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

Inhaltsverzeichnis Anhang 4-I

Anhang 4-I-1:
Zusatzauswertungen der Studie KALM-1 (OL)

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
		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
		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
		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
		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
		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

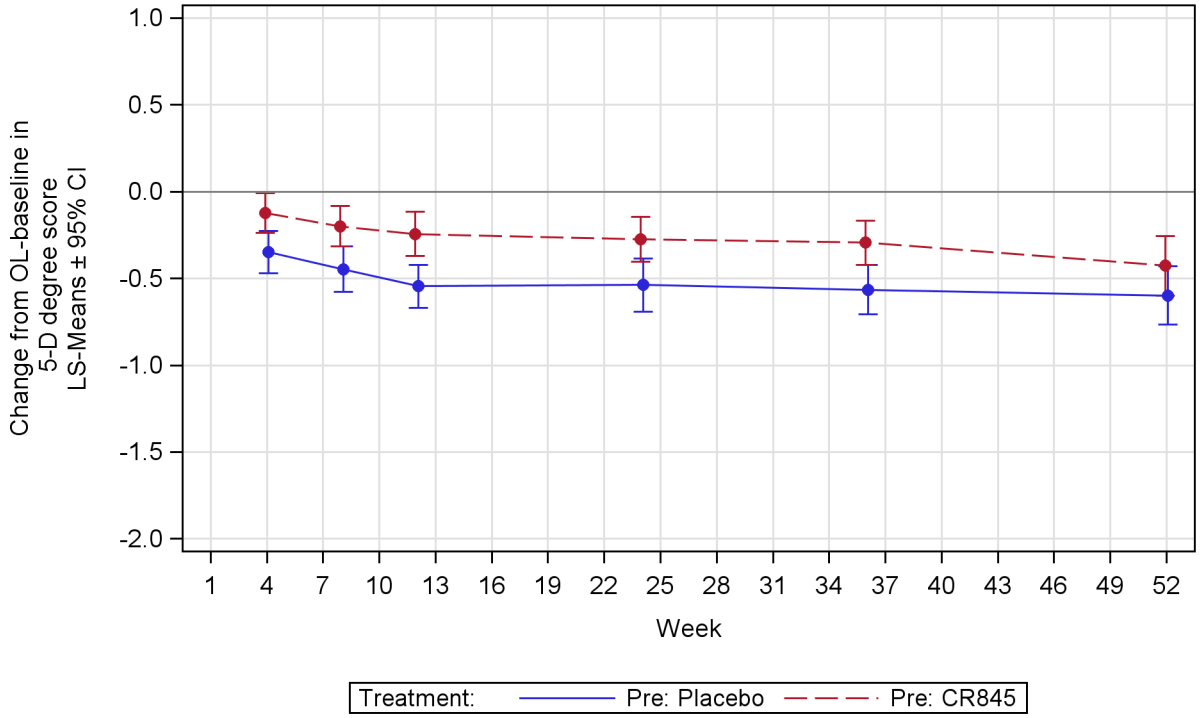
Note: SAF-L = Week 52 Safety set.
N = total number of patients in analysis set. n = number of evaluable values. SD = standard deviation. Q = quantile.
Source Data: afived, created on: 07MAR2022

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

Change from OL-baseline in 5-D degree score				Repeated measures analysis	
				Change from Baseline	
Time	Treatment	N	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.
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.
Source Data: afived, created on: 07MAR2022

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



Pre: Placebo	152	150	142	130	123	94
Pre: CR845	146	141	134	126	121	92

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
Source Data: afived, created on: 07MAR2022

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

		Treatment	N	n (%)	Mean (SD)	Min	Q50	Max
5-D duration score	OL Baseline	Pre: CR845	151	151 (100.0)	1.7 (1.0)	1	1.0	5
		Pre: Placebo	162	162 (100.0)	2.2 (1.3)	1	2.0	5
	OL Week 4	Pre: CR845	151	146 (96.7)	1.5 (0.9)	1	1.0	5
		Pre: Placebo	162	152 (93.8)	1.8 (1.2)	1	1.0	5
	OL Week 8	Pre: CR845	151	141 (93.4)	1.4 (0.9)	1	1.0	5
		Pre: Placebo	162	150 (92.6)	1.7 (1.1)	1	1.0	5
	OL Week 12	Pre: CR845	151	134 (88.7)	1.4 (0.8)	1	1.0	5
		Pre: Placebo	162	142 (87.7)	1.7 (1.1)	1	1.0	5
	OL Week 24	Pre: CR845	151	125 (82.8)	1.5 (0.9)	1	1.0	5
		Pre: Placebo	162	130 (80.2)	1.7 (1.1)	1	1.0	5
	OL Week 36	Pre: CR845	151	120 (79.5)	1.4 (0.8)	1	1.0	5
		Pre: Placebo	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

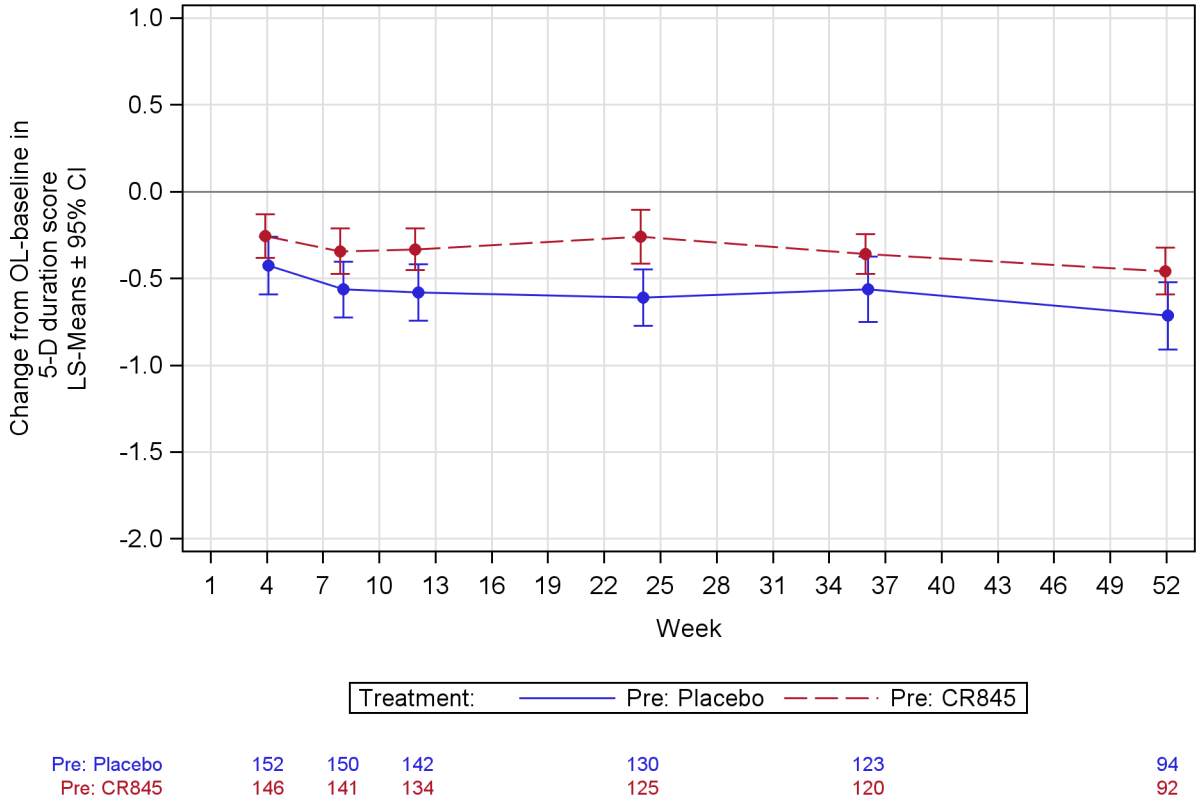
Note: SAF-L = Week 52 Safety set.
N = total number of patients in analysis set. n = number of evaluable values. SD = standard deviation. Q = quantile.
Source Data: afived, created on: 07MAR2022

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

Change from OL-baseline in 5-D duration score				Repeated measures analysis	
				Change from 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)	-0.4 (0.1)	(-0.6, -0.3)
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.
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.
Source Data: afived, created on: 07MAR2022

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



Pre: Placebo	152	150	142	130	123	94
Pre: CR845	146	141	134	125	120	92

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
Source Data: afived, created on: 07MAR2022

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

		Treatment	N	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
		Pre: Placebo	162	162 (100.0)	2.9 (1.0)	1	3.0	5
	OL Week 4	Pre: CR845	151	146 (96.7)	2.5 (0.9)	1	2.0	5
		Pre: Placebo	162	152 (93.8)	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

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Table CT3DWO_LMD0: Change from OL-baseline in 5-D direction score - LSMEANS confidence intervals
SAF-L

Change from OL-baseline in 5-D direction score				Repeated measures analysis	
				Change from 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.
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.
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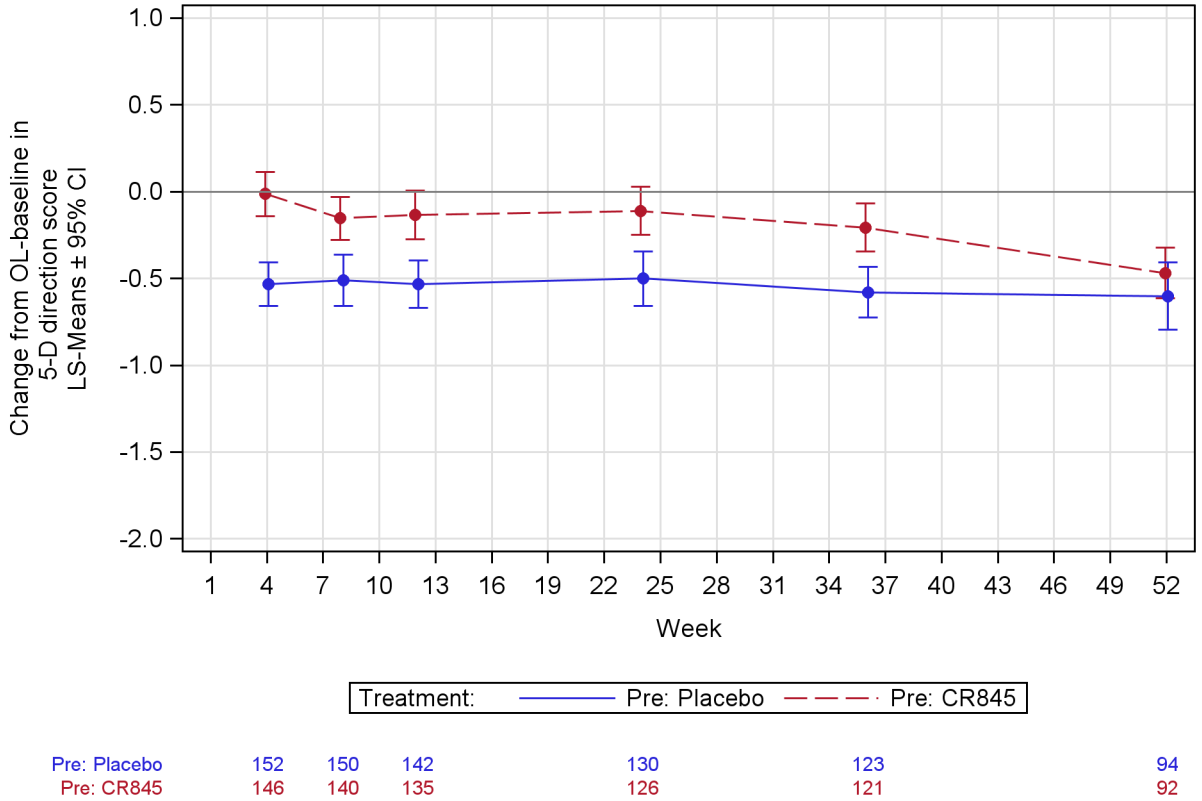
Figure CF3DWO_LMG0: Change from OL-baseline in 5-D direction score - Course of LSMEANS
SAF-L



Pre: Placebo	152	150	142	130	123	94
Pre: CR845	146	140	135	126	121	92

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
		Pre: Placebo	162	162 (100.0)	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
		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.
N = total number of patients in analysis set. n = number of evaluable values. SD = standard deviation. Q = quantile.
Source Data: afived, created on: 07MAR2022

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

Change from OL-baseline in 5-D disability score				Repeated measures analysis	
				Change from Baseline	
Time	Treatment	N	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)	-0.5 (0.1)	(-0.7, -0.3)
OL 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.
N = total number of patients in analysis set. n = number of non-missing values. MMRM = mixed repeated measures model.
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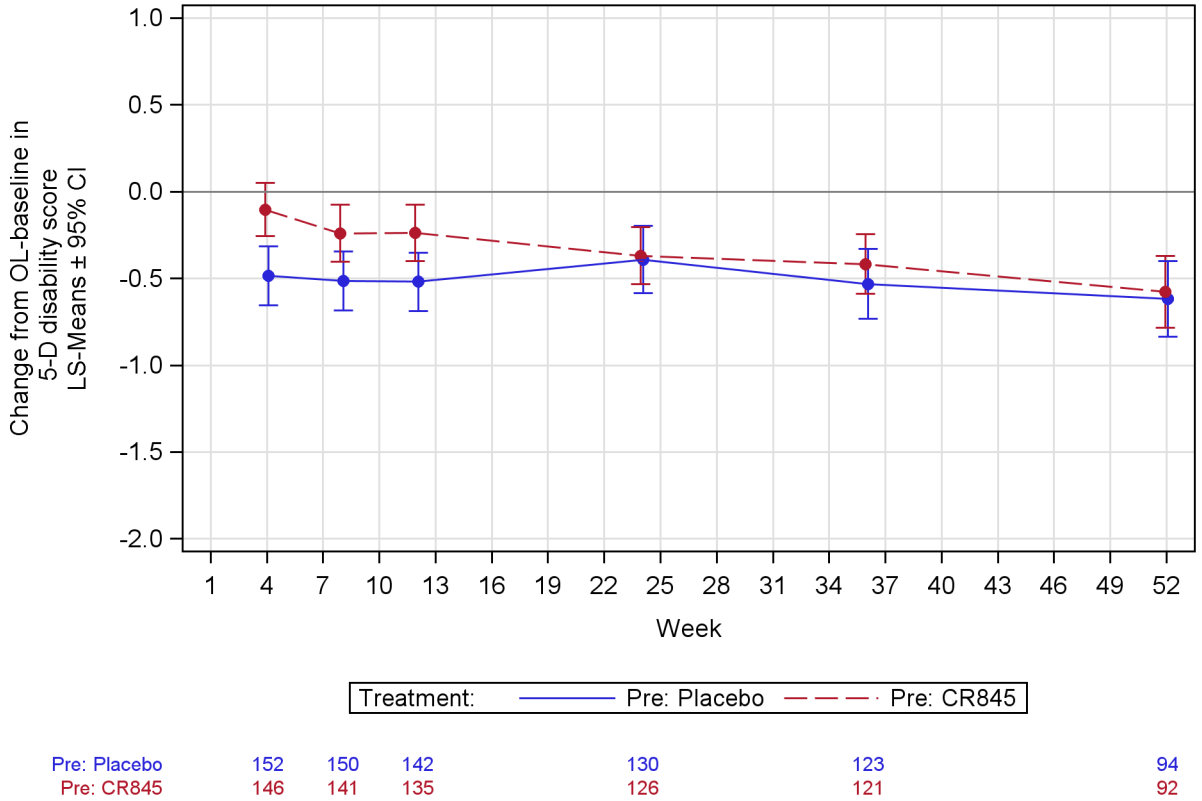
Figure CF3DNO_LMG0: Change from OL-baseline in 5-D disability score - Course of LSMEANS
SAF-L



