1.1)	-3	-1.0	3
	OL Week 52	Pre: CR845	136	94 (69.1)	-0.4(1.0)	-4	0.0	2
		Pre: Placebo	143	97 (67.8)	-0.6 (1.1)	-3	-1.0	3

Note: SAF-C = Week 52 Study Completer Set.

Table PT3DDO_CMD0:	Change from OL-baseline	e in 5-D degree	score - LSMEANS	confidence intervals
		SAF-C		

				Repeated mea	sures analysis
change from C degree score	DL-baseline in 5-D	_		Change fr	om Baseline
Time	Treatment	N	n (%)	LS-Mean (SE)	95% CI
OL Week 4	Pre: CR845	136	135 (99.3)	-0.2 (0.1)	(-0.3, -0.1)
	Pre: Placebo	143	138 (96.5)		(-0.5, -0.3)
OL Week 8	Pre: CR845	136	133 (97.8)	-0.2 (0.1)	(-0.3, -0.1)
	Pre: Placebo	143	140 (97.9)	-0.5 (0.1)	(-0.6, -0.4)
OL Week 12	Pre: CR845	136	133 (97.8)	-0.3 (0.1)	(-0.4, -0.1)
	Pre: Placebo	143	137 (95.8)	-0.6 (0.1)	(-0.7, -0.5)
OL Week 24	Pre: CR845	136	133 (97.8)	-0.3 (0.1)	(-0.4, -0.1)
	Pre: Placebo	143	143 (100.0)	-0.6 (0.1)	(-0.8, -0.5)
OL Week 36	Pre: CR845	136	132 (97.1)	-0.3 (0.1)	(-0.4, -0.2)
	Pre: Placebo	143	141 (98.6)	-0.6 (0.1)	(-0.7, -0.4)
OL Week 52	Pre: CR845	136	94 (69.1)	-0.4 (0.1)	(-0.6, -0.2)
	Pre: Placebo	143	97 (67.8)	-0.6 (0.1)	(-0.8, -0.5)

Note: SAF-C = Week 52 Study Completer Set.

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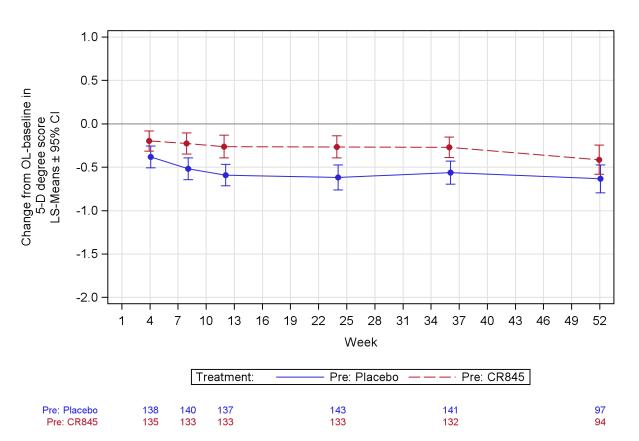


Figure PF3DDO_CMG0: Change from OL-baseline in 5-D degree score - Course of LSMEANS SAF-C

Note: SAF-C = Week 52 Study Completer Set.

Symbols present least square mean (LS-Mean), bars present 95% confidence intervals (CI).

CR845 = Difelikefalin, OL - baseline = Baseline of open label period.

Source Table: PT3DDO CMD0

Table	PT3DLO_	CMHO:	Change	from	OL-baseline	in	5-D	duration	score	
SAF-C										

		Treatment	N n (%)	Mean (SD)	Min	Q50	Max
5-D duration score	OL Baseline	Pre: CR845	136 136 (100	0.0) 1.7 (1.0)	1	1.0	5
o b daración booro	ol baborrino	Pre: Placebo	143 143 (100		1	2.0	5
	OL Week 4	Pre: CR845	136 135 (99	, , ,	1	1.0	5
		Pre: Placebo	143 138 (96		1	1.0	5
	OL Week 8	Pre: CR845	136 133 (97		1	1.0	5
		Pre: Placebo	143 140 (97	.9) 1.6 (1.0)	1	1.0	5
	OL Week 12	Pre: CR845	136 133 (97	.8) 1.4 (0.8)	1	1.0	5
		Pre: Placebo	143 137 (95	.8) 1.7 (1.1)	1	1.0	5
	OL Week 24	Pre: CR845	136 132 (97	.1) 1.4 (0.8)	1	1.0	5
		Pre: Placebo	143 143 (100	0.0) 1.6 (1.0)	1	1.0	5
	OL Week 36	Pre: CR845	136 133 (97	.8) 1.3 (0.7)	1	1.0	5
		Pre: Placebo	143 142 (99	.3) 1.6 (1.1)	1	1.0	5
	OL Week 52	Pre: CR845	136 94 (69.	1) 1.3 (0.7)	1	1.0	5
		Pre: Placebo	143 97 (67.	8) 1.5 (1.0)	1	1.0	5
Change from OL-baseline in 5-D duration score	OL Week 4	Pre: CR845	136 135 (99	.3) -0.2 (0.8)	-4	0.0	3
		Pre: Placebo	143 138 (96	.5) -0.4 (1.4)	-4	0.0	4
	OL Week 8	Pre: CR845	136 133 (97	.8) -0.3 (1.0)	-4	0.0	4
		Pre: Placebo	143 140 (97	.9) -0.6 (1.4)	-4	0.0	2
	OL Week 12	Pre: CR845	136 133 (97	.8) -0.3 (0.9)	-4	0.0	4
		Pre: Placebo	143 137 (95	.8) -0.5 (1.2)	-4	0.0	4
	OL Week 24	Pre: CR845	136 132 (97	.1) -0.3 (1.1)	-4	0.0	4
		Pre: Placebo	143 143 (100	0.0) -0.7 (1.3)	-4	0.0	2
	OL Week 36	Pre: CR845	136 133 (97	.8) -0.4 (0.9)	-4	0.0	2
		Pre: Placebo	143 142 (99	.3) -0.6 (1.4)	-4	0.0	3
	OL Week 52	Pre: CR845	136 94 (69.	1) -0.5 (1.0)	-4	0.0	3
		Pre: Placebo	143 97 (67.	8) -0.8 (1.5)	-4	0.0	3
		Pre: Placebo	143 97 (67.	8) =0.8 (1.5)	-4	0.0	3

Note: SAF-C = Week 52 Study Completer Set.

Table PT3DLO_CMD0:	Change from	OL-baseline	in 5-D	duration	score	- LSMEANS	confidence	intervals
			SAF-	С				

				Repeated mea	sures analysis
duration scor	DL-baseline in 5-D Te			Change fr	om Baseline
Time	Treatment	N	n (%)	LS-Mean (SE)	95% CI
OL Week 4	Pre: CR845	136	135 (99.3)	-0.2 (0.1)	(-0.4, -0.1)
	Pre: Placebo	143	138 (96.5)	-0.5 (0.1)	(-0.6, -0.3)
OL Week 8	Pre: CR845	136	133 (97.8)	-0.3 (0.1)	(-0.4, -0.2)
	Pre: Placebo	143	140 (97.9)	-0.6 (0.1)	(-0.8, -0.4)
OL Week 12	Pre: CR845	136	133 (97.8)	-0.3 (0.1)	(-0.4, -0.2)
	Pre: Placebo	143	137 (95.8)	-0.5 (0.1)	(-0.7, -0.4)
OL Week 24	Pre: CR845	136	132 (97.1)	-0.3 (0.1)	(-0.4, -0.2)
	Pre: Placebo	143	143 (100.0)	-0.7 (0.1)	(-0.8, -0.5)
OL Week 36	Pre: CR845	136	133 (97.8)	-0.4 (0.1)	(-0.5, -0.3)
	Pre: Placebo	143	142 (99.3)	-0.6 (0.1)	(-0.8, -0.4)
OL Week 52	Pre: CR845	136	94 (69.1)	-0.5 (0.1)	(-0.6, -0.3)
	Pre: Placebo	143	97 (67.8)	-0.7 (0.1)	(-0.9, -0.6)

Note: SAF-C = Week 52 Study Completer Set.

Page 1 of 1 Program Name: PF3DLO_MG0.sas Run Date: 11MAR2022:00:03:06

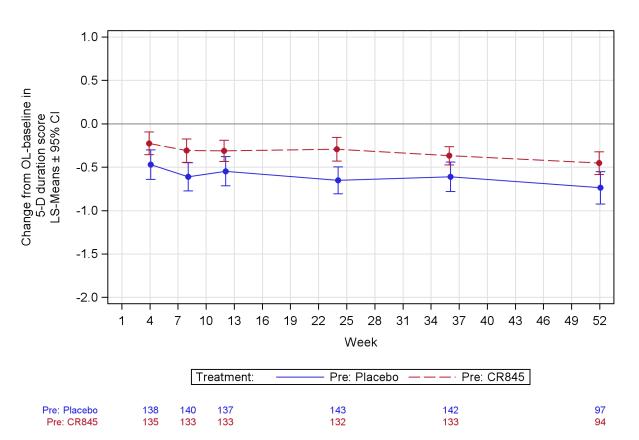


Figure PF3DLO_CMG0: Change from OL-baseline in 5-D duration score - Course of LSMEANS SAF-C

Note: SAF-C = Week 52 Study Completer Set.

Symbols present least square mean (LS-Mean), bars present 95% confidence intervals (CI).

CR845 = Difelikefalin, OL - baseline = Baseline of open label period.

Source Table: PT3DLO CMD0

Table PT3DWO_CMHO: Change from OL-baseline in 5-D direction score SAF-C

		Treatment	Ν	n (%)	Mean (SD)	Min	Q50	Max
5-D direction score	OL Baseline	Pre: CR845	126	126 (100 0)		1	2 0	F
5-D direction score	OL Baseline	Pre: CR845 Pre: Placebo	136 143	136 (100.0) 143 (100.0)	2.5 (0.8) 3.0 (0.9)	1 1	2.0 3.0	5 5
	OL Week 4	Pre: CR845	143	135 (99.3)	2.4 (0.9)	1	2.0	5
	OL Week 4	Pre: CR045 Pre: Placebo	143	138 (96.5)	2.4 (0.9) 2.4 (0.8)	1	2.0	5
	OL Week 8	Pre: CR845	143	138 (96.5)	2.3 (0.8)	1	2.0	5
	OL WEEK 0	Pre: Placebo	143	140 (97.9)	2.3 (0.8)	1	2.0	5
	OL Week 12	Pre: CR845	143	134 (98.5)	2.3 (0.9)	1	2.0	5
	OL Week 12	Pre: CR045 Pre: Placebo	143		2.3 (0.9)	1	2.0	5
	OL Week 24	Pre: CR845	143	137 (95.8) 133 (97.8)	2.3 (0.8)		2.0	
	OL week 24	Pre: CR845 Pre: Placebo	136	, ,	. ,	1	2.0	5 5
	OT Usels 20			143 (100.0)	2.3 (0.9)	1		
	OL Week 36	Pre: CR845 Pre: Placebo	136	132 (97.1)	2.3 (0.8)	1 1	2.0 2.0	5
			143	141 (98.6)	2.3 (0.9)			5
	OL Week 52	Pre: CR845	136	94 (69.1)	2.0 (0.8)	1	2.0	4
		Pre: Placebo	143	97 (67.8)	2.3 (1.0)	1	2.0	5
Change from OL-baseline in 5-D direction score	OL Week 4	Pre: CR845	136	135 (99.3)	-0.1 (0.9)	-3	0.0	3
		Pre: Placebo	143	138 (96.5)	-0.5(1.0)	-3	0.0	2
	OL Week 8	Pre: CR845	136	132 (97.1)	-0.2 (1.0)	-2	0.0	3
		Pre: Placebo	143	140 (97.9)	-0.6(1.1)	-4	-1.0	3
	OL Week 12	Pre: CR845	136	134 (98.5)	-0.1 (1.0)	-3	0.0	3
		Pre: Placebo	143	137 (95.8)	-0.6(1.1)	-4	-1.0	2
	OL Week 24	Pre: CR845	136	133 (97.8)	-0.1 (1.0)	-3	0.0	3
		Pre: Placebo	143	143 (100.0)	-0.6 (1.1)	-3	-1.0	3
	OL Week 36	Pre: CR845	136	132 (97.1)	-0.2 (1.0)	-3	0.0	2
		Pre: Placebo	143	141 (98.6)	-0.6 (1.0)	-3	-1.0	2
	OL Week 52	Pre: CR845	136	94 (69.1)	-0.4(0.9)	-3	0.0	1
		Pre: Placebo	143	97 (67.8)	-0.7 (1.3)	-4	-1.0	3
				· · · · /				