Pre: Placebo	152	150	142	130	123	94
Pre: CR845	146	141	135	126	121	92

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
Source Data: afived, created on: 07MAR2022

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

		Treatment	N	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
		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

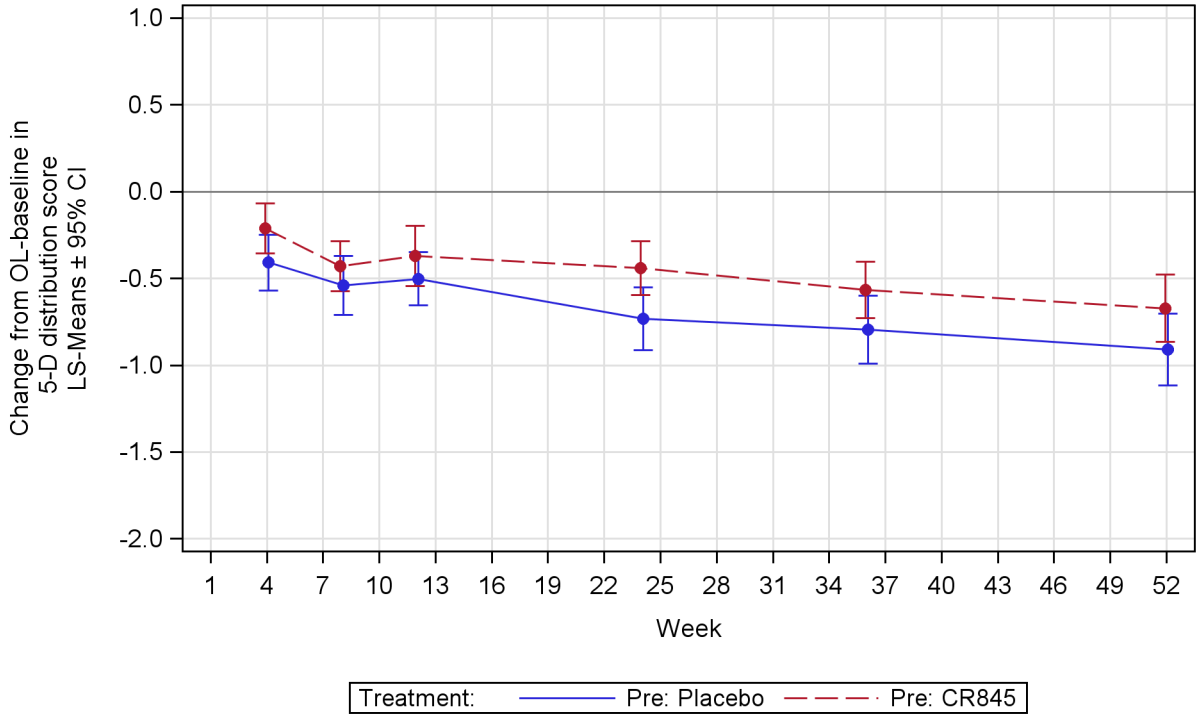
Note: SAF-L = Week 52 Safety set.
N = total number of patients in analysis set. n = number of evaluable values. SD = standard deviation. Q = quantile.
Source Data: afived, created on: 07MAR2022

Table CT3DVO_LMD0: Change from OL-baseline in 5-D distribution score - LSMEANS confidence intervals
SAF-L

Change from OL-baseline in 5-D distribution score				Repeated measures analysis	
				Change from 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.
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.
Source Data: afived, created on: 07MAR2022

Figure CF3DVO_LMG0: Change from OL-baseline in 5-D distribution score - Course of LSMEANS
SAF-L



Pre: Placebo	152	150	142	130	123	94
Pre: CR845	146	141	135	126	122	92

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
Source Data: afived, created on: 07MAR2022

Table CT3DDO_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	122	122 (100.0)	2.5 (0.8)	1	2.0	5
		Pre: Placebo	122	122 (100.0)	2.9 (0.9)	1	3.0	5
	OL Week 4	Pre: CR845	122	121 (99.2)	2.3 (0.8)	1	2.0	5
		Pre: Placebo	122	117 (95.9)	2.5 (0.8)	1	2.0	5
	OL Week 8	Pre: CR845	122	119 (97.5)	2.3 (0.8)	1	2.0	5
		Pre: Placebo	122	119 (97.5)	2.4 (0.8)	1	2.0	5
	OL Week 12	Pre: CR845	122	119 (97.5)	2.3 (0.8)	1	2.0	5
		Pre: Placebo	122	116 (95.1)	2.3 (0.8)	1	2.0	4
	OL Week 24	Pre: CR845	122	119 (97.5)	2.2 (0.8)	1	2.0	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
		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

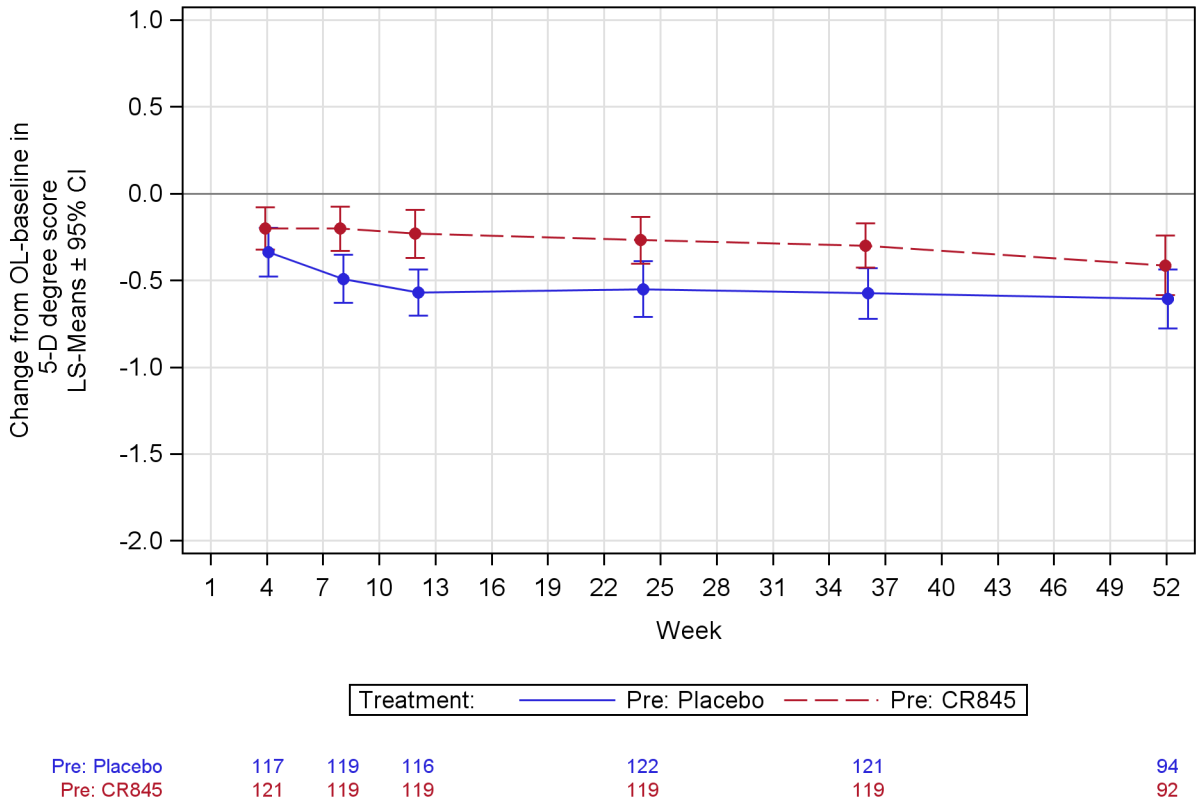
Note: SAF-C = Week 52 Study Completer Set.
N = total number of patients in analysis set. n = number of evaluable values. SD = standard deviation. Q = quantile.
Source Data: afived, created on: 07MAR2022

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

Change from OL-baseline in 5-D degree score				Repeated measures analysis	
				Change from 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.
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.
Source Data: afived, created on: 07MAR2022

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
Source Data: afived, created on: 07MAR2022

Table CT3DLO_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	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

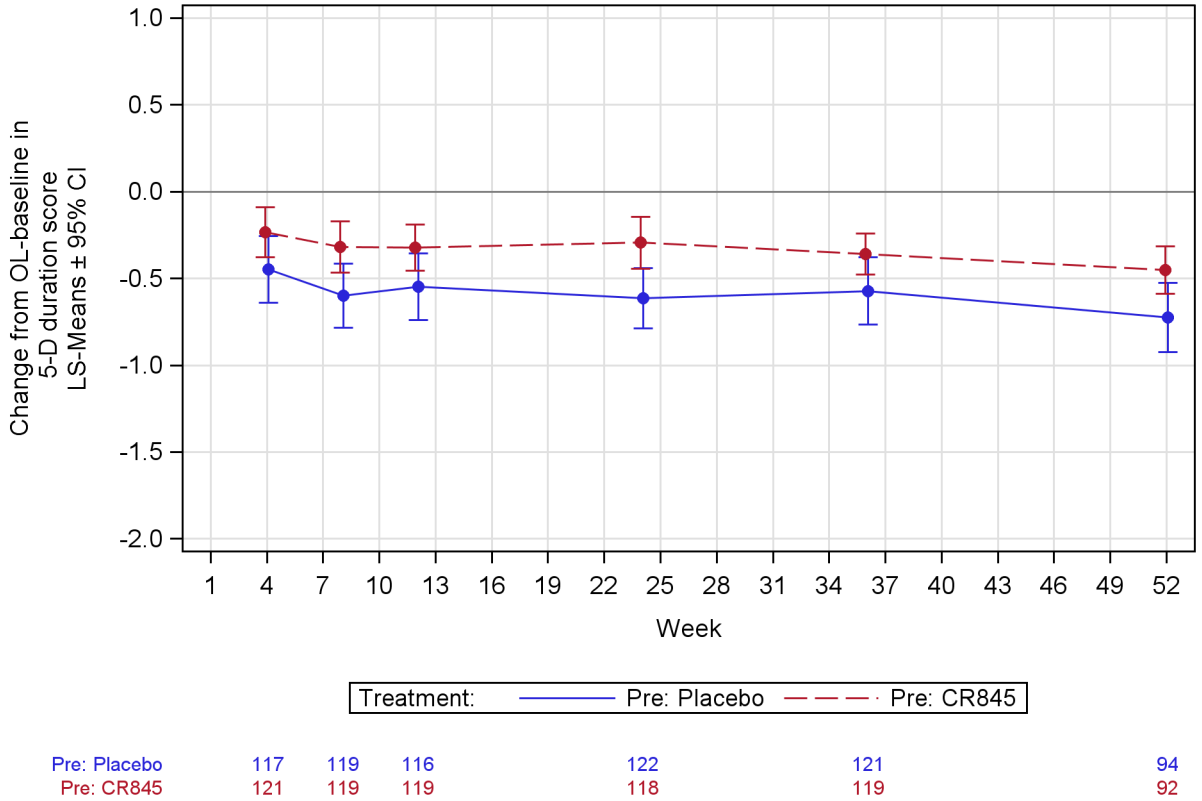
Note: SAF-C = Week 52 Study Completer Set.
N = total number of patients in analysis set. n = number of evaluable values. SD = standard deviation. Q = quantile.
Source Data: afived, created on: 07MAR2022

Table CT3DLO_CMD0: Change from OL-baseline in 5-D duration score - LSMEANS confidence intervals
SAF-C

Change from OL-baseline in 5-D duration score				Repeated measures analysis	
				Change from 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)	-0.4 (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.
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.
Source Data: afived, created on: 07MAR2022

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



Pre: Placebo	117	119	116	122	121	94
Pre: CR845	121	119	119	118	119	92

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
Source Data: afived, created on: 07MAR2022

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	122	122 (100.0)	2.5 (0.8)	1	2.0	5
		Pre: Placebo	122	122 (100.0)	2.9 (1.0)	1	3.0	5
	OL Week 4	Pre: CR845	122	121 (99.2)	2.4 (0.9)	1	2.0	5
		Pre: Placebo	122	117 (95.9)	2.4 (0.8)	1	2.0	5
	OL Week 8	Pre: CR845	122	118 (96.7)	2.3 (0.8)	1	2.0	5
		Pre: Placebo	122	119 (97.5)	2.4 (0.9)	1	2.0	5
	OL Week 12	Pre: CR845	122	120 (98.4)	2.4 (0.9)	1	2.0	5
		Pre: Placebo	122	116 (95.1)	2.4 (0.9)	1	2.0	5
	OL Week 24	Pre: CR845	122	119 (97.5)	2.4 (0.8)	1	2.0	5
		Pre: Placebo	122	122 (100.0)	2.4 (0.9)	1	2.0	5
	OL Week 36	Pre: CR845	122	119 (97.5)	2.3 (0.8)	1	2.0	5
		Pre: Placebo	122	121 (99.2)	2.3 (0.9)	1	2.0	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

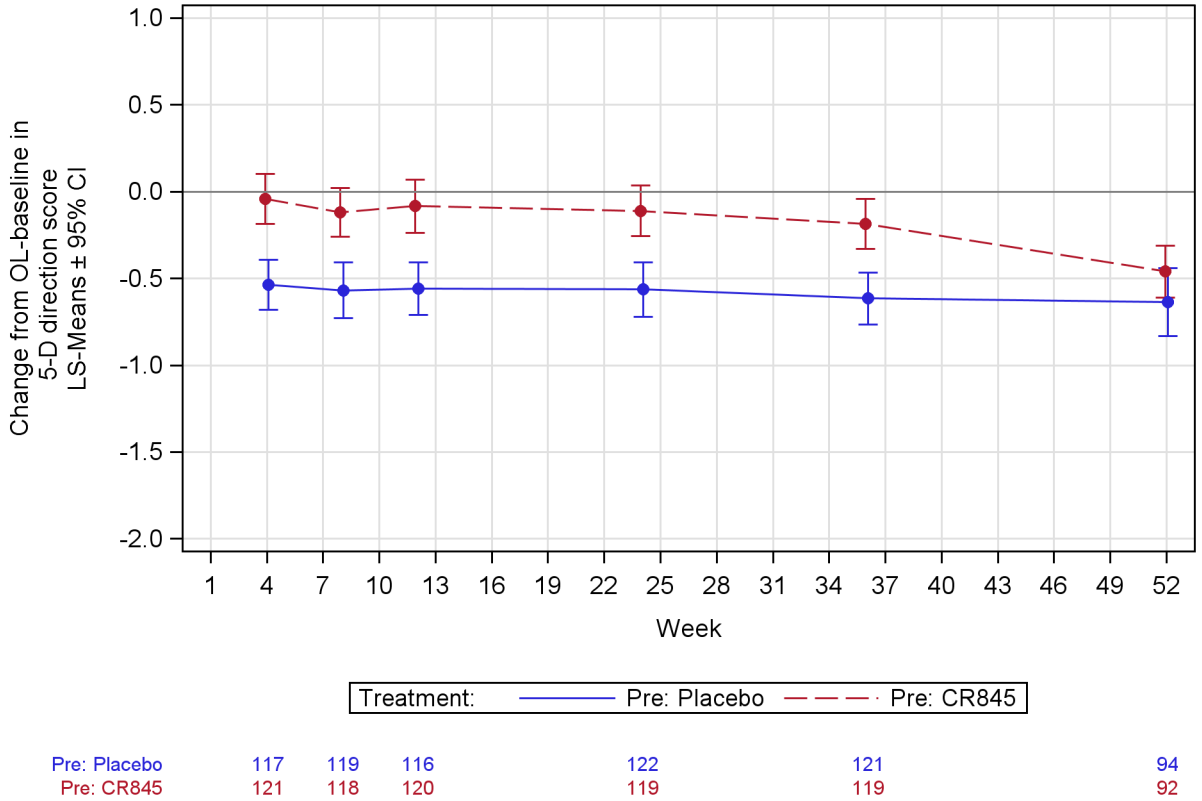
Note: SAF-C = Week 52 Study Completer Set.
N = total number of patients in analysis set. n = number of evaluable values. SD = standard deviation. Q = quantile.
Source Data: afived, created on: 07MAR2022

Table CT3DWO_CMD0: Change from OL-baseline in 5-D direction score - LSMEANS confidence intervals
SAF-C

Change from OL-baseline in 5-D direction score				Repeated measures analysis	
				Change from 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)
	Pre: Placebo	122	117 (95.9)	-0.5 (0.1)	(-0.7, -0.4)
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.
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.
Source Data: afived, created on: 07MAR2022

Figure CF3DWO_CMG0: Change from OL-baseline in 5-D direction score - Course of LSMEANS
SAF-C



Pre: Placebo	117	119	116	122	121	94
Pre: CR845	121	118	120	119	119	92

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
Source Data: afived, created on: 07MAR2022

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

		Treatment	N	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
		Pre: Placebo	122	122 (100.0)	2.8 (1.2)	1	3.0	5
	OL Week 4	Pre: CR845	122	121 (99.2)	2.4 (1.2)	1	2.0	5
		Pre: Placebo	122	117 (95.9)	2.3 (1.1)	1	2.0	5
	OL Week 8	Pre: CR845	122	119 (97.5)	2.2 (1.2)	1	2.0	5
		Pre: Placebo	122	119 (97.5)	2.2 (1.1)	1	2.0	5
	OL Week 12	Pre: CR845	122	120 (98.4)	2.3 (1.2)	1	2.0	5
		Pre: Placebo	122	116 (95.1)	2.2 (1.1)	1	2.0	5
	OL Week 24	Pre: CR845	122	119 (97.5)	2.1 (1.1)	1	2.0	5
		Pre: Placebo	122	122 (100.0)	2.3 (1.2)	1	2.0	5
	OL Week 36	Pre: CR845	122	119 (97.5)	2.1 (1.1)	1	2.0	5
		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
		Pre: Placebo	122	94 (77.0)	2.2 (1.2)	1	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

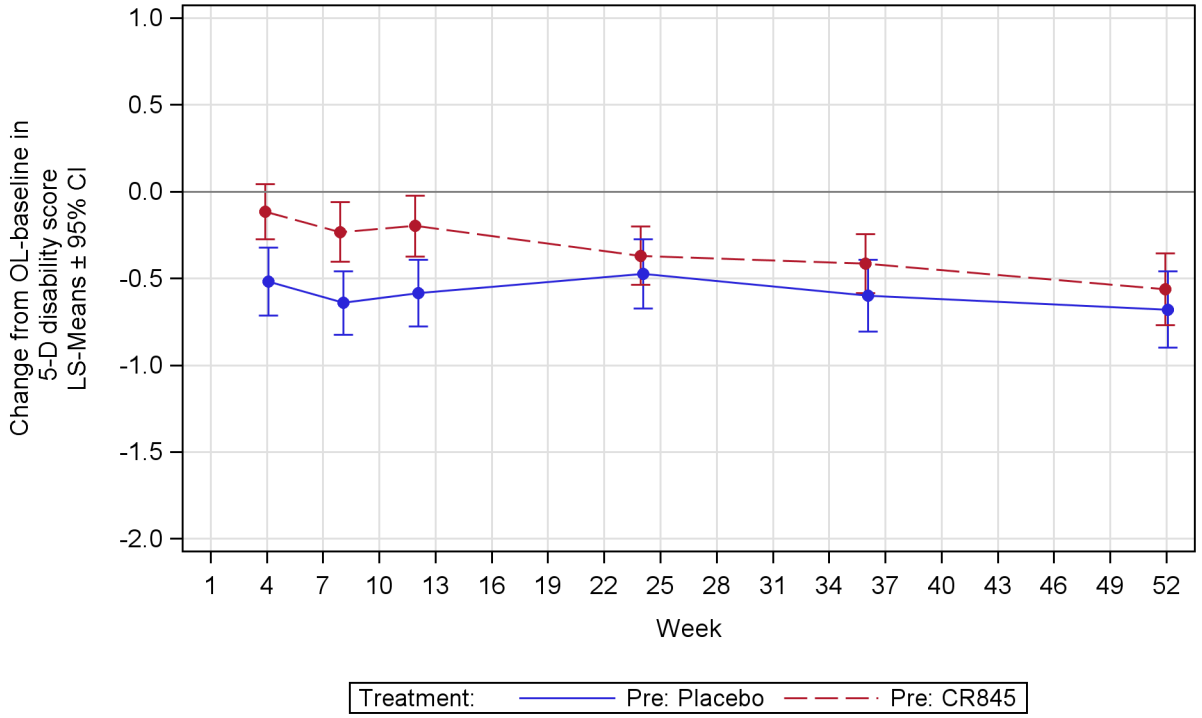
Note: SAF-C = Week 52 Study Completer Set.
N = total number of patients in analysis set. n = number of evaluable values. SD = standard deviation. Q = quantile.
Source Data: afived, created on: 07MAR2022

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

Change from OL-baseline in 5-D disability score				Repeated measures analysis	
				Change from Baseline	
Time	Treatment	N	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	119 (97.5)	-0.2 (0.1)	(-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)
	Pre: Placebo	122	116 (95.1)	-0.6 (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)
	Pre: Placebo	122	94 (77.0)	-0.7 (0.1)	(-0.9, -0.5)

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.
Source Data: afived, created on: 07MAR2022

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



Pre: Placebo	117	119	116	122	121	94
Pre: CR845	121	119	120	119	119	92

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
Source Data: afived, created on: 07MAR2022

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

		Treatment	N	n (%)	Mean (SD)	Min	Q50	Max
5-D distribution score	OL Baseline	Pre: CR845	122	122 (100.0)	2.7 (1.2)	1	3.0	5
		Pre: Placebo	122	122 (100.0)	3.2 (1.2)	1	3.0	5
	OL Week 4	Pre: CR845	122	121 (99.2)	2.5 (1.2)	1	2.0	5
		Pre: Placebo	122	117 (95.9)	2.8 (1.3)	1	3.0	5
	OL Week 8	Pre: CR845	122	119 (97.5)	2.4 (1.2)	1	2.0	5
		Pre: Placebo	122	119 (97.5)	2.6 (1.3)	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 (1.2)	1	3.0	5
	OL Week 24	Pre: CR845	122	119 (97.5)	2.3 (1.2)	1	2.0	5
		Pre: Placebo	122	122 (100.0)	2.4 (1.2)	1	2.0	5
	OL Week 36	Pre: CR845	122	120 (98.4)	2.2 (1.2)	1	2.0	5
		Pre: Placebo	122	121 (99.2)	2.3 (1.2)	1	2.0	5
	OL Week 52	Pre: CR845	122	92 (75.4)	2.1 (1.1)	1	2.0	5
		Pre: Placebo	122	94 (77.0)	2.2 (1.2)	1	2.0	5
Change from OL-baseline in 5-D distribution score	OL Week 4	Pre: CR845	122	121 (99.2)	-0.2 (1.0)	-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

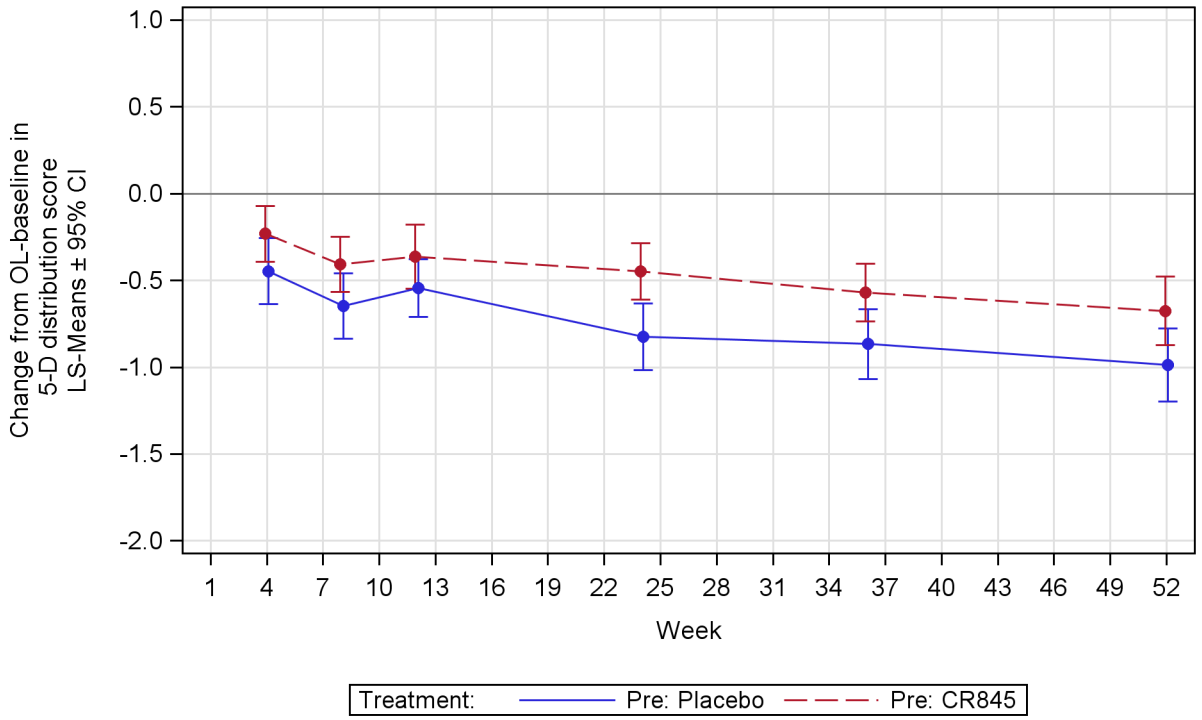
Note: SAF-C = Week 52 Study Completer Set.
N = total number of patients in analysis set. n = number of evaluable values. SD = standard deviation. Q = quantile.
Source Data: afived, created on: 07MAR2022

Table CT3DVO_CMD0: Change from OL-baseline in 5-D distribution score - LSMEANS confidence intervals
SAF-C

Change from OL-baseline in 5-D distribution score				Repeated measures analysis	
				Change from 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)	-0.4 (0.1)	(-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.
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.
Source Data: afived, created on: 07MAR2022

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



Pre: Placebo	117	119	116	122	121	94
Pre: CR845	121	119	120	119	120	92

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
Source Data: afived, created on: 07MAR2022

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

	Pre: CR845		Pre: 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]

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
SAF-L

	Pre: CR845		Pre: Placebo	
TEAEs during OLP	N	n (%) [95 % CI]	N	n (%) [95 % CI]
SOC: Vascular disorders	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

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

	Pre: CR845		Pre: 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]

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

TEAEs during OLP	Pre: CR845 N	Pre: CR845 n (%) [95 % CI]	Pre: Placebo N	Pre: Placebo 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

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

	Pre: CR845		Pre: Placebo	
TEAEs during OLP	N	n (%) [95 % CI]	N	n (%) [95 % CI]
Dyspnoea	151	19 (12.6) [7.7, 19.0]	162	15 (9.3) [5.3, 14.8]
Respiratory failure	151	6 (4.0) [1.5, 8.4]	162	12 (7.4) [3.9, 12.6]
SOC: Skin and subcutaneous tissue disorders	151	17 (11.3) [6.7, 17.4]	162	16 (9.9) [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

Table CT3LA_CMSO: TEAEs during OLP by SOC and PT
SAF-C

TEAEs during OLP	Pre: CR845 N	Pre: CR845 n (%) [95 % CI]	Pre: Placebo N	Pre: Placebo 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]

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 CT3LA_CMSO: TEAEs during OLP by SOC and PT
SAF-C

TEAEs during OLP	Pre: CR845 N	Pre: CR845 n (%) [95 % CI]	Pre: Placebo N	Pre: Placebo 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]

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 CT3LA_CMSO: TEAEs during OLP by SOC and PT
SAF-C

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

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

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. AESI = adverse event of special interest.
Source Data: aae, created on: 03MAR2022

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

	Pre: CR845		Pre: Placebo	
	N	n (%) [95 % CI]	N	n (%) [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]

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. AESI = adverse event of special interest.
Source Data: aae, created on: 03MAR2022

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) [1.9, 9.3]	162	4 (2.5) [0.7, 6.2]

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. AESI = adverse event of special interest.
Source Data: aae, created on: 03MAR2022

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]

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. AESI = adverse event of special interest.
Source Data: aae, created on: 03MAR2022

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]

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. AESI = adverse event of special interest.
Source Data: aae, created on: 03MAR2022

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]

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. AESI = adverse event of special interest.
Source Data: aae, created on: 03MAR2022

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

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

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. AESI = adverse event of special interest.
Source Data: aae, created on: 03MAR2022

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 during OLP	151	4 (2.6) [0.7, 6.6]	162	1 (0.6) [0.0, 3.4]

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. AESI = adverse event of special interest.
Source Data: aae, created on: 03MAR2022

Table CT3LAEUN_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]
AESI unusual feeling/sensation - non-severe during OLP	151	1 (0.7) [0.0, 3.6]	162	0 (0.0) [0.0, 2.3]

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. AESI = adverse event of special interest.
Source Data: aae, created on: 03MAR2022

Table CT3LAERN_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	151	2 (1.3) [0.2, 4.7]	162	3 (1.9) [0.4, 5.3]

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. AESI = adverse event of special interest.
Source Data: aae, created on: 03MAR2022

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]

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. AESI = adverse event of special interest.
Source Data: aae, created on: 03MAR2022

Table CT3LAEFN_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 during OLP	151	25 (16.6) [11.0, 23.5]	162	28 (17.3) [11.8, 24.0]

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. AESI = adverse event of special interest.
Source Data: aae, created on: 03MAR2022

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]

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. AESI = adverse event of special interest.
Source Data: aae, created on: 03MAR2022

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]

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. AESI = adverse event of special interest.
Source Data: aae, created on: 03MAR2022

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]

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. AESI = adverse event of special interest.
Source Data: aae, created on: 03MAR2022

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]

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. AESI = adverse event of special interest.
Source Data: aae, created on: 03MAR2022

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

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

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. AESI = adverse event of special interest.
Source Data: aae, created on: 03MAR2022

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 during OLP	151	7 (4.6) [1.9, 9.3]	162	5 (3.1) [1.0, 7.1]

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. AESI = adverse event of special interest.
Source Data: aae, created on: 03MAR2022

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

	Pre: CR845		Pre: Placebo	
	N	n (%) [95 % CI]	N	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]

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. AESI = adverse event of special interest.
Source Data: aae, created on: 03MAR2022

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

	Pre: CR845		Pre: Placebo	
	N	n (%) [95 % CI]	N	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]