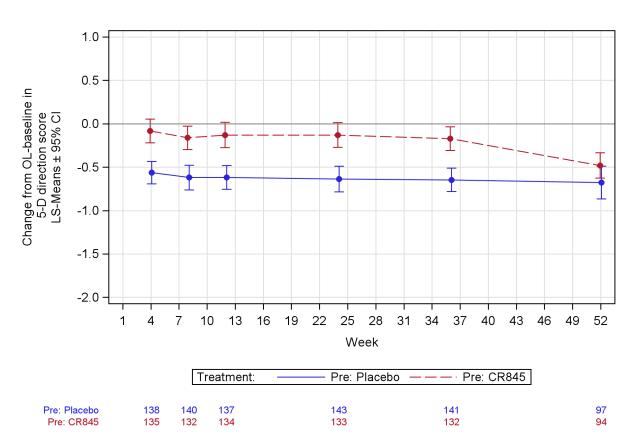
Note: SAF-C = Week 52 Study Completer Set.

Table PT3DWO_CMD0:	Change from	OL-baseline :	in 5-D	direction	score	- LSMEANS	confidence	intervals
			SAF-	·C				

Chango from O	L-baseline in 5-D			Repeated mea	sures analysis			
direction sco		_		Change from Baseline				
Time	Treatment	N	n (%)	LS-Mean (SE)	95% CI			
OL Week 4	Pre: CR845	136	135 (99.3)	-0.1(0.1)	(-0.2, 0.1)			
	Pre: Placebo	143	138 (96.5)	-0.6 (0.1)				
OL Week 8	Pre: CR845	136	132 (97.1)	-0.2 (0.1)	(-0.3, -0.0)			
	Pre: Placebo	143	140 (97.9)	-0.6 (0.1)	(-0.8, -0.5)			
OL Week 12	Pre: CR845	136	134 (98.5)	-0.1 (0.1)	(-0.3, 0.0)			
	Pre: Placebo	143	137 (95.8)	-0.6 (0.1)	(-0.8, -0.5)			
OL Week 24	Pre: CR845	136	133 (97.8)	-0.1 (0.1)	(-0.3, 0.0)			
	Pre: Placebo	143	143 (100.0)	-0.6 (0.1)	(-0.8, -0.5)			
OL Week 36	Pre: CR845	136	132 (97.1)	-0.2 (0.1)	(-0.3, -0.0)			
	Pre: Placebo	143	141 (98.6)	-0.6 (0.1)	(-0.8, -0.5)			
OL Week 52	Pre: CR845	136	94 (69.1)	-0.5 (0.1)	(-0.6, -0.3)			
	Pre: Placebo	143	97 (67.8)	-0.7(0.1)	(-0.9, -0.5)			

Note: SAF-C = Week 52 Study Completer Set.

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Note: SAF-C = Week 52 Study Completer Set.

Symbols present least square mean (LS-Mean), bars present 95% confidence intervals (CI).

CR845 = Difelikefalin, OL - baseline = Baseline of open label period.

Source Table: PT3DWO CMD0

Table PT3DNO_CMHO: Change from OL-baseline in 5-D disability score SAF-C

		Treatment	Ν	n (%)	Mean (SD)	Min	Q50	Max
5-D disability score	OL Baseline	Pre: CR845	136	136 (100.0)	2.4 (1.2)	1	2.0	5
		Pre: Placebo	143	143 (100.0)	2.8 (1.2)	1	3.0	5
	OL Week 4	Pre: CR845	136	135 (99.3)	2.3 (1.2)	1	2.0	5
		Pre: Placebo	143	138 (96.5)	2.3 (1.1)	1	2.0	5
	OL Week 8	Pre: CR845	136	133 (97.8)	2.2 (1.2)	1	2.0	5
		Pre: Placebo	143	140 (97.9)	2.1 (1.0)	1	2.0	5
	OL Week 12	Pre: CR845	136	134 (98.5)	2.2 (1.2)	1	2.0	5
		Pre: Placebo	143	137 (95.8)	2.2 (1.1)	1	2.0	5
	OL Week 24	Pre: CR845	136	133 (97.8)	2.1 (1.1)	1	2.0	5
		Pre: Placebo	143	143 (100.0)	2.3 (1.2)	1	2.0	5
	OL Week 36	Pre: CR845	136	132 (97.1)	2.0 (1.1)	1	2.0	5
		Pre: Placebo	143	141 (98.6)	2.2 (1.2)	1	2.0	5
	OL Week 52	Pre: CR845	136	94 (69.1)	1.9 (1.1)	1	2.0	5
		Pre: Placebo	143	97 (67.8)	2.2 (1.2)	1	2.0	5
Change from OL-baseline in 5-D disability score	OL Week 4	Pre: CR845	136	135 (99.3)	-0.1 (0.9)	-2	0.0	2
-		Pre: Placebo	143	138 (96.5)	-0.5(1.3)	-4	0.0	3
	OL Week 8	Pre: CR845	136	133 (97.8)	-0.2 (1.0)	-3	0.0	3
		Pre: Placebo	143	140 (97.9)	-0.6(1.3)	-4	0.0	2
	OL Week 12	Pre: CR845	136	134 (98.5)	-0.2(1.1)	-3	0.0	3
		Pre: Placebo	143	137 (95.8)	-0.6(1.4)	-4	-1.0	3
	OL Week 24	Pre: CR845	136	133 (97.8)	-0.3 (1.1)	-3	0.0	4
		Pre: Placebo	143	143 (100.0)	-0.5 (1.3)	-4	0.0	3
	OL Week 36	Pre: CR845	136	132 (97.1)	-0.4 (1.1)	-3	0.0	3
		Pre: Placebo	143	141 (98.6)	-0.6(1.4)	-4	0.0	3
	OL Week 52	Pre: CR845	136	94 (69.1)	-0.5 (1.3)	-4	0.0	4
		Pre: Placebo	143	97 (67.8)	-0.7(1.4)	-4	-1.0	4

Note: SAF-C = Week 52 Study Completer Set.

Table PT3DNO_CMD0:	Change	from OL-baseline	in	5-D	disability	score	-	LSMEANS	confidence	intervals
				SAF	-C					

Charles Carro O				Repeated mea	sures analysis
disability sc	L-baseline in 5-D ore			Change fr	om Baseline
Time	Treatment	Ν	n (%)	LS-Mean (SE)	95% CI
OL Week 4	Pre: CR845	136	135 (99.3)	-0.1 (0.1)	(-0.2, 0.1)
	Pre: Placebo	143	138 (96.5)	-0.5 (0.1)	(-0.7, -0.4)
OL Week 8	Pre: CR845	136	133 (97.8)	-0.2 (0.1)	(-0.4, -0.1)
	Pre: Placebo	143	140 (97.9)	-0.6 (0.1)	(-0.8, -0.5)
OL Week 12	Pre: CR845	136	134 (98.5)	-0.2 (0.1)	(-0.4, -0.1)
	Pre: Placebo	143	137 (95.8)	-0.6 (0.1)	(-0.8, -0.4)
OL Week 24	Pre: CR845	136	133 (97.8)	-0.3 (0.1)	(-0.5, -0.1)
	Pre: Placebo	143	143 (100.0)	-0.5 (0.1)	(-0.7, -0.3)
OL Week 36	Pre: CR845	136	132 (97.1)	-0.4 (0.1)	(-0.5, -0.2)
	Pre: Placebo	143	141 (98.6)	-0.6 (0.1)	(-0.8, -0.4)
OL Week 52	Pre: CR845	136	94 (69.1)	-0.5 (0.1)	(-0.7, -0.3)
	Pre: Placebo	143	97 (67.8)	-0.7 (0.1)	(-0.9, -0.5)

Note: SAF-C = Week 52 Study Completer Set.

Page 1 of 1 Program Name: PF3DNO_MG0.sas Run Date: 11MAR2022:00:04:30

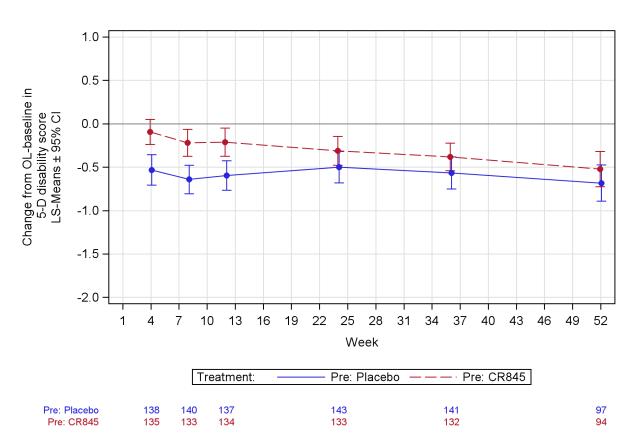


Figure PF3DNO_CMG0: Change from OL-baseline in 5-D disability score - Course of LSMEANS SAF-C

Note: SAF-C = Week 52 Study Completer Set.

Symbols present least square mean (LS-Mean), bars present 95% confidence intervals (CI).

CR845 = Difelikefalin, OL - baseline = Baseline of open label period.

Source Table: PT3DNO CMD0

Table	PT3DVO_	CMHO:	Change	from	OL-baseline	in	5-D	distribution	score
					SAF-C				

	OL Baseline							
5-D distribution score		Pre: CR845	136	136 (100.0)	2.6 (1.3)	1	3.0	5
5-D distribution score		Pre: Placebo	143	136 (100.0) 143 (100.0)	3.1(1.3)	1	3.0	5
	OL Week 4	Pre: CR845	136	135 (99.3)	2.4(1.3)	1	2.0	5
	OD WEEK 4	Pre: Placebo	143	138 (96.5)	2.7(1.3)	1	3.0	5
	OL Week 8	Pre: CR845	136	133 (97.8)	2.2 (1.2)	1	2.0	5
	OF WEEK 0	Pre: Placebo	143	140 (97.9)	2.5 (1.2)	1	2.0	5
	OL Week 12	Pre: CR845	136	134 (98.5)	2.3 (1.3)	1	2.0	5
	02 10001 12	Pre: Placebo	143	137 (95.8)	2.5 (1.2)	1	2.0	5
	OL Week 24	Pre: CR845	136	133 (97.8)	2.2 (1.2)	1	2.0	5
	02 10001 21	Pre: Placebo	143	143 (100.0)	2.3 (1.2)	1	2.0	5
	OL Week 36	Pre: CR845	136	134 (98.5)	2.1 (1.2)	1	2.0	5
		Pre: Placebo	143	142 (99.3)	2.3 (1.2)	1	2.0	5
	OL Week 52	Pre: CR845	136	94 (69.1)	2.1 (1.1)	1	2.0	5
		Pre: Placebo	143	97 (67.8)	2.2 (1.2)	1	2.0	5
Change from OL-baseline in 5-D distribution score	OL Week 4	Pre: CR845	136	135 (99.3)	-0.2 (0.9)	-3	0.0	2
		Pre: Placebo	143	138 (96.5)	-0.4 (1.1)	-4	0.0	2
	OL Week 8	Pre: CR845	136	133 (97.8)	-0.4(0.9)	-4	0.0	2
		Pre: Placebo	143	140 (97.9)	-0.6(1.1)	-4	0.0	2
	OL Week 12	Pre: CR845	136	134 (98.5)	-0.4(1.1)	-4	0.0	3
		Pre: Placebo	143	137 (95.8)	-0.6(1.0)	-4	0.0	2
	OL Week 24	Pre: CR845	136	133 (97.8)	-0.4(1.0)	-4	0.0	2
		Pre: Placebo	143	143 (100.0)	-0.8 (1.2)	-4	-1.0	4
	OL Week 36	Pre: CR845	136	134 (98.5)	-0.5(1.0)	-3	0.0	3
		Pre: Placebo	143	142 (99.3)	-0.8 (1.3)	-4	-1.0	4
	OL Week 52	Pre: CR845	136	94 (69.1)	-0.7 (1.1)	-4	-1.0	3
		Pre: Placebo	143	97 (67.8)	-1.0 (1.3)	-4	-1.0	2

Note: SAF-C = Week 52 Study Completer Set.