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. AESI = adverse event of special interest.
Source Data: aae, created on: 03MAR2022

Table CT3LAEGN_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	122	0 (0.0) [0.0, 3.0]	122	1 (0.8) [0.0, 4.5]

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

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]

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 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]

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 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]

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 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]

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 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) [0.0, 3.0]	122	1 (0.8) [0.0, 4.5]

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

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

	Pre: CR845		Pre: Placebo	
	N	n (%) [95 % CI]	N	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]

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 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 during OLP	122	4 (3.3) [0.9, 8.2]	122	3 (2.5) [0.5, 7.0]

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

	Pre: CR845		Pre: Placebo	
	N	n (%) [95 % CI]	N	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

	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)

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 Baseline	Pre: CR845	189	189 (100.0)	2.6 (0.9)	1	2.0	5
		Pre: Placebo	210	210 (100.0)	2.8 (0.8)	1	3.0	5
	OL Week 4	Pre: CR845	189	173 (91.5)	2.5 (0.9)	1	2.0	5
		Pre: Placebo	210	200 (95.2)	2.3 (0.8)	1	2.0	5
	OL Week 8	Pre: CR845	189	140 (74.1)	2.4 (0.9)	1	2.0	5
		Pre: Placebo	210	162 (77.1)	2.3 (0.8)	1	2.0	5
	OL Week 12	Pre: CR845	189	137 (72.5)	2.3 (0.9)	1	2.0	5
		Pre: Placebo	210	158 (75.2)	2.3 (0.8)	1	2.0	5
	OL Week 24	Pre: CR845	189	71 (37.6)	2.2 (0.9)	1	2.0	5
		Pre: Placebo	210	76 (36.2)	2.2 (0.9)	1	2.0	5
	OL Week 36	Pre: CR845	189	23 (12.2)	2.2 (0.8)	1	2.0	4
		Pre: Placebo	210	30 (14.3)	2.3 (0.9)	1	2.0	4
	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 degree score	OL Week 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 Week 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 Week 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 Week 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 Week 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 Week 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

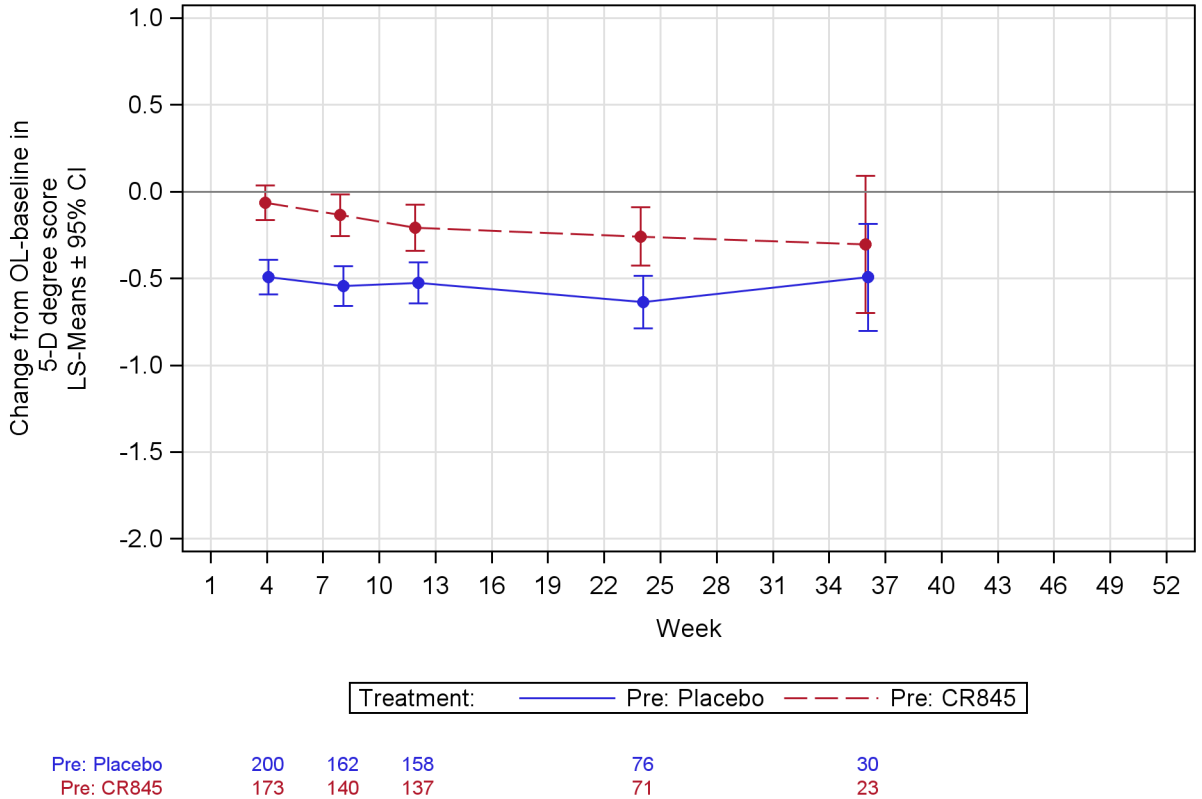
Note: SAF-L = Week 52 Safety set.
N = total number of patients in analysis set. n = number of evaluable values. SD = standard deviation. Q = quantile.
Source Data: afived, created on: 07MAR2022

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

Change from OL-baseline in 5-D degree score				Repeated measures analysis	
				Change from Baseline	
Time	Treatment	N	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)
OL 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)
OL 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)
OL 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.
Source Data: afived, created on: 07MAR2022

Figure DF3DDO_LMG0: Change from OL-baseline in 5-D degree score - Course of LSMEANS
SAF-L



Pre: Placebo	200	162	158	76	30
Pre: CR845	173	140	137	71	23

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
Source Data: afived, created on: 07MAR2022

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

		Treatment	N	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
		Pre: Placebo	210	210 (100.0)	1.9 (1.3)	1	2.0	5
	OL Week 4	Pre: CR845	189	170 (89.9)	1.7 (1.1)	1	1.0	5
		Pre: Placebo	210	200 (95.2)	1.5 (0.9)	1	1.0	5
	OL Week 8	Pre: CR845	189	140 (74.1)	1.6 (1.1)	1	1.0	5
		Pre: Placebo	210	162 (77.1)	1.4 (0.8)	1	1.0	5
	OL Week 12	Pre: CR845	189	137 (72.5)	1.6 (1.1)	1	1.0	5
		Pre: Placebo	210	158 (75.2)	1.4 (0.9)	1	1.0	5
	OL Week 24	Pre: CR845	189	70 (37.0)	1.4 (0.9)	1	1.0	5
		Pre: Placebo	210	76 (36.2)	1.4 (1.0)	1	1.0	5
	OL Week 36	Pre: CR845	189	24 (12.7)	1.2 (0.5)	1	1.0	3
		Pre: Placebo	210	31 (14.8)	1.2 (0.4)	1	1.0	2
	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

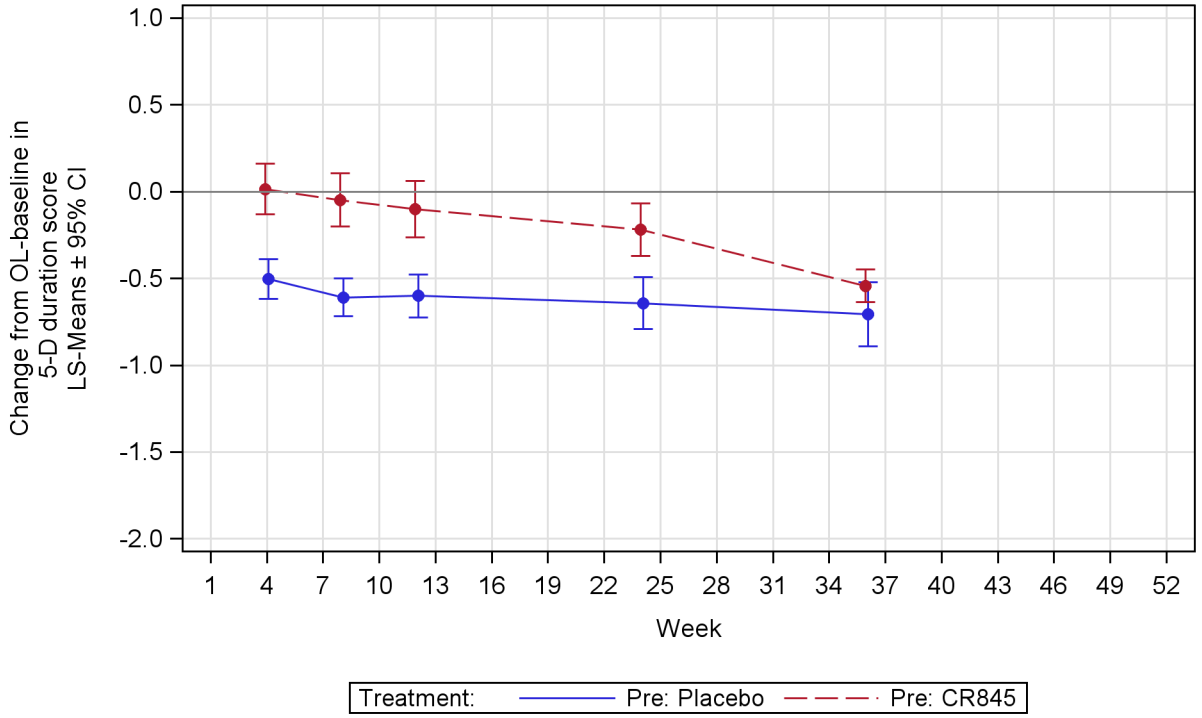
Note: SAF-L = Week 52 Safety set.
N = total number of patients in analysis set. n = number of evaluable values. SD = standard deviation. Q = quantile.
Source Data: afived, created on: 07MAR2022

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

				Repeated measures analysis	
Change from OL-baseline in 5-D duration score				Change from Baseline	
Time	Treatment	N	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.
Source Data: afived, created on: 07MAR2022

Figure DF3DLO_LMG0: Change from OL-baseline in 5-D duration score - Course of LSMEANS
SAF-L



Pre: Placebo	200	162	158	76	31
Pre: CR845	170	140	137	70	24

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
Source Data: afived, created on: 07MAR2022

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

		Treatment	N	n (%)	Mean (SD)	Min	Q50	Max
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

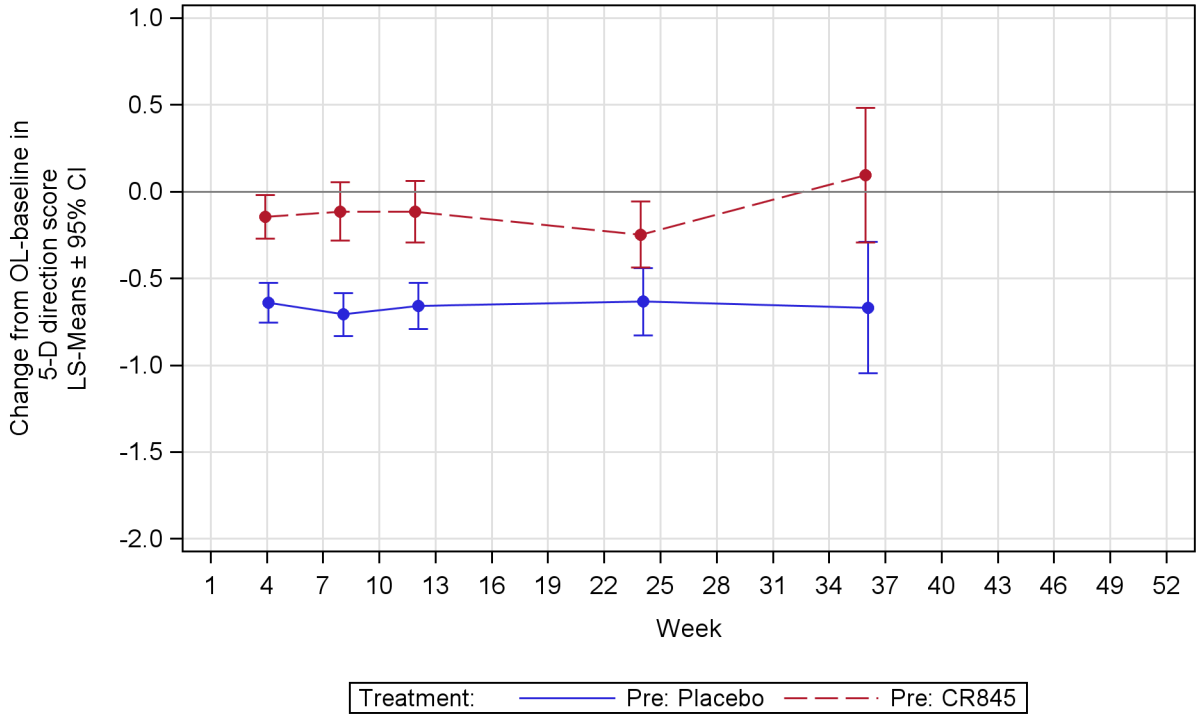
Note: SAF-L = Week 52 Safety set.
N = total number of patients in analysis set. n = number of evaluable values. SD = standard deviation. Q = quantile.
Source Data: afived, created on: 07MAR2022

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

Change from OL-baseline in 5-D direction score				Repeated measures analysis	
				Change from 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)
	Pre: Placebo	210	200 (95.2)	-0.6 (0.1)	(-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.
Source Data: afived, created on: 07MAR2022

Figure DF3DWO_LMG0: Change from OL-baseline in 5-D direction score - Course of LSMEANS
SAF-L



Pre: Placebo	200	162	158	76	30
Pre: CR845	172	140	137	71	23

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
Source Data: afived, created on: 07MAR2022

Table DT3DNO_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	189	189 (100.0)	2.4 (1.3)	1	2.0	5
		Pre: Placebo	210	210 (100.0)	2.5 (1.2)	1	2.0	5
	OL Week 4	Pre: CR845	189	173 (91.5)	2.3 (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)	2.0 (1.2)	1	2.0	5
		Pre: Placebo	210	162 (77.1)	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
		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
		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
		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
		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

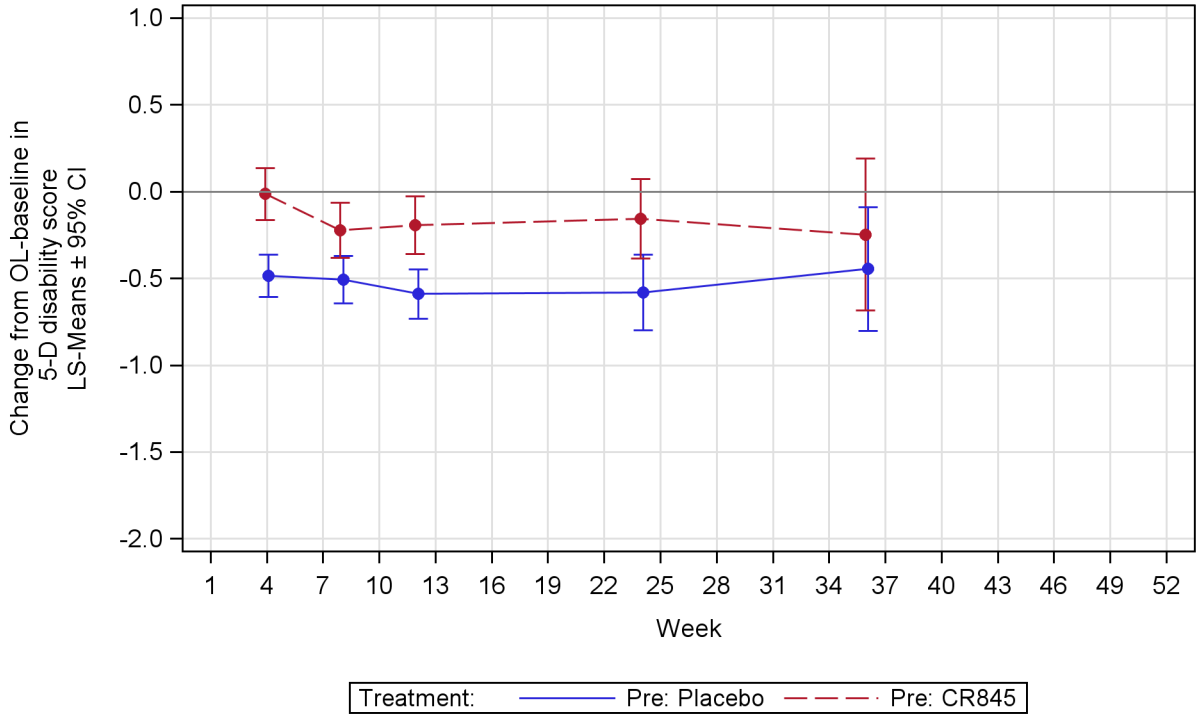
Note: SAF-L = Week 52 Safety set.
N = total number of patients in analysis set. n = number of evaluable values. SD = standard deviation. Q = quantile.
Source Data: afived, created on: 07MAR2022

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

Change from OL-baseline in 5-D disability score				Repeated measures analysis	
				Change from Baseline	
Time	Treatment	N	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.
Source Data: afived, created on: 07MAR2022

Figure DF3DNO_LMG0: Change from OL-baseline in 5-D disability score - Course of LSMEANS
SAF-L



Pre: Placebo	200	162	158	76	30
Pre: CR845	173	140	137	71	23

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
Source Data: afived, created on: 07MAR2022

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

		Treatment	N	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
		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

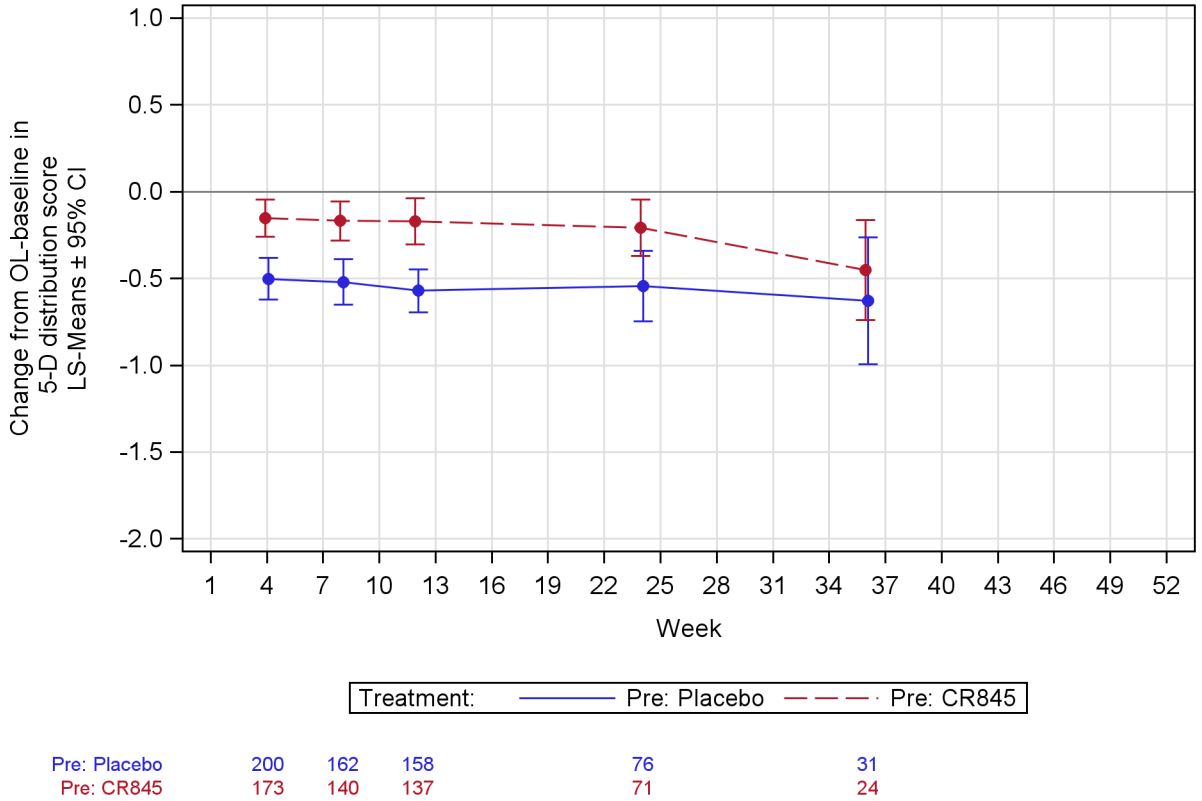
Note: SAF-L = Week 52 Safety set.
N = total number of patients in analysis set. n = number of evaluable values. SD = standard deviation. Q = quantile.
Source Data: afived, created on: 07MAR2022

Table DT3DVO_LMD0: Change from OL-baseline in 5-D distribution score - LSMEANS confidence intervals
SAF-L

Change from OL-baseline in 5-D distribution score				Repeated measures analysis	
				Change from Baseline	
Time	Treatment	N	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)	-0.5 (0.1)	(-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.
Source Data: afived, created on: 07MAR2022

Figure DF3DVO_LMG0: Change from OL-baseline in 5-D distribution 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. No display of Week 52 due to the low patient numbers.
Source Table: DT3DVO_LMD0
Source Data: afived, created on: 07MAR2022

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

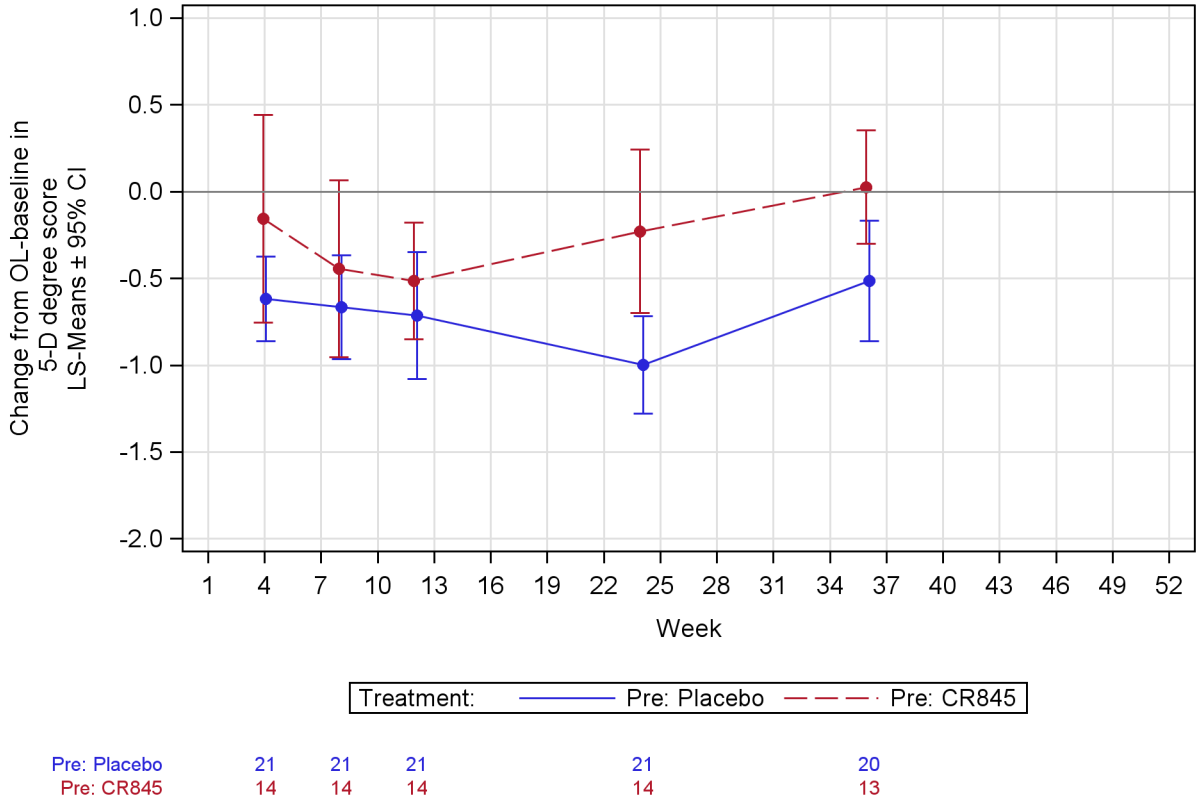
Note: SAF-C = Week 52 Study Completer Set.
N = total number of patients in analysis set. n = number of evaluable values. SD = standard deviation. Q = quantile.
Source Data: afived, created on: 07MAR2022

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

Change from OL-baseline in 5-D degree score				Repeated measures analysis	
				Change from Baseline	
Time	Treatment	N	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.
Source Data: afived, created on: 07MAR2022

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
Source Data: afived, created on: 07MAR2022

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

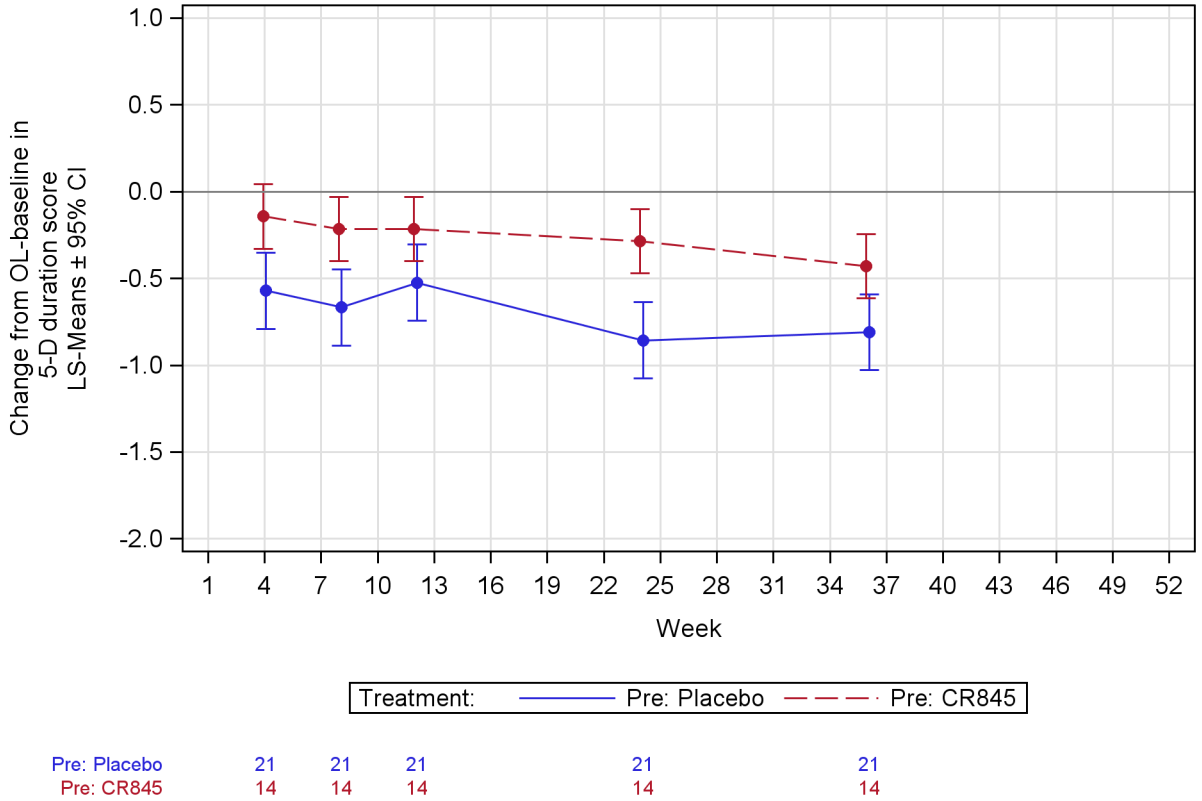
Note: SAF-C = Week 52 Study Completer Set.
N = total number of patients in analysis set. n = number of evaluable values. SD = standard deviation. Q = quantile.
Source Data: afived, created on: 07MAR2022

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

Change from OL-baseline in 5-D duration score				Repeated measures analysis	
				Change from Baseline	
Time	Treatment	N	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)
OL 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)
OL 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

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
Source Data: afived, created on: 07MAR2022

Table DT3DWO_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	14	14 (100.0)	2.4 (1.2)	1	2.0	5
		Pre: Placebo	21	21 (100.0)	3.0 (0.7)	2	3.0	4
	OL Week 4	Pre: CR845	14	14 (100.0)	2.0 (1.0)	1	2.0	4
		Pre: Placebo	21	21 (100.0)	2.3 (0.7)	1	2.0	4
	OL Week 8	Pre: CR845	14	14 (100.0)	1.9 (0.9)	1	2.0	4
		Pre: Placebo	21	21 (100.0)	2.1 (0.7)	1	2.0	3
	OL Week 12	Pre: CR845	14	14 (100.0)	1.9 (1.0)	1	2.0	4
		Pre: Placebo	21	21 (100.0)	2.1 (0.7)	1	2.0	4
	OL Week 24	Pre: CR845	14	14 (100.0)	2.1 (1.1)	1	2.0	4
		Pre: Placebo	21	21 (100.0)	2.0 (0.9)	1	2.0	5
	OL Week 36	Pre: CR845	14	13 (92.9)	2.5 (0.9)	2	2.0	4
		Pre: Placebo	21	20 (95.2)	2.3 (0.7)	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 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