Table PT3DVO_CMD0:	Change f	Erom	OL-baseline	in	5-D	distribution	score	-	LSMEANS	confidence	intervals
					SAI	F-C					

Change from OL-baseline in 5-D distribution score				Change from Baseline			
Time	Treatment	N	n (%)	LS-Mean (SE)	95% CI		
or	D (D) (F	100	105 (00 0)				
OL Week 4	Pre: CR845	136	135 (99.3)	()	, , ,		
	Pre: Placebo	143	138 (96.5)	-0.4(0.1)	(-0.6, -0.3)		
OL Week 8	Pre: CR845	136	133 (97.8)	-0.4 (0.1)	(-0.5, -0.2)		
	Pre: Placebo	143	140 (97.9)	-0.6 (0.1)	(-0.8, -0.5)		
OL Week 12	Pre: CR845	136	134 (98.5)	-0.4(0.1)	(-0.5, -0.2)		
	Pre: Placebo	143	137 (95.8)		(-0.7, -0.4)		
OL Week 24	Pre: CR845	136	133 (97.8)	-0.4(0.1)	(-0.6, -0.3)		
	Pre: Placebo	143	143 (100.0)	-0.8 (0.1)	(-1.0, -0.6)		
DL Week 36	Pre: CR845	136	134 (98.5)	-0.5 (0.1)	(-0.7, -0.4)		
	Pre: Placebo	143	142 (99.3)		(-1.0, -0.6)		
OL Week 52	Pre: CR845	136	94 (69.1)	-0.6 (0.1)	(-0.8, -0.5)		
	Pre: Placebo	143	97 (67.8)	-0.9 (0.1)	(-1.1, -0.7)		

Note: SAF-C = Week 52 Study Completer Set.

Page 1 of 1 Program Name: PF3DVO_MG0.sas Run Date: 11MAR2022:00:05:15

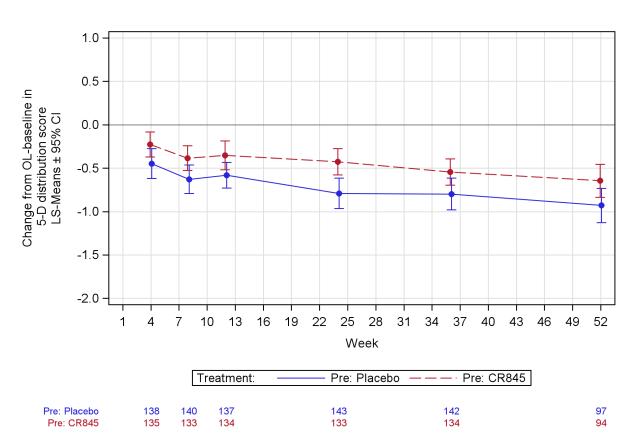


Figure PF3DVO_CMG0: Change from OL-baseline in 5-D distribution score - Course of LSMEANS SAF-C

Note: SAF-C = Week 52 Study Completer Set.

Symbols present least square mean (LS-Mean), bars present 95% confidence intervals (CI).

CR845 = Difelikefalin, OL - baseline = Baseline of open label period.

Source Table: PT3DVO CMD0

Page 1 of 1 Program Name: PT3aae_p_I1.sas Run Date: 09MAR2022:15:09:36

Table PT3LA_LMI1: TEAEs during first quarter of OLP SAF-L

	Pre: CR845		Pre: Placebo	
	N	n (%) [95 % CI]	N	n (%) [95 % CI]
	- 11	[95 % CI]	N	[93 % CI]
TEAEs during OLP	340	176 (51.8) [46.3, 57.2]	372	220 (59.1) [54.0, 64.2]

Note: SAF-L = Week 52 Safety set. N = total number of patients in analysis set. n = number of patients with events during OLP. OLP = open label period. 95% CI = 95% confidence interval according to Clopper Pearson. TEAE = treatment emergent adverse event. Source Data: aae_p, created on: 03MAR2022

Page 1 of 4 Program Name: PT3aae_p_SO.sas Run Date: 03MAR2022:18:11:35

		Pre: CR845		Pre: Placebo	
TEAEs during OLP	N	n (%) [95 % CI]	N	n (%) [95 % CI]	
SOC: Blood and lymphatic system disorders	340	17 (5.0) [2.9, 7.9]	372	18 (4.8) [2.9, 7.5]	
SOC: Cardiac disorders	340	44 (12.9) [9.6, 17.0]	372	53 (14.2) [10.9, 18.2]	
SOC: Eye disorders	340	11 (3.2) [1.6, 5.7]	372	14 (3.8) [2.1, 6.2]	
SOC: Gastrointestinal disorders	340	106 (31.2) [26.3, 36.4]	372	127 (34.1) [29.3, 39.2]	
Abdominal pain	340	20 (5.9) [3.6, 8.9]	372	19 (5.1) [3.1, 7.9]	
Abdominal pain upper	340	6 (1.8) [0.7, 3.8]	372	14 (3.8) [2.1, 6.2]	
Constipation	340	18 (5.3) [3.2, 8.2]	372	17 (4.6) [2.7, 7.2]	
Diarrhoea	340	36 (10.6) [7.5, 14.4]	372	38 (10.2) [7.3, 13.8]	
Nausea	340	31 (9.1) [6.3, 12.7]	372	31 (8.3) [5.7, 11.6]	
Vomiting	340	22 (6.5) [4.1, 9.6]	372	31 (8.3) [5.7, 11.6]	
SOC: General disorders and administration site conditions	340	66 (19.4) [15.3, 24.0]	372	64 (17.2) [13.5, 21.4]	
Asthenia	340	15 (4.4) [2.5, 7.2]	372	13 (3.5) [1.9, 5.9]	
Chest pain	340	10 (2.9) [1.4, 5.3]	372	7 (1.9) [0.8, 3.8]	
Non-cardiac chest pain	340	13 (3.8) [2.1, 6.4]	372	6 (1.6) [0.6, 3.5]	
Pyrexia	340	6 (1.8) [0.7, 3.8]	372	12 (3.2) [1.7, 5.6]	

Table PT3LA_LMSO: TEAEs during OLP by SOC and PT $_{\rm SAF-L}$

Note: SAF-L = Week 52 Safety set. Only events are displayed with an incidence of at least 10 percent in a treatment group or 10 patients with an incidence of at least 1 percent in a treatment group.

N = total number of patients in analysis set. n = number of patients with events during OLP. OLP = open label period.

- 95% CI = 95% confidence interval according to Clopper Pearson. TEAE = treatment emergent adverse event. SOC = system organ class. PT = preferred term.
- Source Data: aae_p, created on: 03MAR2022

		Pre: CR845	Р	re: Placebo
TEAEs during OLP	N	n (%) [95 % CI]	N	n (%) [95 % CI]
SOC: Hepatobiliary disorders	340	5 (1.5) [0.5, 3.4]	372	10 (2.7) [1.3, 4.9]
SOC: Infections and infestations	340	105 (30.9) [26.0, 36.1]	372	127 (34.1) [29.3, 39.2]
Bronchitis	340	11 (3.2) [1.6, 5.7]	372	14 (3.8) [2.1, 6.2]
Nasopharyngitis	340	15 (4.4) [2.5, 7.2]	372	18 (4.8) [2.9, 7.5]
Pneumonia	340	31 (9.1) [6.3, 12.7]	372	28 (7.5) [5.1, 10.7]
Sepsis	340	14 (4.1) [2.3, 6.8]	372	13 (3.5) [1.9, 5.9]
Upper respiratory tract infection	340	13 (3.8) [2.1, 6.4]	372	14 (3.8) [2.1, 6.2]
Urinary tract infection	340	11 (3.2) [1.6, 5.7]	372	10 (2.7) [1.3, 4.9]
SOC: Injury, poisoning and procedural complications	340	98 (28.8) [24.1, 34.0]	372	106 (28.5) [24.0, 33.4]
Arteriovenous fistula site complication	340	7 (2.1) [0.8, 4.2]	372	14 (3.8) [2.1, 6.2]
Arteriovenous fistula thrombosis	340	7 (2.1) [0.8, 4.2]	372	16 (4.3) [2.5, 6.9]
Fall	340	38 (11.2) [8.0, 15.0]	372	43 (11.6) [8.5, 15.3]
Procedural hypotension	340	4 (1.2) [0.3, 3.0]	372	10 (2.7) [1.3, 4.9]
SOC: Investigations	340	20 (5.9) [3.6, 8.9]	372	33 (8.9) [6.2, 12.2]
SOC: Metabolism and nutrition disorders	340	66 (19.4) [15.3, 24.0]	372	67 (18.0) [14.2, 22.3]
Fluid overload	340	20 (5.9) [3.6, 8.9]	372	13 (3.5) [1.9, 5.9]

Table PT3LA_LMSO: TEAEs during OLP by SOC and PT $_{\rm SAF-L}$

Note: SAF-L = Week 52 Safety set. Only events are displayed with an incidence of at least 10 percent in a treatment group or 10 patients with an incidence of at least 1 percent in a treatment group.

N = total number of patients in analysis set. n = number of patients with events during OLP. OLP = open label period.

- 95% CI = 95% confidence interval according to Clopper Pearson. TEAE = treatment emergent adverse event. SOC = system organ class. PT = preferred term.
- Source Data: aae_p, created on: 03MAR2022

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		Pre: CR845	Р	re: Placebo
TEAEs during OLP	N	n (%) [95 % CI]	N	n (%) [95 % CI]
Hyperkalaemia	340	25 (7.4) [4.8, 10.7]	372	30 (8.1) [5.5, 11.3]
SOC: Musculoskeletal and connective tissue disorders	340	61 (17.9) [14.0, 22.4]	372	80 (21.5) [17.4, 26.0]
Arthralgia	340	11 (3.2) [1.6, 5.7]	372	5 (1.3) [0.4, 3.1]
Back pain	340	11 (3.2) [1.6, 5.7]	372	19 (5.1) [3.1, 7.9]
Muscle spasms	340	15 (4.4) [2.5, 7.2]	372	22 (5.9) [3.7, 8.8]
Pain in extremity	340	13 (3.8) [2.1, 6.4]	372	22 (5.9) [3.7, 8.8]
SOC: Nervous system disorders	340	65 (19.1) [15.1, 23.7]	372	82 (22.0) [17.9, 26.6]
Dizziness	340	20 (5.9) [3.6, 8.9]	372	23 (6.2) [4.0, 9.1]
Headache	340	24 (7.1) [4.6, 10.3]	372	12 (3.2) [1.7, 5.6]
Syncope	340	12 (3.5) [1.8, 6.1]	372	8 (2.2) [0.9, 4.2]
SOC: Psychiatric disorders	340	39 (11.5) [8.3, 15.3]	372	34 (9.1) [6.4, 12.5]
Mental status changes	340	16 (4.7) [2.7, 7.5]	372	8 (2.2) [0.9, 4.2]
SOC: Renal and urinary disorders	340	6 (1.8) [0.7, 3.8]	372	17 (4.6) [2.7, 7.2]
SOC: Respiratory, thoracic and mediastinal disorders	340	73 (21.5) [17.2, 26.2]	372	84 (22.6) [18.4, 27.2]
Chronic obstructive pulmonary disease	340	6 (1.8) [0.7, 3.8]	372	13 (3.5) [1.9, 5.9]

Table PT3LA_LMSO: TEAEs during OLP by SOC and PT $_{\rm SAF-L}$

Note: SAF-L = Week 52 Safety set. Only events are displayed with an incidence of at least 10 percent in a treatment group or 10 patients with an incidence of at least 1 percent in a treatment group.