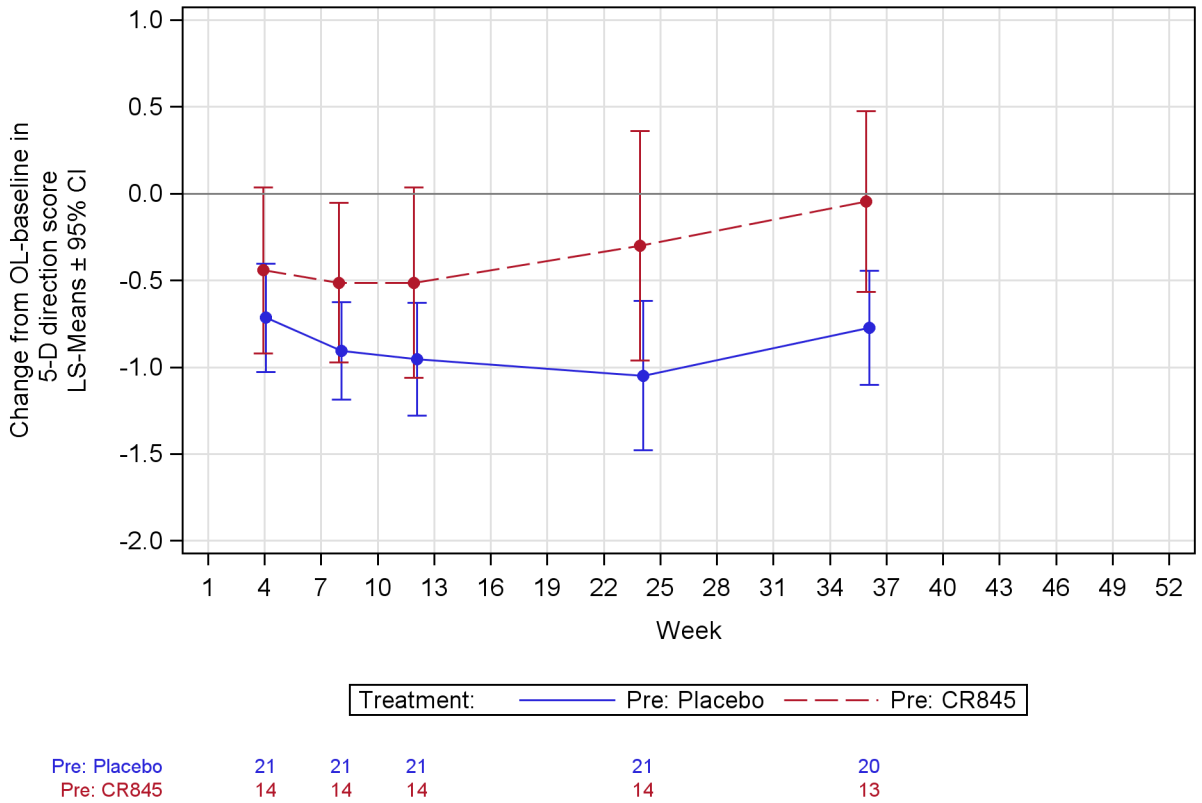
Note: SAF-C = Week 52 Study Completer Set.
N = total number of patients in analysis set. n = number of evaluable values. SD = standard deviation. Q = quantile.
Source Data: afived, created on: 07MAR2022

Table DT3DWO_CMD0: Change from OL-baseline in 5-D direction score - LSMEANS confidence intervals
SAF-C

Change from OL-baseline in 5-D direction score				Repeated measures analysis	
				Change from Baseline	
Time	Treatment	N	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.
Source Data: afived, created on: 07MAR2022

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
Source Data: afived, created on: 07MAR2022

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

		Treatment	N	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
		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
		Pre: Placebo	21	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	5
		Pre: Placebo	21	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
		Pre: Placebo	21	21 (100.0)	2.0 (0.9)	1	2.0	4
	OL Week 24	Pre: CR845	14	14 (100.0)	1.9 (1.5)	1	1.0	5
		Pre: Placebo	21	21 (100.0)	2.0 (1.0)	1	2.0	4
	OL Week 36	Pre: CR845	14	13 (92.9)	1.6 (1.1)	1	1.0	5
		Pre: Placebo	21	20 (95.2)	2.3 (1.0)	1	2.0	5
	OL Week 52	Pre: CR845	14	2 (14.3)	1.5 (0.7)	1	1.5	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

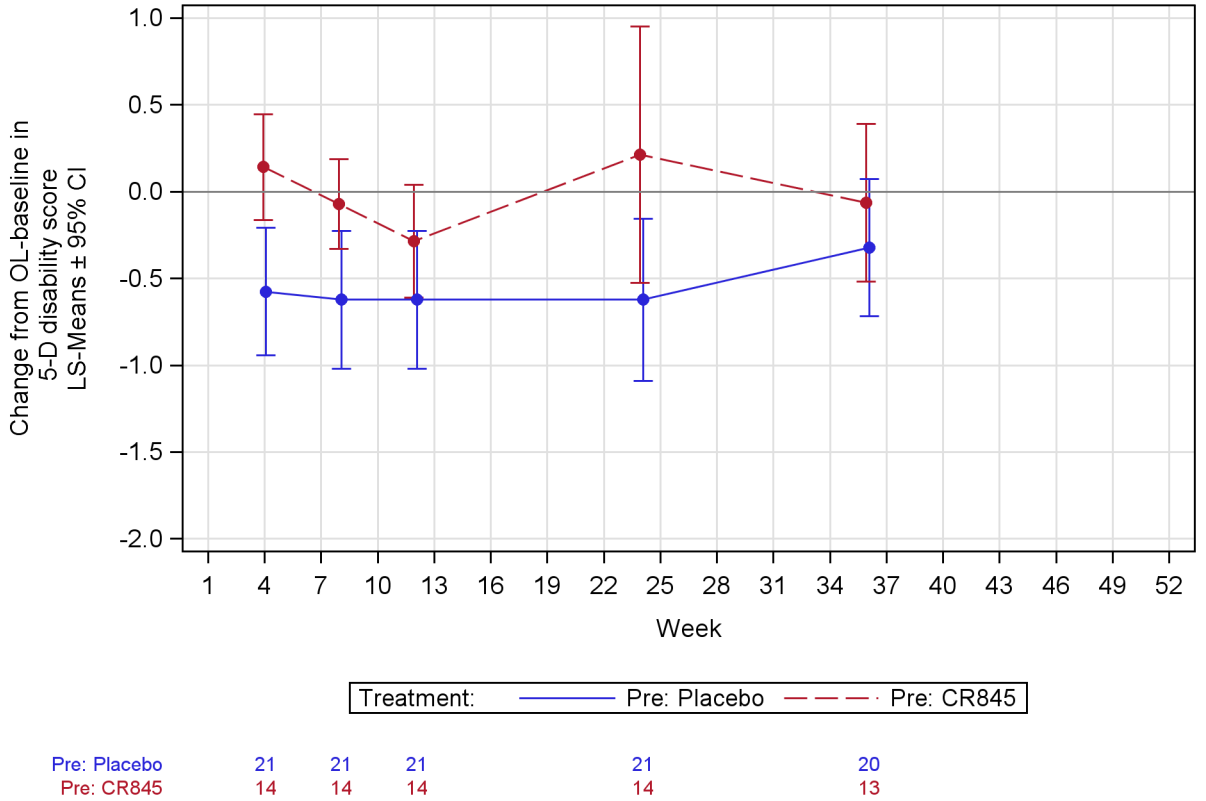
Note: SAF-C = Week 52 Study Completer Set.
N = total number of patients in analysis set. n = number of evaluable values. SD = standard deviation. Q = quantile.
Source Data: afived, created on: 07MAR2022

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

Change from OL-baseline in 5-D disability score				Repeated measures analysis	
				Change from Baseline	
Time	Treatment	N	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)
OL 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)
OL 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.
Source Data: afived, created on: 07MAR2022

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	N	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

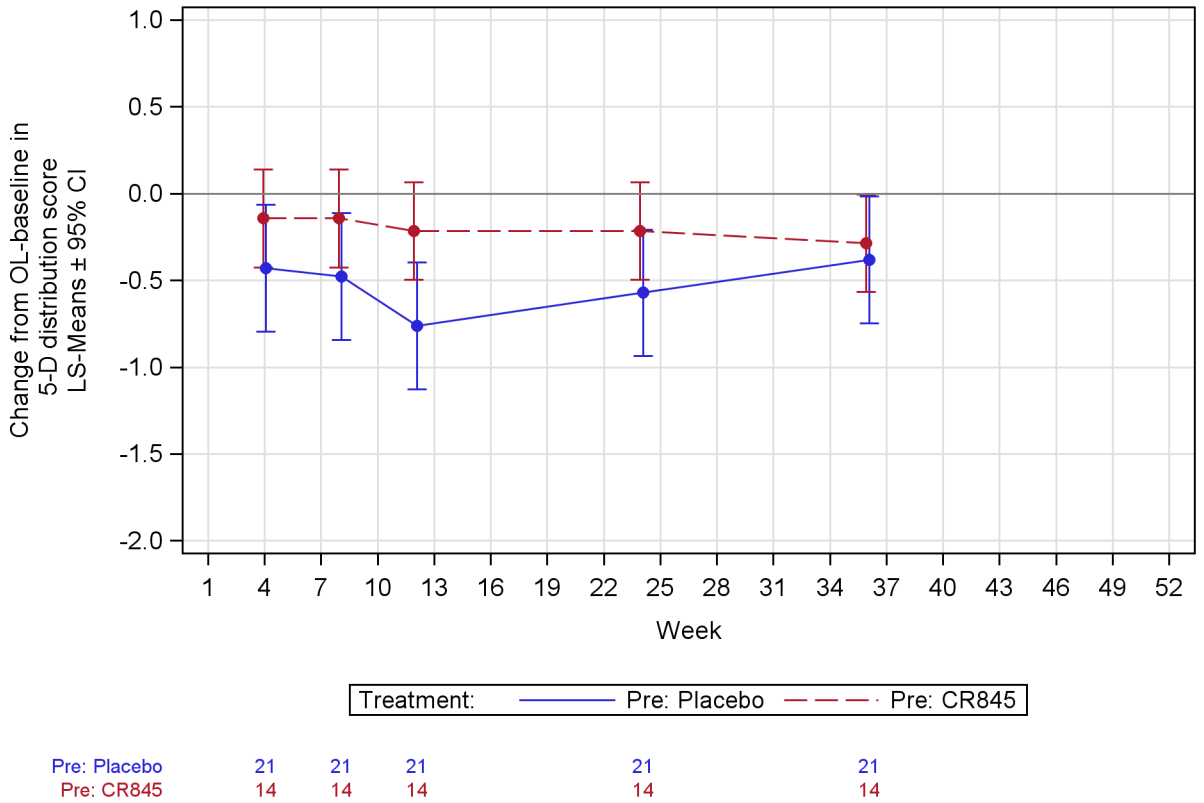
Note: SAF-C = Week 52 Study Completer Set.
N = total number of patients in analysis set. n = number of evaluable values. SD = standard deviation. Q = quantile.
Source Data: afived, created on: 07MAR2022

Table DT3DVO_CMD0: Change from OL-baseline in 5-D distribution score - LSMEANS confidence intervals
SAF-C

Change from OL-baseline in 5-D distribution score				Repeated measures analysis	
				Change from Baseline	
Time	Treatment	N	n (%)	LS-Mean (SE)	95% CI
OL 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)
OL 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)
OL 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)
OL 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)
OL 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
Source Data: afived, created on: 07MAR2022

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

TEAEs during OLP	Pre: CR845 N	Pre: CR845 n (%) [95 % CI]	Pre: Placebo N	Pre: Placebo 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	8 (4.2) [1.8, 8.2]	210	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]

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
SAF-L

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

Table DT3LA_LMSO: TEAEs during OLP by SOC and PT
SAF-L

TEAEs during OLP	Pre: CR845 N	Pre: CR845 n (%) [95 % CI]	Pre: Placebo N	Pre: Placebo 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 (3.3) [1.4, 6.7]
SOC: Musculoskeletal and connective tissue disorders	189	25 (13.2) [8.7, 18.9]	210	29 (13.8) [9.4, 19.2]

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: 03MAR2022

Table DT3LA_LMSO: TEAEs during OLP by SOC and PT
SAF-L

TEAEs during OLP	Pre: CR845 N	Pre: CR845 n (%) [95 % CI]	Pre: Placebo N	Pre: Placebo n (%) [95 % CI]
SOC: Nervous system disorders	189	16 (8.5) [4.9, 13.4]	210	36 (17.1) [12.3, 22.9]
Dizziness	189	4 (2.1) [0.6, 5.3]	210	10 (4.8) [2.3, 8.6]
SOC: Psychiatric disorders	189	14 (7.4) [4.1, 12.1]	210	17 (8.1) [4.8, 12.6]
SOC: Renal and urinary disorders	189	2 (1.1) [0.1, 3.8]	210	10 (4.8) [2.3, 8.6]
SOC: Respiratory, thoracic and mediastinal disorders	189	25 (13.2) [8.7, 18.9]	210	29 (13.8) [9.4, 19.2]
SOC: Skin and subcutaneous tissue disorders	189	15 (7.9) [4.5, 12.8]	210	13 (6.2) [3.3, 10.4]
SOC: Vascular disorders	189	26 (13.8) [9.2, 19.5]	210	29 (13.8) [9.4, 19.2]
Hypotension	189	10 (5.3) [2.6, 9.5]	210	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

Table DT3LA_CMSO: TEAEs during OLP by SOC and PT
SAF-C

TEAEs during OLP	Pre: CR845 N	Pre: CR845 n (%) [95 % CI]	Pre: Placebo N	Pre: Placebo 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) [0.0, 23.2]	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) [1.8, 42.8]	21	3 (14.3) [3.0, 36.3]

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 DT3LA_CMSO: TEAEs during OLP by SOC and PT
SAF-C

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

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.
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) [0.0, 1.9]	210	0 (0.0) [0.0, 1.7]

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. AESI = adverse event of special interest.
Source Data: aae, created on: 03MAR2022

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

	Pre: CR845		Pre: Placebo	
	N	n (%) [95 % CI]	N	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]

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. AESI = adverse event of special interest.
Source Data: aae, created on: 03MAR2022

Table DT3LAEVN_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	189	4 (2.1) [0.6, 5.3]	210	7 (3.3) [1.4, 6.7]

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. AESI = adverse event of special interest.
Source Data: aae, created on: 03MAR2022

Table DT3LAEYN_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	189	0 (0.0) [0.0, 1.9]	210	4 (1.9) [0.5, 4.8]

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. AESI = adverse event of special interest.
Source Data: aae, created on: 03MAR2022

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]

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. AESI = adverse event of special interest.
Source Data: aae, created on: 03MAR2022

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]

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. AESI = adverse event of special interest.
Source Data: aae, created on: 03MAR2022

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

	Pre: CR845		Pre: Placebo	
	N	n (%) [95 % CI]	N	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]

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. AESI = adverse event of special interest.
Source Data: aae, created on: 03MAR2022

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 during OLP	189	3 (1.6) [0.3, 4.6]	210	1 (0.5) [0.0, 2.6]

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. AESI = adverse event of special interest.
Source Data: aae, created on: 03MAR2022

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]
AESI unusual feeling/sensation - non-severe during OLP	189	7 (3.7) [1.5, 7.5]	210	4 (1.9) [0.5, 4.8]

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. AESI = adverse event of special interest.
Source Data: aae, created on: 03MAR2022

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]

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. AESI = adverse event of special interest.
Source Data: aae, created on: 03MAR2022

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) [0.0, 1.9]	210	1 (0.5) [0.0, 2.6]

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. AESI = adverse event of special interest.
Source Data: aae, created on: 03MAR2022

Table DT3LAEFN_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 during OLP	189	22 (11.6) [7.4, 17.1]	210	18 (8.6) [5.2, 13.2]

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. AESI = adverse event of special interest.
Source Data: aae, created on: 03MAR2022

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]

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. AESI = adverse event of special interest.
Source Data: aae, created on: 03MAR2022

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]

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. AESI = adverse event of special interest.
Source Data: aae, created on: 03MAR2022

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]

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. AESI = adverse event of special interest.
Source Data: aae, created on: 03MAR2022

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]

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. AESI = adverse event of special interest.
Source Data: aae, created on: 03MAR2022

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

	Pre: CR845		Pre: Placebo	
	N	n (%) [95 % CI]	N	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]

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. AESI = adverse event of special interest.
Source Data: aae, created on: 03MAR2022

Table DT3LAEEN_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 during OLP	189	3 (1.6) [0.3, 4.6]	210	3 (1.4) [0.3, 4.1]

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. AESI = adverse event of special interest.
Source Data: aae, created on: 03MAR2022

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

	Pre: CR845		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]

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. AESI = adverse event of special interest.
Source Data: aae, created on: 03MAR2022