N = total number of patients in analysis set. n = number of patients with events during OLP. OLP = open label period.

- 95% CI = 95% confidence interval according to Clopper Pearson. TEAE = treatment emergent adverse event. SOC = system organ class. PT = preferred term.
- Source Data: aae_p, created on: 03MAR2022

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		Pre: CR845	Р	re: Placebo
TEAEs during OLP	N	n (%) [95 % CI]	N	n (%) [95 % CI]
Cough	340	19 (5.6) [3.4, 8.6]		18 (4.8) [2.9, 7.5]
Dyspnoea	340	25 (7.4) [4.8, 10.7]		21 (5.6)
Respiratory failure	340	10 (2.9) [1.4, 5.3]		16 (4.3) [2.5, 6.9]
SOC: Skin and subcutaneous tissue disorders	340	32 (9.4) [6.5, 13.0]		29 (7.8) [5.3, 11.0]
Pruritus	340	10 (2.9) [1.4, 5.3]		4 (1.1) [0.3, 2.7]
SOC: Vascular disorders	340	68 (20.0) [15.9, 24.7]	372	66 (17.7) [14.0, 22.0]
Hypertension	340	. ,		14 (3.8) [2.1, 6.2]
Hypotension	340	34 (10.0) [7.0, 13.7]		31 (8.3) [5.7, 11.6]

Table PT3LA_LMSO: TEAEs during OLP by SOC and PT SAF-L

Note: SAF-L = Week 52 Safety set. Only events are displayed with an incidence of at least 10 percent in a treatment group or 10 patients with an incidence of at least 1 percent in a treatment group.

N = total number of patients in analysis set. n = number of patients with events during OLP. OLP = open label period.

95% CI = 95% confidence interval according to Clopper Pearson. TEAE = treatment emergent adverse event. SOC = system organ class. PT = preferred term.

Source Data: aae_p, created on: 03MAR2022

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		Pre: CR845	Р	re: Placebo
TEAEs during OLP	N	n (%) [95 % CI]	N	n (%) [95 % CI]
SOC: Cardiac disorders	136	23 (16.9) [11.0, 24.3]	143	30 (21.0) [14.6, 28.6]
SOC: Gastrointestinal disorders	136	62 (45.6) [37.0, 54.3]	143	66 (46.2) [37.8, 54.7]
Abdominal pain	136	8 (5.9) [2.6, 11.3]	143	11 (7.7) [3.9, 13.3]
Abdominal pain upper	136	4 (2.9) [0.8, 7.4]	143	11 (7.7) [3.9, 13.3]
Constipation	136	10 (7.4) [3.6, 13.1]	143	11 (7.7) [3.9, 13.3]
Diarrhoea	136	25 (18.4) [12.3, 25.9]	143	21 (14.7) [9.3, 21.6]
Nausea	136	23 (16.9) [11.0, 24.3]	143	22 (15.4) [9.9, 22.4]
Vomiting	136	13 (9.6) [5.2, 15.8]	143	17 (11.9) [7.1, 18.4]
SOC: General disorders and administration site conditions	136	38 (27.9) [20.6, 36.3]	143	36 (25.2) [18.3, 33.1]
Non-cardiac chest pain	136	12 (8.8) [4.6, 14.9]	143	5 (3.5) [1.1, 8.0]
SOC: Infections and infestations	136	50 (36.8) [28.7, 45.5]	143	57 (39.9) [31.8, 48.4]
Nasopharyngitis	136	6 (4.4) [1.6, 9.4]	143	12 (8.4) [4.4, 14.2]
Pneumonia	136	14 (10.3) [5.7, 16.7]	143	13 (9.1) [4.9, 15.0]
SOC: Injury, poisoning and procedural complications	136	43 (31.6) [23.9, 40.1]	143	59 (41.3) [33.1, 49.8]
Arteriovenous fistula thrombosis	136	1 (0.7) [0.0, 4.0]	143	10 (7.0) [3.4, 12.5]
Fall	136	19 (14.0) [8.6, 21.0]	143	28 (19.6) [13.4, 27.0]

Table PT3LA_CMSO: TEAEs during OLP by SOC and PT $${\rm SAF-C}$$

Note: SAF-C = Week 52 Study Completer Set. Only events are displayed with an incidence of at least 10 percent in a treatment group or 10 patients with an incidence of at least 1 percent in a treatment group.

N = total number of patients in analysis set. n = number of patients with events during OLP. OLP = open label period.

- 95% CI = 95% confidence interval according to Clopper Pearson. TEAE = treatment emergent adverse event. SOC = system organ class. PT = preferred term.
- Source Data: aae_p, created on: 03MAR2022

		Pre: CR845		re: Placebo
		n (%)		n (%)
TEAEs during OLP	N	[95 % CI]	N	[95 % CI]
SOC: Investigations	136	10 (7.4)	143	16 (11.2)
5		[3.6, 13.1]		[6.5, 17.5]
SOC: Metabolism and nutrition disorders	136	31 (22.8)	143	39 (27.3)
Fluid overload	136	[16.0, 30.8] 8 (5.9)	143	[20.2, 35.3] 11 (7.7)
Fluid Overload	130	[2.6, 11.3]	143	[3.9, 13.3]
Hyperkalaemia	136	12 (8.8)	143	21 (14.7)
11		[4.6, 14.9]		[9.3, 21.6]
SOC: Musculoskeletal and connective	136	35 (25.7)	143	45 (31.5)
tissue disorders	120	[18.6, 33.9]	4.40	[24.0, 39.8]
Back pain	136	5 (3.7) [1.2, 8.4]	143	11 (7.7) [3.9, 13.3]
Muscle spasms	136	12 (8.8)	143	9 (6.3)
	100	[4.6, 14.9]	110	[2.9, 11.6]
Pain in extremity	136	8 (5.9)	143	13 (9.1)
-		[2.6, 11.3]		[4.9, 15.0]
SOC: Nervous system disorders	136	42 (30.9)	143	41 (28.7)
Dizziness	136	[23.2, 39.4] 16 (11.8)	143	[21.4, 36.8] 13 (9.1)
DIZZINESS	130	[6.9, 18.4]	143	[4.9, 15.0]
Headache	136	19 (14.0)	143	8 (5.6)
		[8.6, 21.0]		[2.4, 10.7]
SOC: Psychiatric disorders	136	18 (13.2)	143	12 (8.4)
		[8.0, 20.1]		[4.4, 14.2]
SOC: Respiratory, thoracic and	136	42 (30.9)	143	49 (34.3)
mediastinal disorders	100	[23.2, 39.4]	110	[26.5, 42.7]
Cough	136	15 (11.0)	143	12 (8.4)
		[6.3, 17.5]		[4.4, 14.2]
Dyspnoea	136	15 (11.0)	143	12 (8.4)
		[6.3, 17.5]		[4.4, 14.2]

Table PT3LA_CMSO: TEAEs during OLP by SOC and PT SAF-C

Note: SAF-C = Week 52 Study Completer Set. Only events are displayed with an incidence of at least 10 percent in a treatment group or 10 patients with an incidence of at least 1 percent in a treatment group.

N = total number of patients in analysis set. n = number of patients with events during OLP. OLP = open label period.

- 95% CI = 95% confidence interval according to Clopper Pearson. TEAE = treatment emergent adverse event. SOC = system organ class. PT = preferred term.
- Source Data: aae_p, created on: 03MAR2022

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	Pre: CR845		Pre: Placebo	
TEAEs during OLP	N	n (%) [95 % CI]	N	n (%) [95 % CI]
Respiratory failure	136	3 (2.2) [0.5, 6.3]	143	10 (7.0) [3.4, 12.5]
SOC: Skin and subcutaneous tissue disorders	136	15 (11.0) [6.3, 17.5]	143	14 (9.8) [5.5, 15.9]
SOC: Vascular disorders	136	38 (27.9) [20.6, 36.3]	143	38 (26.6) [19.5, 34.6]
Hypotension	136	23 (16.9) [11.0, 24.3]	143	20 (14.0) [8.8, 20.8]

Table PT3LA_CMSO: TEAEs during OLP by SOC and PT $${\rm SAF-C}$$

Note: SAF-C = Week 52 Study Completer Set. Only events are displayed with an incidence of at least 10 percent in a treatment group or 10 patients with an incidence of at least 1 percent in a treatment group.

N = total number of patients in analysis set. n = number of patients with events during OLP. OLP = open label period.

95% CI = 95% confidence interval according to Clopper Pearson. TEAE = treatment emergent adverse event. SOC = system organ class. PT = preferred term.

Source Data: aae_p, created on: 03MAR2022

Table PT3LAEGN_LMI1: AESI gait disturbance - non-severe during first quarter of OLP SAF-L

	Pre: CR845		Pre: Placebo	
	N	n (%) [95 % CI]	N	n (%) [95 % CI]
AESI gait disturbance - non-severe during OLP	340	0 (0.0)	372	0 (0.0)

Table PT3LAEFN_LMI1: AESI falls/injuries - non-severe during first quarter of OLP SAF-L

	F	Pre: CR845		Pre: Placebo	
		n (%)		n (%)	
	N	[95 % CI]	N	[95 % CI]	
AESI falls/injuries - non-severe during OLP	340	21 (6.2) [3.9, 9.3]	372	25 (6.7) [4.4, 9.8]	

Table PT3LAEVN_LMI1: AESI dizziness - non-severe during first quarter of OLP SAF-L

	Pre: CR845		Pre: Placebo	
	N	n (%) [95 % CI]	N	n (%) [95 % CI]
AESI dizziness - non-severe during OLP	340	11 (3.2) [1.6, 5.7]	372	11 (3.0) [1.5, 5.2]

Table PT3LAEYN_LMI1: AESI syncope - non-severe during first quarter of OLP SAF-L

	Pre: CR845		Pre: Placebo	
	N	n (%) [95 % CI]	N	n (%) [95 % CI]
AESI syncope - non-severe during OLP	340	3 (0.9) [0.2, 2.6]	372	5 (1.3) [0.4, 3.1]

Table PT3LAEON_LMI1: AESI somnolence - non-severe during first quarter of OLP SAF-L

	Pre: CR845		Pre: Placebo	
	N	n (%) [95 % CI]	N	n (%) [95 % CI]
AESI somnolence - non-severe during OLP	340	1 (0.3) [0.0, 1.6]	372	1 (0.3) [0.0, 1.5]

Table PT3LAEKN_LMI1: AESI seizures - non-severe during first quarter of OLP SAF-L

	F	Pre: CR845		Pre: Placebo	
	N	n (%) [95 % CI]	N	n (%) [95 % CI]	
AESI seizures - non-severe during OLP	340	0 (0.0)	372	1 (0.3) [0.0, 1.5]	

Table PT3LAEMN_LMI1: AESI mental status change - non-severe during first quarter of OLP SAF-L

	F	Pre: CR845		Pre: Placebo	
		n (%)		n (%)	
	N	[95 % CI]	N	[95 % CI]	
AESI mental status change – non-severe during OLP	340	4 (1.2) [0.3, 3.0]	372	10 (2.7) [1.3, 4.9]	