Table DT3LAERN_LMIO: AESI tachycardia/palpitation - non-severe during 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	2 (1.0) [0.1, 3.4]

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. AESI = adverse event of special interest.
Source Data: aae, created on: 03MAR2022

Table DT3LAEGN_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	14	0 (0.0) [0.0, 23.2]	21	0 (0.0) [0.0, 16.1]

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 DT3LAEFN_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	14	2 (14.3) [1.8, 42.8]	21	4 (19.0) [5.4, 41.9]

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 DT3LAEVN_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	14	1 (7.1) [0.2, 33.9]	21	1 (4.8) [0.1, 23.8]

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 DT3LAEYN_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	14	1 (7.1) [0.2, 33.9]	21	0 (0.0) [0.0, 16.1]

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 DT3LAEON_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	14	0 (0.0) [0.0, 23.2]	21	0 (0.0) [0.0, 16.1]

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 DT3LAEKN_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	14	0 (0.0) [0.0, 23.2]	21	1 (4.8) [0.1, 23.8]

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

	Pre: CR845		Pre: Placebo	
	N	n (%) [95 % CI]	N	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]

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 DT3LAEEN_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 during OLP	14	0 (0.0) [0.0, 23.2]	21	0 (0.0) [0.0, 16.1]

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

	Pre: CR845		Pre: Placebo	
	N	n (%) [95 % CI]	N	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]

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 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]

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-3: Zusatzauswertungen der gepoolten Analyse

Table PT3DDO_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	340	340 (100.0)	2.6 (0.8)	1	2.0	5
		Pre: Placebo	372	372 (100.0)	2.8 (0.9)	1	3.0	5
	OL Week 4	Pre: CR845	340	319 (93.8)	2.4 (0.8)	1	2.0	5
		Pre: Placebo	372	352 (94.6)	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
		Pre: Placebo	372	312 (83.9)	2.3 (0.9)	1	2.0	5
	OL Week 12	Pre: CR845	340	271 (79.7)	2.3 (0.9)	1	2.0	5
		Pre: Placebo	372	300 (80.6)	2.3 (0.8)	1	2.0	5
	OL Week 24	Pre: CR845	340	197 (57.9)	2.2 (0.8)	1	2.0	5
		Pre: Placebo	372	206 (55.4)	2.3 (0.9)	1	2.0	5
	OL Week 36	Pre: CR845	340	144 (42.4)	2.2 (0.8)	1	2.0	5
		Pre: Placebo	372	153 (41.1)	2.3 (0.8)	1	2.0	5
	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

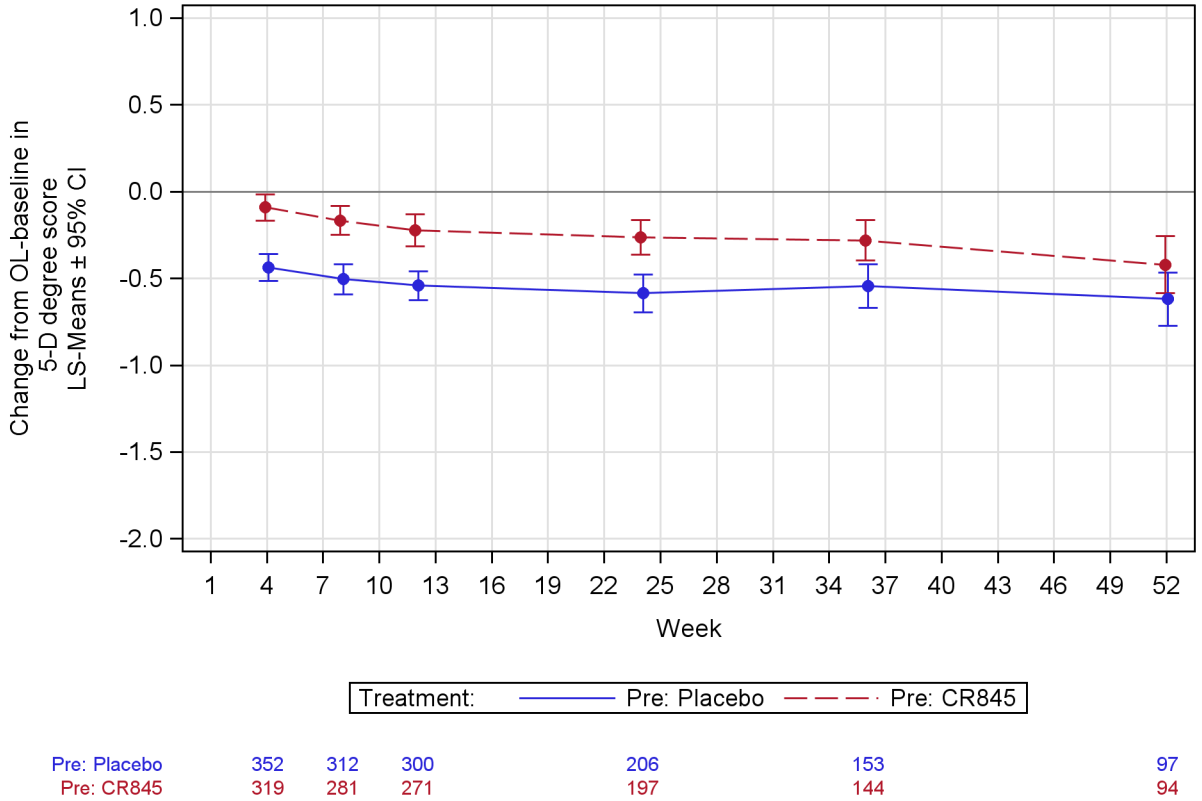
Note: SAF-L = Week 52 Safety set.
N = total number of patients in analysis set. n = number of evaluable values. SD = standard deviation. Q = quantile.
Source Data: afived_p, created on: 07MAR2022

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

Change from OL-baseline in 5-D degree score				Repeated measures analysis	
				Change from Baseline	
Time	Treatment	N	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.
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.
Source Data: afived_p, created on: 07MAR2022

Figure PF3DDO_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: PT3DDO_LMD0
Source Data: afived_p, created on: 07MAR2022

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

		Treatment	N	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
		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

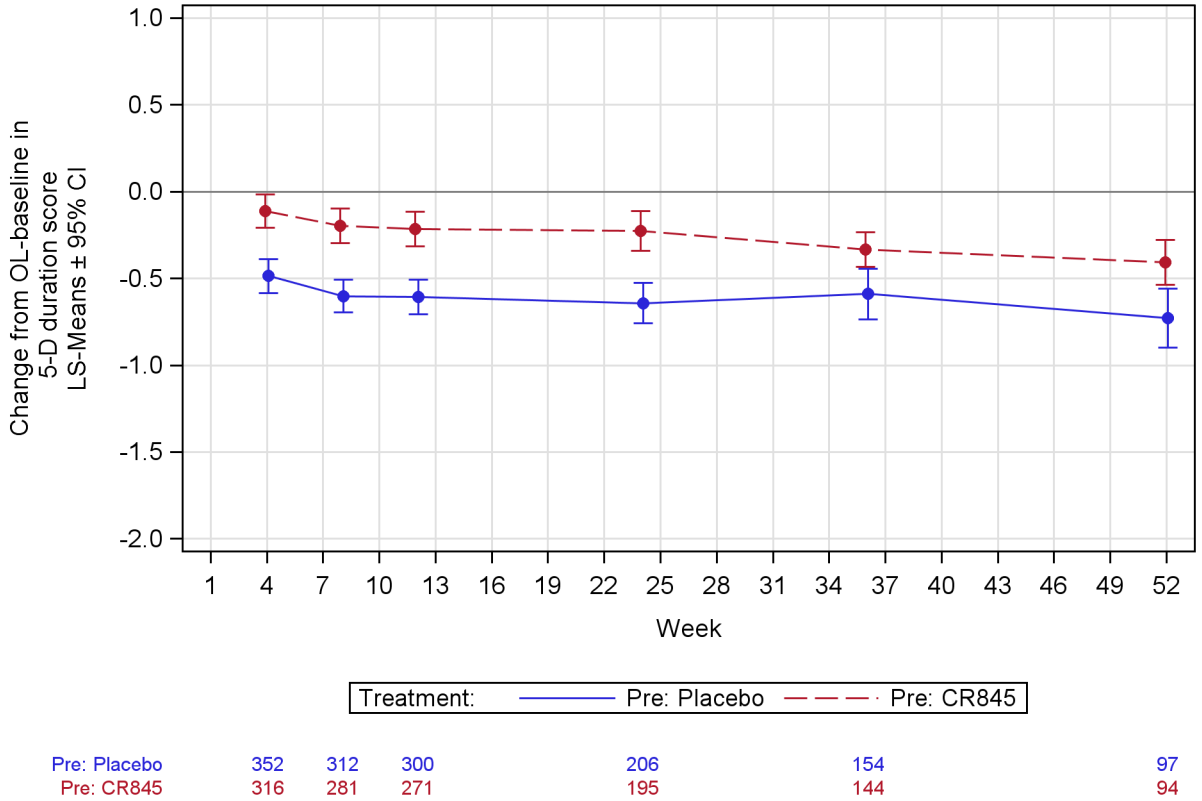
Note: SAF-L = Week 52 Safety set.
N = total number of patients in analysis set. n = number of evaluable values. SD = standard deviation. Q = quantile.
Source Data: afived_p, created on: 07MAR2022

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

Change from OL-baseline in 5-D duration score				Repeated measures analysis	
				Change from 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)
OL 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)
OL 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)
OL 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)
OL 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.
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.
Source Data: afived_p, created on: 07MAR2022

Figure PF3DLO_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: PT3DLO_LMD0
Source Data: afived_p, created on: 07MAR2022

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

		Treatment	N	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
		Pre: Placebo	372	372 (100.0)	2.9 (1.0)	1	3.0	5
	OL Week 4	Pre: CR845	340	318 (93.5)	2.5 (0.9)	1	2.0	5
		Pre: Placebo	372	352 (94.6)	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
		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

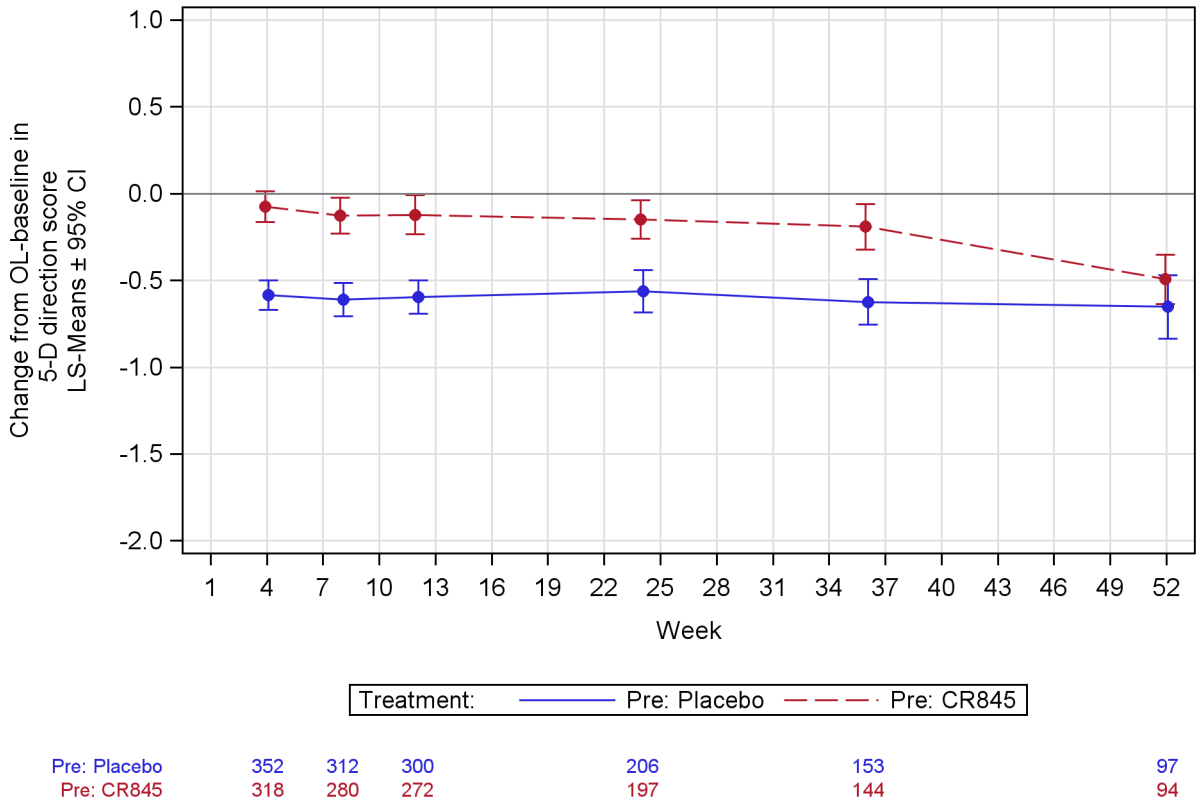
Note: SAF-L = Week 52 Safety set.
N = total number of patients in analysis set. n = number of evaluable values. SD = standard deviation. Q = quantile.
Source Data: afived_p, created on: 07MAR2022

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

Change from OL-baseline in 5-D direction score				Repeated measures analysis	
				Change from 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)	(-0.8, -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.
Source Data: afived_p, created on: 07MAR2022

Figure PF3DWO_LMG0: Change from OL-baseline in 5-D direction 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: PT3DWO_LMD0
Source Data: afived_p, created on: 07MAR2022

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

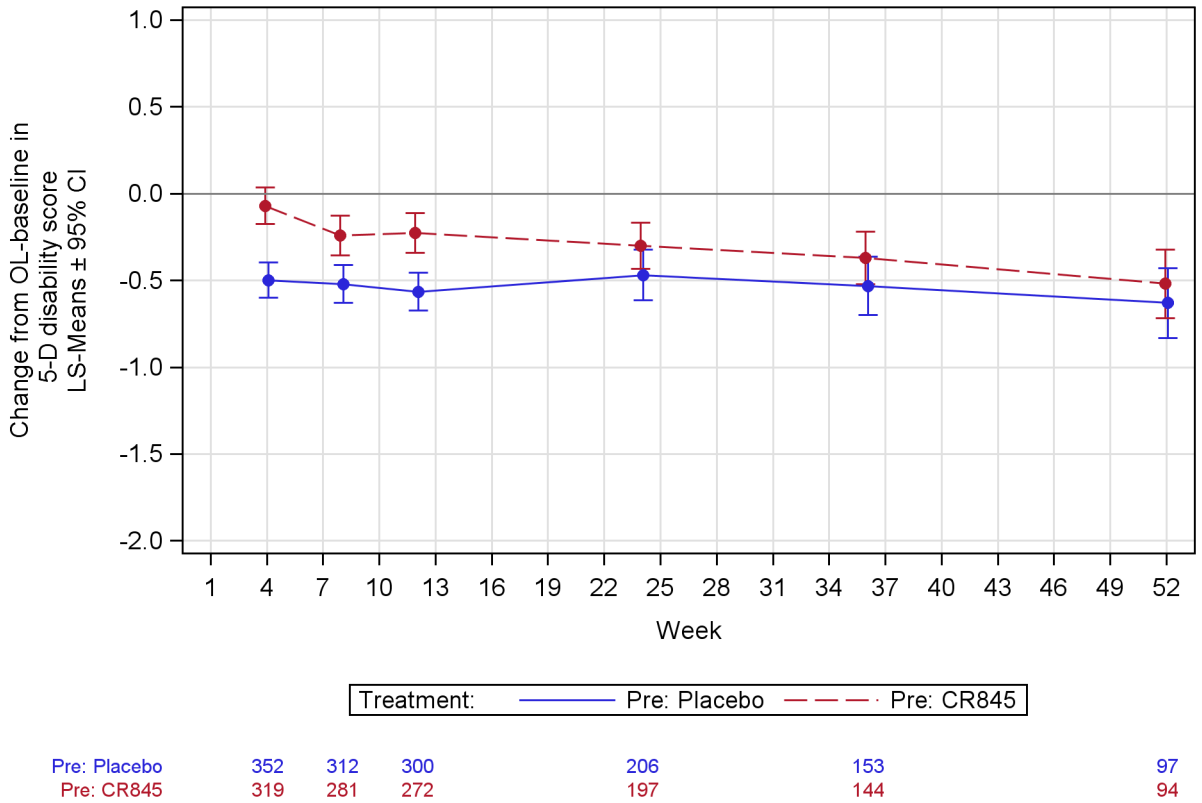
Note: SAF-L = Week 52 Safety set.
N = total number of patients in analysis set. n = number of evaluable values. SD = standard deviation. Q = quantile.
Source Data: afived_p, created on: 07MAR2022