Table PT3LAEEN_LMI1: AESI mood change - non-severe during first quarter of OLP SAF-L

	Pre: CR845		Pre: Placebo	
	N	n (%) [95 % CI]	N	n (%) [95 % CI]
AESI mood change - non-severe	340	7 (2.1)	372	2 (0.5)
during OLP		[0.8, 4.2]		[0.1, 1.9]

Table PT3LAEUN_LMI1: AESI unusual feeling/sensation - non-severe during first quarter of OLP SAF-L

	Pre: CR845		Pr	Pre: Placebo	
		n (%)		n (%)	
	N	[95 % CI]	N	[95 % CI]	
AESI unusual feeling/sensation - non-severe during OLP	340	8 (2.4) [1.0, 4.6]	372	4 (1.1) [0.3, 2.7]	

Table PT3LAERN_LMI1: AESI tachycardia/palpitation - non-severe during first quarter of OLP SAF-L

	Pre: CR845		Pre: Placebo	
	N	n (%) [95 % CI]	N	n (%) [95 % CI]
AESI tachycardia/palpitation -	340	4 (1.2) [0.3, 3.0]	372	4 (1.1) [0.3, 2.7]
non-severe during OLP				

Table PT3LAEGN_LMIO: AESI gait disturbance - non-severe during OLP SAF-L

	Pre: CR845		Pre: Placebo	
	N	n (%) [95 % CI]	N	n (%) [95 % CI]
AESI gait disturbance - non-severe during OLP	340	1 (0.3) [0.0, 1.6]	372	2 (0.5) [0.1, 1.9]

Table PT3LAEFN_LMIO: AESI falls/injuries - non-severe during OLP SAF-L

	Pre: CR845		Pre: Placebo		_
	N	n (%) [95 % CI]	N	n (%) [95 % CI]	-
AESI falls/injuries - non-severe	340	47 (13.8)	• • • •	46 (12.4)	-
during OLP		[10.3, 18.0]		[9.2, 16.1]	

Table PT3LAEVN_LMIO: AESI dizziness - non-severe during OLP SAF-L

	Pre: CR845		Pre: Placebo	
	N	n (%) [95 % CI]	N	n (%) [95 % CI]
AESI dizziness - non-severe during OLP	340	22 (6.5) [4.1, 9.6]	372	23 (6.2) [4.0, 9.1]

Table PT3LAEYN_LMIO: AESI syncope - non-severe during OLP SAF-L

	Pre: CR845		Pre: Placebo	
	N	n (%) [95 % CI]	N	n (%) [95 % CI]
AESI syncope - non-severe during OLP	340	10 (2.9) [1.4, 5.3]	372	8 (2.2) [0.9, 4.2]

Table PT3LAEON_LMIO: AESI somnolence - non-severe during OLP SAF-L

	Pre: CR845		Pre: Placebo	
	N	n (%) [95 % CI]	N	n (%) [95 % CI]
AESI somnolence - non-severe during OLP	340	2 (0.6) [0.1, 2.1]	372	1 (0.3) [0.0, 1.5]

Table PT3LAEKN_LMIO: AESI seizures - non-severe during OLP SAF-L

	Pre: CR845		Pr	Pre: Placebo	
	N	n (%) [95 % CI]	N	n (%) [95 % CI]	
AESI seizures - non-severe during OLP	340	1 (0.3) [0.0, 1.6]	372	4 (1.1) [0.3, 2.7]	

Table PT3LAEMN_LMIO: AESI mental status change - non-severe during OLP SAF-L

	Pre: CR845		Pr	Pre: Placebo	
		n (%)		n (%)	
	N	[95 % CI]	N	[95 % CI]	
AESI mental status	340	15 (4.4)	372	17 (4.6)	
change - non-severe during OLP		[2.5, 7.2]		[2.7, 7.2]	

Table PT3LAEEN_LMIO: AESI mood change - non-severe during OLP SAF-L

	Pre: CR845		Pr	Pre: Placebo	
	N	n (%) [95 % CI]	N	n (%) [95 % CI]	
AESI mood change - non-severe during OLP	340	10 (2.9) [1.4, 5.3]	372	8 (2.2) [0.9, 4.2]	

Table PT3LAEUN_LMIO: AESI unusual feeling/sensation - non-severe during OLP SAF-L

	Pre: CR845		Pr	e: Placebo
		n (%)		n (%)
	N	[95 % CI]	N	[95 % CI]
AESI unusual feeling/sensation - non-severe during OLP	340	15 (4.4) [2.5, 7.2]	372	12 (3.2) [1.7, 5.6]

Table PT3LAERN_LMIO: AESI tachycardia/palpitation - non-severe during OLP SAF-L

	Pre: CR845		Pre: Placebo	
		n (%)		n (%)
	N	[95 % CI]	N	[95 % CI]
AESI tachycardia/palpitation - non-severe during OLP	340	12 (3.5) [1.8, 6.1]	372	12 (3.2) [1.7, 5.6]

Table PT3LAEGN_CMIO: AESI gait disturbance - non-severe during OLP SAF-C

	Pre: CR845		Pre: Placebo	
	N	n (%) [95 % CI]	N	n (%) [95 % CI]
AESI gait disturbance - non-severe during OLP	136	0 (0.0)	143	1 (0.7) [0.0, 3.8]

Table PT3LAEFN_CMIO: AESI falls/injuries - non-severe during OLP SAF-C

	Pre: CR845		Pre: Placebo	
	N	n (%) [95 % CI]	N	n (%) [95 % CI]
AESI falls/injuries - non-severe	136	22 (16.2)	143	28 (19.6)
during OLP		[10.4, 23.5]		[13.4, 27.0]

Table PT3LAEVN_CMIO: AESI dizziness - non-severe during OLP SAF-C

	Pre: CR845		Pre: Placebo	
	N	n (%) [95 % CI]	N	n (%) [95 % CI]
AESI dizziness - non-severe during OLP	136	16 (11.8) [6.9, 18.4]	143	13 (9.1) [4.9, 15.0]

Table PT3LAEYN_CMIO: AESI syncope - non-severe during OLP SAF-C

	Pre: CR845		Pre: Placebo		_
	N	n (%) [95 % CI]	N	n (%) [95 % CI]	_
AESI syncope - non-severe during OLP	136	7 (5.1) [2.1, 10.3]	143	4 (2.8) [0.8, 7.0]	-

Table PT3LAEON_CMIO: AESI somnolence - non-severe during OLP SAF-C

	Pre: CR845		Pre: Placebo	
	N	n (%) [95 % CI]	N	n (%) [95 % CI]
AESI somnolence - non-severe during OLP	136	1 (0.7) [0.0, 4.0]	143	0 (0.0) [0.0, 2.5]

Table PT3LAEKN_CMIO: AESI seizures - non-severe during OLP SAF-C

	Pre: CR845		Pre: Placebo	
	N	n (%) [95 % CI]	N	n (%) [95 % CI]
AESI seizures - non-severe during OLP	136	0 (0.0) [0.0, 2.7]	143	2 (1.4) [0.2, 5.0]

Table PT3LAEMN_CMIO: AESI mental status change - non-severe during OLP SAF-C

	Pre: CR845		Pre: Placebo	
		n (%)		n (%)
	N	[95 % CI]	N	[95 % CI]
AESI mental status change - non-severe during OLP	136	8 (5.9) [2.6, 11.3]	143	5 (3.5) [1.1, 8.0]

Table PT3LAEEN_CMIO: AESI mood change - non-severe during OLP SAF-C

	Pre: CR845		Pre: Placebo		
	N	n (%) [95 % CI]	N	n (%) [95 % CI]	-
AESI mood change - non-severe	136	4 (2.9)	143	3 (2.1)	-
during OLP		[0.8, 7.4]		[0.4, 6.0]	

Table PT3LAEUN_CMIO: AESI unusual feeling/sensation - non-severe during OLP SAF-C

	H	Pre: CR845		e: Placebo
	N	n (%) [95 % CI]	N	n (%) [95 % CI]
	IN	[95 % CI]	N	[93 % [1]
AESI unusual feeling/sensation - non-severe during OLP	136	8 (5.9) [2.6, 11.3]	143	7 (4.9) [2.0, 9.8]

Table PT3LAERN_CMIO: AESI tachycardia/palpitation - non-severe during OLP SAF-C

	Pre: CR845		Pre: Placebo	
		n (%)		n (%)
	N	[95 % CI]	N	[95 % CI]
AESI tachycardia/palpitation - non-severe during OLP	136	9 (6.6) [3.1, 12.2]	143	9 (6.3) [2.9, 11.6]

Anhang 4-I-4: Zusatzauswertungen der Studie CLIN3101

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ET1LAEKN_LMIO: AESI seizures - non-severe during OLP - Cohort SAF-L	27
ET1LAEMN_LMIO: AESI mental status change - non-severe during OLP - Cohort SAF-L	28
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	Pre: CR845		Р	Pre: Placebo		re: De Novo
TEAEs during OLP	N	n (%) [95 % CI]	N	n (%) [95 % CI]	N	n (%) [95 % CI]
SOC: Cardiac disorders	52	11 (21.2) [11.1, 34.7]	30	1 (3.3) [0.1, 17.2]	206	16 (7.8) [4.5, 12.3]
SOC: Gastrointestinal disorders	52	10 (19.2) [9.6, 32.5]	30	5 (16.7) [5.6, 34.7]	206	47 (22.8) [17.3, 29.2]
Diarrhoea	52	5 (9.6) [3.2, 21.0]	30	2 (6.7) [0.8, 22.1]	206	13 (6.3) [3.4, 10.5]
Nausea	52	6 (11.5) [4.4, 23.4]	30	2 (6.7) [0.8, 22.1]	206	15 (7.3) [4.1, 11.7]
Vomiting	52	4 (7.7) [2.1, 18.5]	30	1 (3.3) [0.1, 17.2]	206	10 (4.9) [2.4, 8.7]
SOC: General disorders and administration site conditions	52	15 (28.8) [17.1, 43.1]	30	6 (20.0) [7.7, 38.6]	206	25 (12.1) [8.0, 17.4]
SOC: Infections and infestations	52	8 (15.4) [6.9, 28.1]	30	4 (13.3) [3.8, 30.7]	206	39 (18.9) [13.8, 25.0]
SOC: Injury, poisoning and procedural complications	52	10 (19.2) [9.6, 32.5]	30	3 (10.0) [2.1, 26.5]	206	30 (14.6) [10.0, 20.1]
Fall	52	6 (11.5) [4.4, 23.4]	30	2 (6.7) [0.8, 22.1]	206	8 (3.9) [1.7, 7.5]
SOC: Metabolism and nutrition disorders	52	3 (5.8) [1.2, 15.9]	30	2 (6.7) [0.8, 22.1]	206	25 (12.1) [8.0, 17.4]
SOC: Musculoskeletal and connective tissue disorders	52	5 (9.6) [3.2, 21.0]	30	1 (3.3) [0.1, 17.2]	206	14 (6.8) [3.8, 11.1]
SOC: Nervous system disorders	52	9 (17.3) [8.2, 30.3]	30	3 (10.0) [2.1, 26.5]	206	29 (14.1) [9.6, 19.6]
SOC: Respiratory, thoracic and mediastinal disorders	52	7 (13.5) [5.6, 25.8]	30	4 (13.3) [3.8, 30.7]	206	19 (9.2) [5.6, 14.0]

Table ET1LA_LMS1: TEAEs during first quarter of OLP by SOC and PT SAF-L

Note: SAF-L = Week 52 Safety set. Only events are displayed with an incidence of at least 10 percent in a treatment group or 10 patients with an incidence of at least 1 percent in a treatment group.

- 95% CI = 95% confidence interval according to Clopper Pearson. TEAE = treatment emergent adverse event. SOC = system organ class. PT = preferred term.
- Source Data: aae, created on: 12MAR2022

	Pre: CR845		Pre: Placebo		Pre: De Novo	
TEAEs during OLP	N	n (%) [95 % CI]	N	n (%) [95 % CI]	N	n (%) [95 % CI]
SOC: Skin and subcutaneous tissue disorders	52	3 (5.8) [1.2, 15.9]	30	1 (3.3) [0.1, 17.2]	206	11 (5.3) [2.7, 9.4]
SOC: Vascular disorders	52	9 (17.3) [8.2, 30.3]	30	6 (20.0) [7.7, 38.6]	206	21 (10.2) [6.4, 15.2]
Hypotension	52	3 (5.8) [1.2, 15.9]	30	4 (13.3) [3.8, 30.7]	206	9 (4.4) [2.0, 8.1]

Table ET1LA_LMS1: TEAEs during first quarter of OLP by SOC and PT SAF-L

Note: SAF-L = Week 52 Safety set. Only events are displayed with an incidence of at least 10 percent in a treatment group or 10 patients with an incidence of at least 1 percent in a treatment group.

N = total number of patients in analysis set. n = number of patients with events during OLP. OLP = open label period.

95% CI = 95% confidence interval according to Clopper Pearson. TEAE = treatment emergent adverse event. SOC = system organ class. PT = preferred term.

Source Data: aae, created on: 12MAR2022

Table ET1LA_LMSO: TEAEs during OLP by SOC and PT $_{\rm SAF-L}$

	Pre: CR845		Р	Pre: Placebo		re: De Novo
TEAEs during OLP	N	n (%) [95 % CI]	N	n (%) [95 % CI]	N	n (%) [95 % CI]
SOC: Cardiac disorders	52	20 (38.5) [25.3, 53.0]	30	9 (30.0) [14.7, 49.4]	206	41 (19.9) [14.7, 26.0]
Acute myocardial infarction	52	6 (11.5) [4.4, 23.4]	30	3 (10.0) [2.1, 26.5]	206	7 (3.4) [1.4, 6.9]
SOC: Eye disorders	52	2 (3.8) [0.5, 13.2]	30	1 (3.3) [0.1, 17.2]	206	11 (5.3) [2.7, 9.4]
SOC: Gastrointestinal disorders	52	24 (46.2) [32.2, 60.5]	30	14 (46.7) [28.3, 65.7]	206	77 (37.4) [30.8, 44.4]
Abdominal pain	52	5 (9.6) [3.2, 21.0]	30	4 (13.3) [3.8, 30.7]	206	11 (5.3) [2.7, 9.4]
Diarrhoea	52	10 (19.2) [9.6, 32.5]	30	7 (23.3) [9.9, 42.3]	206	28 (13.6) [9.2, 19.0]
Nausea	52	13 (25.0) [14.0, 38.9]	30	5 (16.7) [5.6, 34.7]	206	30 (14.6) [10.0, 20.1]
Vomiting	52	10 (19.2) [9.6, 32.5]	30	5 (16.7) [5.6, 34.7]	206	23 (11.2) [7.2, 16.3]
SOC: General disorders and administration site conditions	52	24 (46.2) [32.2, 60.5]	30	9 (30.0) [14.7, 49.4]	206	49 (23.8) [18.1, 30.2]
Fatigue	52	3 (5.8) [1.2, 15.9]	30	3 (10.0) [2.1, 26.5]	206	4 (1.9) [0.5, 4.9]
Non-cardiac chest pain	52	7 (13.5) [5.6, 25.8]	30	1 (3.3) [0.1, 17.2]	206	21 (10.2) [6.4, 15.2]
SOC: Infections and infestations	52	20 (38.5) [25.3, 53.0]	30	11 (36.7) [19.9, 56.1]	206	84 (40.8) [34.0, 47.8]
Pneumonia	52	4 (7.7) [2.1, 18.5]	30	0 (0.0) [0.0, 11.6]	206	14 (6.8) [3.8, 11.1]
Upper respiratory tract infection	52	2 (3.8) [0.5, 13.2]	30	0 (0.0) [0.0, 11.6]	206	12 (5.8) [3.0, 10.0]
Viral upper respiratory tract infection	52	2 (3.8) [0.5, 13.2]	30	2 (6.7) [0.8, 22.1]	206	10 (4.9) [2.4, 8.7]

Note: SAF-L = Week 52 Safety set. Only events are displayed with an incidence of at least 10 percent in a treatment group or 10 patients with an incidence of at least 1 percent in a treatment group.

N = total number of patients in analysis set. n = number of patients with events during OLP. OLP = open label period.

95% CI = 95% confidence interval according to Clopper Pearson. TEAE = treatment emergent adverse event. SOC = system organ class. PT = preferred term.

Source Data: aae, created on: 12MAR2022

Table ET1LA_LMSO: TEAEs during OLP by SOC and PT $_{\rm SAF-L}$

		Pre: CR845	Ρ	Pre: Placebo		re: De Novo
TEAEs during OLP	N	n (%) [95 % CI]	N	n (%) [95 % CI]	N	n (%) [95 % CI]
SOC: Injury, poisoning and procedural complications	52	21 (40.4) [27.0, 54.9]	30	8 (26.7) [12.3, 45.9]	206	60 (29.1) [23.0, 35.8]
Fall	52	12 (23.1) [12.5, 36.8]	30	6 (20.0) [7.7, 38.6]	206	25 (12.1) [8.0, 17.4]
SOC: Investigations	52	7 (13.5) [5.6, 25.8]	30	4 (13.3) [3.8, 30.7]	206	18 (8.7) [5.3, 13.5]
SOC: Metabolism and nutrition disorders	52	15 (28.8) [17.1, 43.1]	30	4 (13.3) [3.8, 30.7]	206	48 (23.3) [17.7, 29.7]
Fluid overload	52	1 (1.9) [0.0, 10.3]	30	1 (3.3) [0.1, 17.2]	206	18 (8.7) [5.3, 13.5]
Hyperkalaemia	52	7 (13.5) [5.6, 25.8]	30	2 (6.7) [0.8, 22.1]	206	16 (7.8) [4.5, 12.3]
SOC: Musculoskeletal and connective tissue disorders	52	17 (32.7) [20.3, 47.1]	30	4 (13.3) [3.8, 30.7]	206	39 (18.9) [13.8, 25.0]
Pain in extremity	52	5 (9.6) [3.2, 21.0]	30	1 (3.3) [0.1, 17.2]	206	10 (4.9) [2.4, 8.7]
SOC: Nervous system disorders	52	22 (42.3) [28.7, 56.8]	30	7 (23.3) [9.9, 42.3]	206	49 (23.8) [18.1, 30.2]
Dizziness	52	4 (7.7) [2.1, 18.5]	30	4 (13.3) [3.8, 30.7]	206	16 (7.8) [4.5, 12.3]
SOC: Psychiatric disorders	52	13 (25.0) [14.0, 38.9]	30	4 (13.3) [3.8, 30.7]	206	19 (9.2) [5.6, 14.0]
SOC: Respiratory, thoracic and mediastinal disorders	52	13 (25.0) [14.0, 38.9]	30	8 (26.7) [12.3, 45.9]	206	43 (20.9) [15.5, 27.1]
Dyspnoea	52	3 (5.8) [1.2, 15.9]	30	0 (0.0) [0.0, 11.6]	206	14 (6.8) [3.8, 11.1]
Respiratory failure	52	0 (0.0) [0.0, 6.8]	30	3 (10.0) [2.1, 26.5]	206	5 (2.4) [0.8, 5.6]

Note: SAF-L = Week 52 Safety set. Only events are displayed with an incidence of at least 10 percent in a treatment group or 10 patients with an incidence of at least 1 percent in a treatment group.

- 95% CI = 95% confidence interval according to Clopper Pearson. TEAE = treatment emergent adverse event. SOC = system organ class. PT = preferred term.
- Source Data: aae, created on: 12MAR2022

Table ET1LA_LMSO: TEAEs during OLP by SOC and PT SAF-L

		Pre: CR845 Pre: Placebo		Pre: De Novo		
TEAEs during OLP	N	n (%) [95 % CI]	N	n (%) [95 % CI]	N	n (%) [95 % CI]
SOC: Skin and subcutaneous tissue disorders	52	7 (13.5) [5.6, 25.8]	30	4 (13.3) [3.8, 30.7]	206	24 (11.7) [7.6, 16.8]
SOC: Vascular disorders	52	15 (28.8) [17.1, 43.1]	30	10 (33.3) [17.3, 52.8]	206	52 (25.2) [19.5, 31.7]
Hypertension	52	2 (3.8) [0.5, 13.2]	30	1 (3.3) [0.1, 17.2]	206	10(4.9) [2.4, 8.7]
Hypotension	52	10 (19.2) [9.6, 32.5]	30	6 (20.0) [7.7, 38.6]	206	21 (10.2) [6.4, 15.2]

Note: SAF-L = Week 52 Safety set. Only events are displayed with an incidence of at least 10 percent in a treatment group or 10 patients with an incidence of at least 1 percent in a treatment group.

N = total number of patients in analysis set. n = number of patients with events during OLP. OLP = open label period.

95% CI = 95% confidence interval according to Clopper Pearson. TEAE = treatment emergent adverse event. SOC = system organ class. PT = preferred term.

Source Data: aae, created on: 12MAR2022

Table ET1LA_CMSO: TEAEs during OLP by SOC and PT $${\rm SAF-C}$$

			Pre: CR845	45 Pre: Placebo		Pre: De Novo	
TEAEs	during OLP	N	n (%) [95 % CI]	N	n (%) [95 % CI]	N	n (%) [95 % CI]
101100	during obi		[30 % 01]		[50 % 01]		[50 % 01]
SOC: (Cardiac disorders	39	15 (38.5)	20	6 (30.0)	119	26 (21.8)
			[23.4, 55.4]		[11.9, 54.3]		[14.8, 30.4]
i	Acute myocardial infarction	39	5 (12.8)	20	1 (5.0)	119	3 (2.5)
			[4.3, 27.4]		[0.1, 24.9]		[0.5, 7.2]
i	Angina pectoris	39	4 (10.3)	20	2 (10.0)	119	4 (3.4)
			[2.9, 24.2]		[1.2, 31.7]		[0.9, 8.4]
]	Bradycardia	39	2 (5.1)	20	2 (10.0)	119	2 (1.7)
			[0.6, 17.3]		[1.2, 31.7]		[0.2, 5.9]
SOC:	Gastrointestinal disorders	39	20 (51.3)	20	11 (55.0)	119	46 (38.7)
			[34.8, 67.6]		[31.5, 76.9]		[29.9, 48.0]
i	Abdominal pain	39	4 (10.3)	20	3 (15.0)	119	6 (5.0)
			[2.9, 24.2]		[3.2, 37.9]		[1.9, 10.7]
Ĺ	Abdominal pain lower	39	0 (0.0)	20	2 (10.0)	119	0 (0.0)
			[0.0, 9.0]		[1.2, 31.7]		[0.0, 3.1]
]	Diarrhoea	39	9 (23.1)	20	6 (30.0)	119	19 (16.0)
			[11.1, 39.3]		[11.9, 54.3]		[9.9, 23.8]
]	Faeces discoloured	39	0 (0.0)	20	2 (10.0)	119	0 (0.0)
			[0.0, 9.0]		[1.2, 31.7]		[0.0, 3.1]
]	Haemorrhoids	39	1 (2.6)	20	2 (10.0)	119	1 (0.8)
			[0.1, 13.5]		[1.2, 31.7]		[0.0, 4.6]
]	Nausea	39	11 (28.2)	20	5 (25.0)	119	22 (18.5)
		20	[15.0, 44.9]	20	[8.7, 49.1]	110	[12.0, 26.6]
	Vomiting	39	8 (20.5)	20	4 (20.0)	119	14 (11.8)
			[9.3, 36.5]		[5.7, 43.7]		[6.6, 19.0]
SOC: (General disorders and	39	21 (53.8)	20	5 (25.0)	119	33 (27.7)
i	administration site conditions		[37.2, 69.9]		[8.7, 49.1]		[19.9, 36.7]
i	Asthenia	39	4 (10.3)	20	2 (10.0)	119	4 (3.4)
			[2.9, 24.2]		[1.2, 31.7]		[0.9, 8.4]
]	Fatigue	39	2 (5.1)	20	2 (10.0)	119	4 (3.4)
			[0.6, 17.3]		[1.2, 31.7]		[0.9, 8.4]
	Infusion site extravasation	39	4 (10.3)	20	2 (10.0)	119	2 (1.7)
			[2.9, 24.2]		[1.2, 31.7]		[0.2, 5.9]
1	Non-cardiac chest pain	39	7 (17.9)	20	1 (5.0)	119	16 (13.4)
			[7.5, 33.5]		[0.1, 24.9]		[7.9, 20.9]

Note: SAF-C = Week 52 Study Completer Set. Only events are displayed with an incidence of at least 10 percent in a treatment group or 10 patients with an incidence of at least 1 percent in a treatment group.

- 95% CI = 95% confidence interval according to Clopper Pearson. TEAE = treatment emergent adverse event. SOC = system organ class. PT = preferred term.
- Source Data: aae, created on: 12MAR2022

Table ET1LA_CMSO: TEAEs during OLP by SOC and PT $${\rm SAF-C}$$

	_	Pre: CR845	Р	re: Placebo	Pre: De Novo	
TEAEs during OLP	N	n (%) [95 % CI]	N	n (%) [95 % CI]	N	n (%) [95 % CI]
Pain	39	1 (2.6) [0.1, 13.5]	20	2 (10.0) [1.2, 31.7]	119	2 (1.7) [0.2, 5.9]
SOC: Immune system disorders	39	4 (10.3) [2.9, 24.2]	20	2 (10.0) [1.2, 31.7]	119	1 (0.8) [0.0, 4.6]
SOC: Infections and infestations	39	17 (43.6) [27.8, 60.4]	20	7 (35.0) [15.4, 59.2]	119	59 (49.6) [40.3, 58.9]
Upper respiratory tract infection	39	1 (2.6) [0.1, 13.5]	20	0 (0.0) [0.0, 16.8]	119	10 (8.4) [4.1, 14.9]
Viral upper respiratory tract infection	39	2 (5.1) [0.6, 17.3]	20	2 (10.0) [1.2, 31.7]	119	8 (6.7) [2.9, 12.8]
SOC: Injury, poisoning and procedural complications	39	17 (43.6) [27.8, 60.4]	20	6 (30.0) [11.9, 54.3]	119	43 (36.1) [27.5, 45.4]
Fall	39	10 (25.6) [13.0, 42.1]	20	5 (25.0) [8.7, 49.1]	119	18 (15.1) [9.2, 22.8]
SOC: Investigations	39	4 (10.3) [2.9, 24.2]	20	3 (15.0) [3.2, 37.9]	119	14 (11.8) [6.6, 19.0]
SOC: Metabolism and nutrition disorders	39	12 (30.8) [17.0, 47.6]	20	3 (15.0) [3.2, 37.9]	119	28 (23.5) [16.2, 32.2]
Fluid overload	39	1 (2.6) [0.1, 13.5]	20	1 (5.0) [0.1, 24.9]	119	10 (8.4) [4.1, 14.9]
Hyperkalaemia	39	5 (12.8) [4.3, 27.4]	20	1 (5.0) [0.1, 24.9]	119	10 (8.4) [4.1, 14.9]
SOC: Musculoskeletal and connective tissue disorders	39	16 (41.0) [25.6, 57.9]	20	3 (15.0) [3.2, 37.9]	119	32 (26.9) [19.2, 35.8]
Arthralgia	39	4 (10.3) [2.9, 24.2]	20	2 (10.0) [1.2, 31.7]	119	7 (5.9) [2.4, 11.7]
Muscle spasms	39	4 (10.3) [2.9, 24.2]	20	0 (0.0) [0.0, 16.8]	119	4 (3.4) [0.9, 8.4]
Pain in extremity	39	5 (12.8) [4.3, 27.4]	20	1 (5.0) [0.1, 24.9]	119	7 (5.9) [2.4, 11.7]

Note: SAF-C = Week 52 Study Completer Set. Only events are displayed with an incidence of at least 10 percent in a treatment group or 10 patients with an incidence of at least 1 percent in a treatment group.

- 95% CI = 95% confidence interval according to Clopper Pearson. TEAE = treatment emergent adverse event. SOC = system organ class. PT = preferred term.
- Source Data: aae, created on: 12MAR2022

Table ET1LA_CMSO: TEAEs during OLP by SOC and PT $_{\rm SAF-C}$

		Pre: CR845 Pre: Placebo		re: Placebo	Pre: De Novo	
		n (%)		n (%)		n (%)
TEAEs during OLP	N	[95 % CI]	Ν	[95 % CI]	Ν	[95 % CI]
		15 (00 5)	~~~		440	
SOC: Nervous system disorders	39	15 (38.5) [23.4, 55.4]	20	6 (30.0) [11.9, 54.3]	119	31 (26.1) [18.4, 34.9]
Dizziness	39	2 (5.1)	20	4 (20.0)	119	11 (9.2)
		[0.6, 17.3]		[5.7, 43.7]		[4.7, 15.9]
Syncope	39	4 (10.3)	20	1 (5.0)	119	5 (4.2)
		[2.9, 24.2]		[0.1, 24.9]		[1.4, 9.5]
SOC: Psychiatric disorders	39	11 (28.2)	20	3 (15.0)	119	14 (11.8)
-		[15.0, 44.9]		[3.2, 37.9]		[6.6, 19.0]
Anxiety	39	5 (12.8)	20	0 (0.0)	119	2 (1.7)
		[4.3, 27.4]		[0.0, 16.8]		[0.2, 5.9]
Depression	39	2 (5.1)	20	2 (10.0)	119	1 (0.8)
		[0.6, 17.3]		[1.2, 31.7]		[0.0, 4.6]
Mental status changes	39	4 (10.3)	20	1 (5.0)	119	6 (5.0)
		[2.9, 24.2]		[0.1, 24.9]		[1.9, 10.7]
SOC: Renal and urinary disorders	39	2 (5.1)	20	2 (10.0)	119	3 (2.5)
		[0.6, 17.3]		[1.2, 31.7]		[0.5, 7.2]
SOC: Respiratory, thoracic and	39	7 (17.9)	20	7 (35.0)	119	29 (24.4)
mediastinal disorders		[7.5, 33.5]		[15.4, 59.2]		[17.0, 33.1]
Pulmonary oedema	39	1 (2.6)	20	2 (10.0)	119	2 (1.7)
-		[0.1, 13.5]		[1.2, 31.7]		[0.2, 5.9]
Respiratory failure	39	0 (0.0)	20	2 (10.0)	119	5 (4.2)
		[0.0, 9.0]		[1.2, 31.7]		[1.4, 9.5]
SOC: Skin and subcutaneous tissue	39	7 (17.9)	20	4 (20.0)	119	15 (12.6)
disorders		[7.5, 33.5]		[5.7, 43.7]		[7.2, 19.9]
Skin ulcer	39	0 (0.0)	20	2 (10.0)	119	1 (0.8)
		[0.0, 9.0]		[1.2, 31.7]		[0.0, 4.6]
SOC: Vascular disorders	39	13 (33.3)	20	5 (25.0)	119	35 (29.4)
		[19.1, 50.2]		[8.7, 49.1]		[21.4, 38.5]

Note: SAF-C = Week 52 Study Completer Set. Only events are displayed with an incidence of at least 10 percent in a treatment group or 10 patients with an incidence of at least 1 percent in a treatment group.

- 95% CI = 95% confidence interval according to Clopper Pearson. TEAE = treatment emergent adverse event. SOC = system organ class. PT = preferred term.
- Source Data: aae, created on: 12MAR2022

	Pre: CR845 Pre: Placebo n (%) n (%) N [95 % CI] N [95 % CI]		Pı	ce: De Novo		
TEAEs during OLP					N	n (%) [95 % CI]
Hypotension	39	9 (23.1) [11.1, 39.3]	20	4 (20.0) [5.7, 43.7]	119	16 (13.4) [7.9, 20.9]

Table ET1LA_CMSO: TEAEs during OLP by SOC and PT $_{\rm SAF-C}$

Note: SAF-C = Week 52 Study Completer Set. Only events are displayed with an incidence of at least 10 percent in a treatment group or 10 patients with an incidence of at least 1 percent in a treatment group.

N = total number of patients in analysis set. n = number of patients with events during OLP. OLP = open label period.

95% CI = 95% confidence interval according to Clopper Pearson. TEAE = treatment emergent adverse event. SOC = system organ class. PT = preferred term.

Source Data: aae, created on: 12MAR2022

Table ET1LAEGN_LMI1:	AESI gait	disturbance -	non-severe	during	first	quarter	of	OLP
		SAF-L						

	I	Pre: CR845	P	re: Placebo	Pre: De Novo		
	N	n (%) [95 % CI]	N	n (%) [95 % CI]	N	n (%) [95 % CI]	
AESI gait disturbance - non-severe during OLP	52	0 (0.0) [0.0, 6.8]	30	0 (0.0) [0.0, 11.6]	206	0 (0.0) [0.0, 1.8]	

Table ET1LAEFN_LMI1: AESI falls/injuries - non-severe during first quarter of OLP SAF-L

		Pre: CR845	Р	re: Placebo	Pre: De Novo		
	N	n (%) [95 % CI]	N	n (%) [95 % CI]	N	n (%) [95 % CI]	
AESI falls/injuries - non-severe during OLP	52	6 (11.5) [4.4, 23.4]	30	2 (6.7) [0.8, 22.1]	206	10(4.9) [2.4, 8.7]	

Table ET1LAEVN_LMI1:	AESI	dizziness	-	non-severe	during	first	quarter	of	OLP
			SA	F-L					

		Pre: CR845		845 Pre: Placebo		re: De Novo
		n (%)		n (%)		n (%)
	N	[95 % CI]	N	[95 % CI]	N	[95 % CI]
AESI dizziness - non-severe during	52	3 (5.8)	30	0 (0.0)	206	8 (3.9)
OLP		[1.2, 15.9]		[0.0, 11.6]		[1.7, 7.5]

Table	ET1LAEYN_	LMI1:	AESI	syncope	-	non-severe	during	first	quarter	of	OLP
					S	SAF-L					

		Pre: CR845		re: Placebo	Pre: De Novo		
	N	n (%) [95 % CI]	N	n (%) [95 % CI]	N	n (%) [95 % CI]	
AESI syncope - non-severe during	52	2 (3.8)	30	0 (0.0)	206	1 (0.5)	
OLP	52	[0.5, 13.2]	50	[0.0, 11.6]	200	[0.0, 2.7]	

Table ET1LAEON_LMI1:	AESI	somnolence -	non-severe	during	first	quarter	of	OLP
		SAI	F-L					

]	Pre: CR845		Pre: Placebo		e: De Novo
	N	n (%)	N	n (%)	NT	n (%)
	N	[95 % CI]	N	[95 % CI]	11	[95 % CI]
AESI somnolence - non-severe during	52	0 (0.0)	30	0 (0.0)	206	2 (1.0)
OLP		[0.0, 6.8]		[0.0, 11.6]		[0.1, 3.5]

Table ET1LAEKN_LMI1:	AESI	seizures	-	non-severe	during	first	quarter	of	OLP	
			Si	AF-L						

	1	Pre: CR845	CR845 Pre: P		Pı	Pre: De Novo	
	21	n (%)		n (%)		n (%)	
	N	[95 % CI]	N	[95 % CI]	N	[95 % CI]	
AESI seizures - non-severe during	52	0 (0.0)	30	0 (0.0)	206	1 (0.5)	
OLP		[0.0, 6.8]		[0.0, 11.6]		[0.0, 2.7]	

Table ET1LAEMN_LMI1: AESI mental status change - non-severe during first quarter of OLP SAF-L

		Pre: CR845	Р	re: Placebo	Pı	re: De Novo
	N	n (%) [95 % CI]	N	n (%) [95 % CI]	N	n (%) [95 % CI]
AESI mental status	52	1 (1.9)	30	0 (0.0)	206	2 (1.0)
change - non-severe during OLP	01	[0.0, 10.3]	00	[0.0, 11.6]	200	[0.1, 3.5]

Table ET1LAEEN_LMI1: AESI mood change - non-severe during first quarter of OLP SAF-L

		Pre: CR845	Р	re: Placebo	Pre: De Novo		
	N	n (%) [95 % CI]	N	n (%) [95 % CI]	N	n (%) [95 % CI]	
AESI mood change - non-severe during OLP	52	2 (3.8) [0.5, 13.2]	30	0 (0.0) [0.0, 11.6]	206	1 (0.5) [0.0, 2.7]	

Table ET1LAEUN_LMI1: AESI unusual feeling/sensation - non-severe during first quarter of OLP SAF-L

	Pre: CR845		Pre: Placebo		Pr	e: De Novo
	N	n (%) [95 % CI]	N	n (%) [95 % CI]	N	n (%) [95 % CI]
AESI unusual feeling/sensation - non-severe during OLP	52	2 (3.8) [0.5, 13.2]	30	1 (3.3) [0.1, 17.2]	206	5 (2.4) [0.8, 5.6]

Table ET1LAERN_LMI1: AESI tachycardia/palpitation - non-severe during first quarter of OLP SAF-L

	Pre: CR845		Р	re: Placebo	Pre: De Novo		
	N	n (%) [95 % CI]	N	n (%) [95 % CI]	N	n (%) [95 % CI]	
AESI tachycardia/palpitation - non-severe during OLP	52	3 (5.8) [1.2, 15.9]	30	0 (0.0) [0.0, 11.6]	206	3 (1.5) [0.3, 4.2]	

Table ET1LAEGN_LMIO: AESI gait disturbance - non-severe during OLP SAF-L

	Pre: CR845		P	re: Placebo	Pre: De Novo	
	N	n (%) [95 % CI]	N	n (%) [95 % CI]	N	n (%) [95 % CI]
AESI gait disturbance - non-severe during OLP	52	0 (0.0) [0.0, 6.8]	30	0 (0.0) [0.0, 11.6]	206	0 (0.0) [0.0, 1.8]

Table ET1LAEFN_LMIO: AESI falls/injuries - non-severe during OLP SAF-L

		Pre: CR845	Р	re: Placebo	Pre: De Novo	
	N	n (%) [95 % CI]	N	n (%) [95 % CI]	N	n (%) [95 % CI]
- AESI falls/injuries - non-severe during OLP	52	13 (25.0) [14.0, 38.9]	30	6 (20.0) [7.7, 38.6]	206	28 (13.6) [9.2, 19.0]

Table ET1LAEVN_LMIO: AESI dizziness - non-severe during OLP SAF-L

		Pre: CR845	Р	re: Placebo	Pre: De Novo		
	N	n (%) [95 % CI]	N	n (%) [95 % CI]	N	n (%) [95 % CI]	
AESI dizziness - non-severe during OLP	52	4 (7.7) [2.1, 18.5]	30	4 (13.3) [3.8, 30.7]	206	15 (7.3) [4.1, 11.7]	

Table ET1LAEYN_LMIO: AESI syncope - non-severe during OLP SAF-L

	n (%) 95 % CI] N [n (%) [95 % CI]
	55 % CI N [
AESI syncope - non-severe during 52 5 (9.6) 30 OLP [3.2, 21.0] [0	1 (3.3) 206	4 (1.9) 0.5, 4.9]

Table ET1LAEON_LMIO: AESI somnolence - non-severe during OLP SAF-L

		Pre: CR845	P	re: Placebo	Pre: De Novo		
	N	n (%) [95 % CI]	N	n (%) [95 % CI]	N	n (%) [95 % CI]	
AESI somnolence - non-severe during OLP	52	$\begin{array}{c} 1 & (1.9) \\ [0.0, \ 10.3] \end{array}$	30	0 (0.0) [0.0, 11.6]	206	2(1.0) [0.1, 3.5]	

Table ET1LAEKN_LMIO: AESI seizures - non-severe during OLP SAF-L

		Pre: CR845	P	re: Placebo	Pr	e: De Novo
	N	n (%) [95 % CI]	N	n (%) [95 % CI]	N	n (%) [95 % CI]
AESI seizures - non-severe during	52	2 (3.8)	30	0 (0.0)	206	2 (1.0)
OLP		[0.5, 13.2]		[0.0, 11.6]		[0.1, 3.5]

Table ET1LAEMN_LMIO: AESI mental status change - non-severe during OLP SAF-L

		Pre: CR845		re: Placebo	Pre: De Novo	
	N	n (%) [95 % CI]	Ν	n (%) [95 % CI]	N	n (%) [95 % CI]
AESI mental status	52	8 (15.4)	30	1 (3.3)	206	11 (5.3)
change - non-severe during OLP	56	[6.9, 28.1]	50	[0.1, 17.2]	200	[2.7, 9.4]

Table ET1LAEEN_LMIO: AESI mood change - non-severe during OLP SAF-L

		Pre: CR845		re: Placebo	Pre: De Novo	
	N	n (%) [95 % CI]	N	n (%) [95 % CI]	N	n (%) [95 % CI]
AESI mood change - non-severe during OLP	52	5 (9.6) [3.2, 21.0]	30	0 (0.0) [0.0, 11.6]	206	3 (1.5) [0.3, 4.2]

Table	ET1LAEUN_LMIO:	AESI	unusual	feeling/sensation	-	non-severe	during	OLP
				SAF-L				

		Pre: CR845	Р	re: Placebo	Pre: De Novo		
	N	n (%) [95 % CI]	N	n (%) [95 % CI]	N	n (%) [95 % CI]	
AESI unusual	52	5 (9.6)	30	2 (6.7)	206	11 (5.3)	
feeling/sensation - non-severe during OLP	52	[3.2, 21.0]	50	[0.8, 22.1]	200	[2.7, 9.4]	

Table ET1LAERN_LMIO:	AESI	tachycardia/palpitation	_	non-severe	during	OLP
		SAF-L				

		Pre: CR845		re: Placebo	Pre: De Novo		
	N	n (%) N [95 % CI]		n (%) [95 % CI]	n (%) N [95 % CI]		
AESI tachycardia/palpitation - non-severe during OLP	52	5 (9.6) [3.2, 21.0]	30	1 (3.3) [0.1, 17.2]	206	4 (1.9) [0.5, 4.9]	

Table ET1LAEGN_CMIO: AESI gait disturbance - non-severe during OLP SAF-C

	I	Pre: CR845 Pre: Placebo Pre: De Novo		e: De Novo		
	N	n (%) [95 % CI]	N	n (%) [95 % CI]	N	n (%) [95 % CI]
AESI gait disturbance - non-severe during OLP	39	0 (0.0) [0.0, 9.0]	20	0 (0.0) [0.0, 16.8]	119	0 (0.0) [0.0, 3.1]

Table ET1LAEFN_CMIO: AESI falls/injuries - non-severe during OLP SAF-C

		Pre: CR845 Pre: Placebo Pre: De Novo		re: De Novo		
	N	n (%) [95 % CI]	N	n (%) [95 % CI]	N	n (%) [95 % CI]
AESI falls/injuries - non-severe	39	11 (28.2)	20	5 (25.0)	119	19 (16.0)
during OLP		[15.0, 44.9]		[8.7, 49.1]		[9.9, 23.8]

Table ET1LAEVN_CMIO: AESI dizziness - non-severe during OLP SAF-C

		Pre: CR845	Р	re: Placebo	Pı	re: De Novo
	N	n (%) [95 % CI]	N	n (%) [95 % CI]	N	n (%) [95 % CI]
AESI dizziness - non-severe during	39	2 (5.1)	20	4 (20.0)	119	11 (9.2)
OLP		[0.6, 17.3]		[5.7, 43.7]		[4.7, 15.9]

Table ET1LAEYN_CMIO: AESI syncope - non-severe during OLP SAF-C

		Pre: CR845 Pre: Placebo Pre: De Novo		e: De Novo		
	N	n (%) [95 % CI]	Ν	n (%) [95 % CI]	N	n (%) [95 % CI]
AESI syncope - non-severe during	39	4 (10.3)	20	1 (5.0)	119	3 (2.5)
OLP	55	[2.9, 24.2]	20	[0.1, 24.9]	117	[0.5, 7.2]

Table ET1LAEON_CMIO: AESI somnolence - non-severe during OLP SAF-C

	Pre: CR845 Pre: Placebo Pre: De Novo		re: De Novo			
	N	n (%) [95 % CI]	N	n (%) [95 % CI]	N	n (%) [95 % CI]
AESI somnolence - non-severe during OLP	39	1 (2.6) [0.1, 13.5]	20	0 (0.0) [0.0, 16.8]	119	0 (0.0) [0.0, 3.1]

Table ET1LAEKN_CMIO: AESI seizures - non-severe during OLP SAF-C

		Pre: CR845	Р	re: Placebo	Pı	ce: De Novo
	N	n (%) [95 % CI]	N	n (%) [95 % CI]	N	n (%) [95 % CI]
AESI seizures - non-severe during	39	2 (5.1)	20	0 (0.0)	119	1 (0.8)
OLP		[0.6, 17.3]		[0.0, 16.8]		[0.0, 4.6]

Table ET1LAEMN_CMIO: AESI mental status change - non-severe during OLP SAF-C

		Pre: CR845 Pre: Placebo Pre: De Novo		re: De Novo		
	N	n (%) [95 % CI]	Ν	n (%) [95 % CI]	N	n (%) [95 % CI]
AESI mental status	39	7 (17.9)	20	1 (5.0)	119	8 (6.7)
change - non-severe during OLP	05	[7.5, 33.5]	20	[0.1, 24.9]	110	[2.9, 12.8]

Table ET1LAEEN_CMIO: AESI mood change - non-severe during OLP SAF-C

		Pre: CR845	Р	re: Placebo	Pr	e: De Novo
	N	n (%) [95 % CI]	N	n (%) [95 % CI]	N	n (%) [95 % CI]
AESI mood change - non-severe during OLP	39	5 (12.8) [4.3, 27.4]	20	0 (0.0) [0.0, 16.8]	119	3 (2.5) [0.5, 7.2]

Table ET1LAEUN_CMIO:	AESI	unusual	feeling/sensation	_	non-severe during C)LP
			SAF-C			

	Pre: CR845		Р	re: Placebo	Pr	Pre: De Novo	
	N	n (%) [95 % CI]	N	n (%) [95 % CI]	N	n (%) [95 % CI]	
AESI unusual feeling/sensation - non-severe during OLP	39	4 (10.3) [2.9, 24.2]	20	2 (10.0) [1.2, 31.7]	119	5 (4.2) [1.4, 9.5]	

Table	ET1LAERN_	CMIO:	AESI	tachycardia/palpitation	- non-se	evere	during	OLP
				SAF-C				

]	Pre: CR845		Pre: Placebo		ce: De Novo
	N	n (%) [95 % CI]	N	n (%) [95 % CI]	N	n (%) [95 % CI]
AESI tachycardia/palpitation - non-severe during OLP	39	5 (12.8) [4.3, 27.4]	20	0 (0.0) [0.0, 16.8]	119	1 (0.8) [0.0, 4.6]