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

Change from OL-baseline in 5-D disability score				Repeated measures analysis	
				Change from 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)	-0.5 (0.1)	(-0.6, -0.4)
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.
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.
Source Data: afived_p, created on: 07MAR2022

Figure PF3DNO_LMG0: Change from OL-baseline in 5-D disability score - Course of LSMEANS
SAF-L



Pre: Placebo	352	312	300	206	153	97
Pre: CR845	319	281	272	197	144	94

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
Source Data: afived_p, created on: 07MAR2022

Table PT3DVO_LMHO: Change from OL-baseline in 5-D distribution score
SAF-L

		Treatment	N	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
		Pre: Placebo	372	372 (100.0)	2.8 (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)	2.4 (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

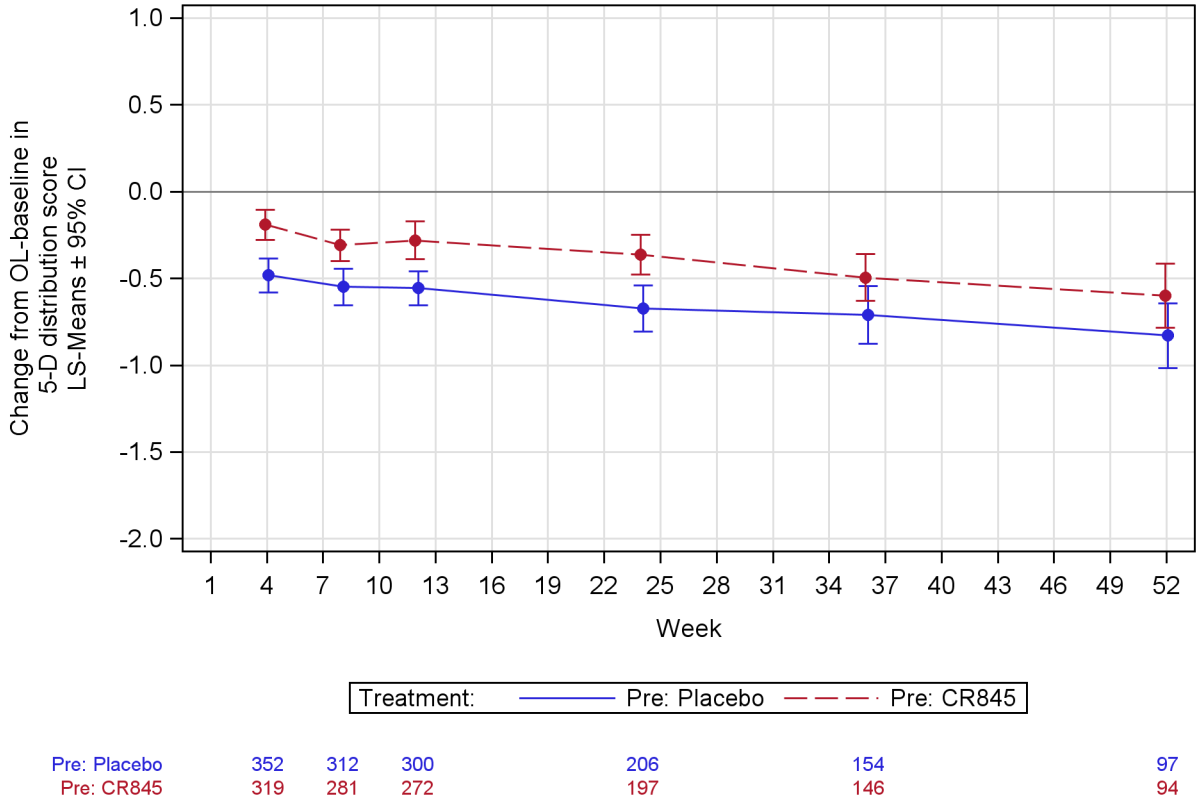
Note: SAF-L = Week 52 Safety set.
N = total number of patients in analysis set. n = number of evaluable values. SD = standard deviation. Q = quantile.
Source Data: afived_p, created on: 07MAR2022

Table PT3DVO_LMD0: Change from OL-baseline in 5-D distribution score - LSMEANS confidence intervals
SAF-L

Change from OL-baseline in 5-D distribution score				Repeated measures analysis	
				Change from Baseline	
Time	Treatment	N	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.
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.
Source Data: afived_p, created on: 07MAR2022

Figure PF3DVO_LMG0: Change from OL-baseline in 5-D distribution 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: PT3DVO_LMD0
Source Data: afived_p, created on: 07MAR2022

Table PT3DDO_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	136	136 (100.0)	2.5 (0.9)	1	2.0	5
		Pre: Placebo	143	143 (100.0)	2.9 (0.9)	1	3.0	5
	OL Week 4	Pre: CR845	136	135 (99.3)	2.3 (0.8)	1	2.0	5
		Pre: Placebo	143	138 (96.5)	2.5 (0.8)	1	2.0	5
	OL Week 8	Pre: CR845	136	133 (97.8)	2.2 (0.8)	1	2.0	5
		Pre: Placebo	143	140 (97.9)	2.3 (0.8)	1	2.0	5
	OL Week 12	Pre: CR845	136	133 (97.8)	2.2 (0.8)	1	2.0	5
		Pre: Placebo	143	137 (95.8)	2.3 (0.8)	1	2.0	4
	OL Week 24	Pre: CR845	136	133 (97.8)	2.2 (0.8)	1	2.0	5
		Pre: Placebo	143	143 (100.0)	2.3 (0.9)	1	2.0	5
	OL Week 36	Pre: CR845	136	132 (97.1)	2.2 (0.8)	1	2.0	5
		Pre: Placebo	143	141 (98.6)	2.3 (0.8)	1	2.0	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

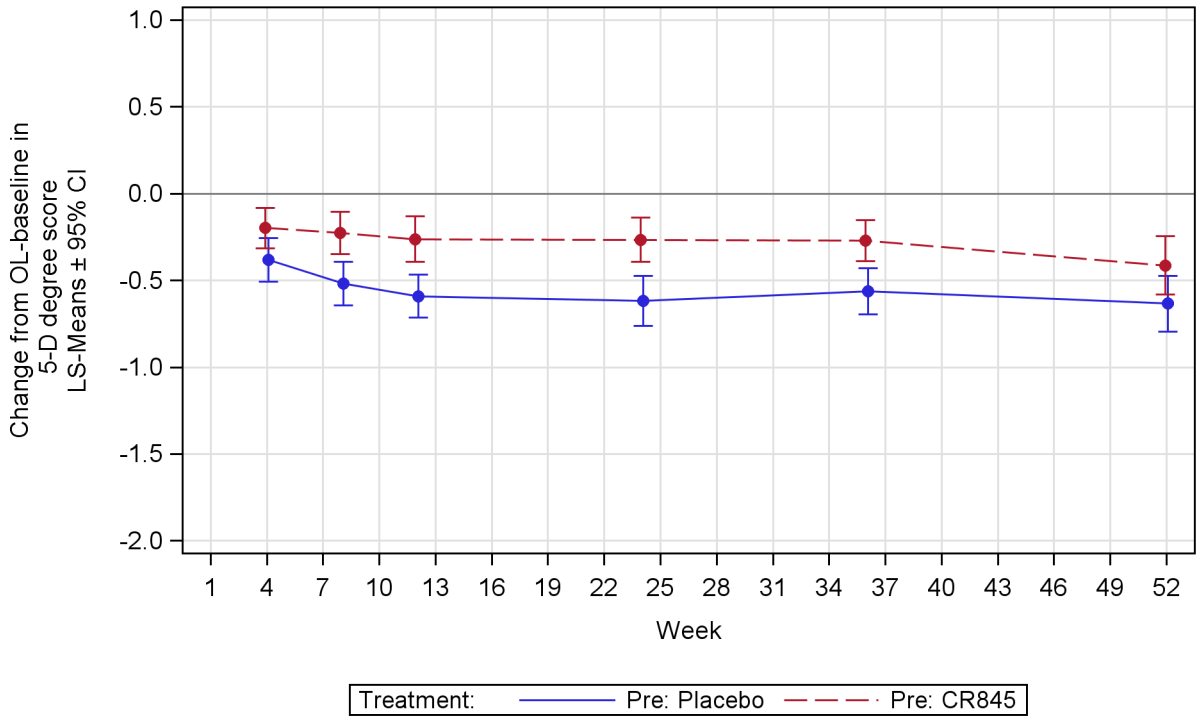
Note: SAF-C = Week 52 Study Completer Set.
N = total number of patients in analysis set. n = number of evaluable values. SD = standard deviation. Q = quantile.
Source Data: afived_p, created on: 07MAR2022

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

Change from OL-baseline in 5-D degree score				Repeated measures analysis	
				Change from 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)	-0.4 (0.1)	(-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.
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.
Source Data: afived_p, created on: 07MAR2022

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



Pre: Placebo	138	140	137	143	141	97
Pre: CR845	135	133	133	133	132	94

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
Source Data: afived_p, created on: 07MAR2022

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)	1.7 (1.0)	1	1.0	5
		Pre: Placebo	143	143 (100.0)	2.2 (1.3)	1	2.0	5
	OL Week 4	Pre: CR845	136	135 (99.3)	1.5 (1.0)	1	1.0	5
		Pre: Placebo	143	138 (96.5)	1.8 (1.1)	1	1.0	5
	OL Week 8	Pre: CR845	136	133 (97.8)	1.4 (0.9)	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)	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)	-0.7 (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

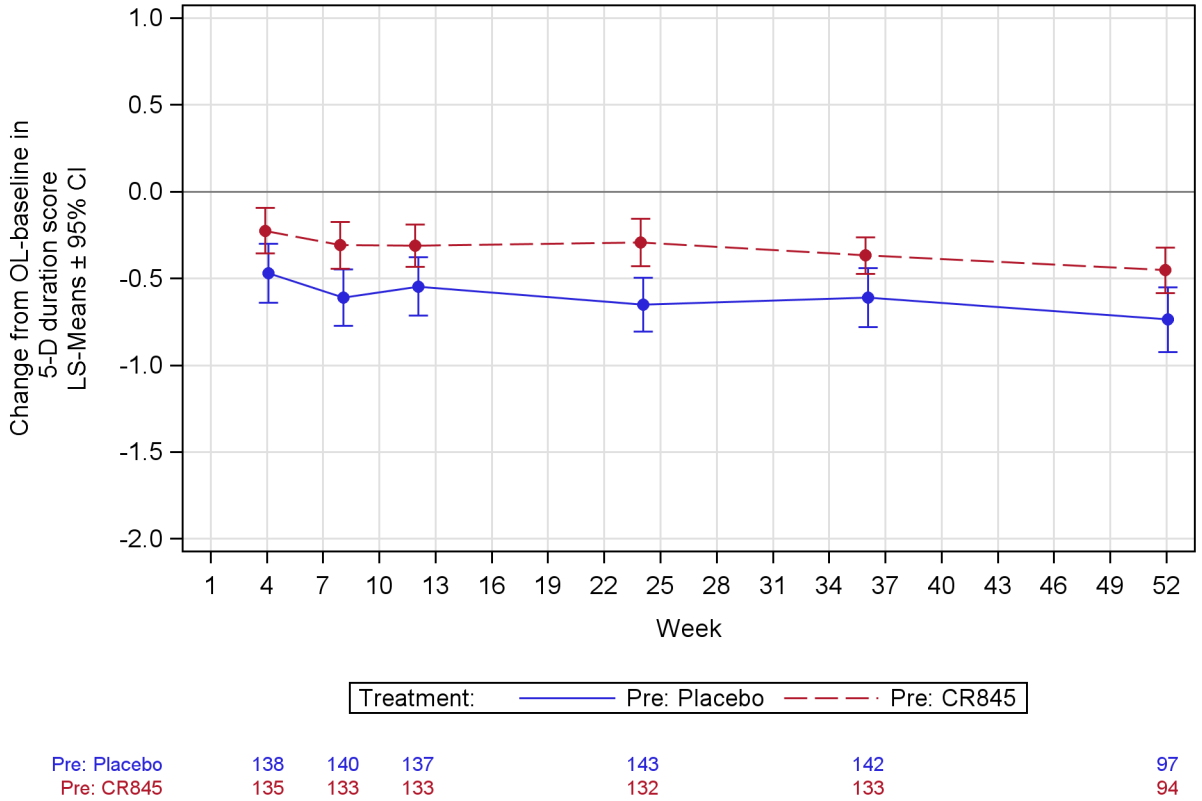
Note: SAF-C = Week 52 Study Completer Set.
N = total number of patients in analysis set. n = number of evaluable values. SD = standard deviation. Q = quantile.
Source Data: afived_p, created on: 07MAR2022

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

Change from OL-baseline in 5-D duration score				Repeated measures analysis	
				Change from 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.
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.
Source Data: afived_p, created on: 07MAR2022

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



Pre: Placebo	138	140	137	143	142	97
Pre: CR845	135	133	133	132	133	94

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
Source Data: afived_p, created on: 07MAR2022

Table PT3DWO_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	136	136 (100.0)	2.5 (0.8)	1	2.0	5
		Pre: Placebo	143	143 (100.0)	3.0 (0.9)	1	3.0	5
	OL Week 4	Pre: CR845	136	135 (99.3)	2.4 (0.9)	1	2.0	5
		Pre: Placebo	143	138 (96.5)	2.4 (0.8)	1	2.0	5
	OL Week 8	Pre: CR845	136	132 (97.1)	2.3 (0.8)	1	2.0	5
		Pre: Placebo	143	140 (97.9)	2.3 (0.9)	1	2.0	5
	OL Week 12	Pre: CR845	136	134 (98.5)	2.3 (0.9)	1	2.0	5
		Pre: Placebo	143	137 (95.8)	2.3 (0.8)	1	2.0	5
	OL Week 24	Pre: CR845	136	133 (97.8)	2.3 (0.9)	1	2.0	5
		Pre: Placebo	143	143 (100.0)	2.3 (0.9)	1	2.0	5
	OL Week 36	Pre: CR845	136	132 (97.1)	2.3 (0.8)	1	2.0	5
		Pre: Placebo	143	141 (98.6)	2.3 (0.9)	1	2.0	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

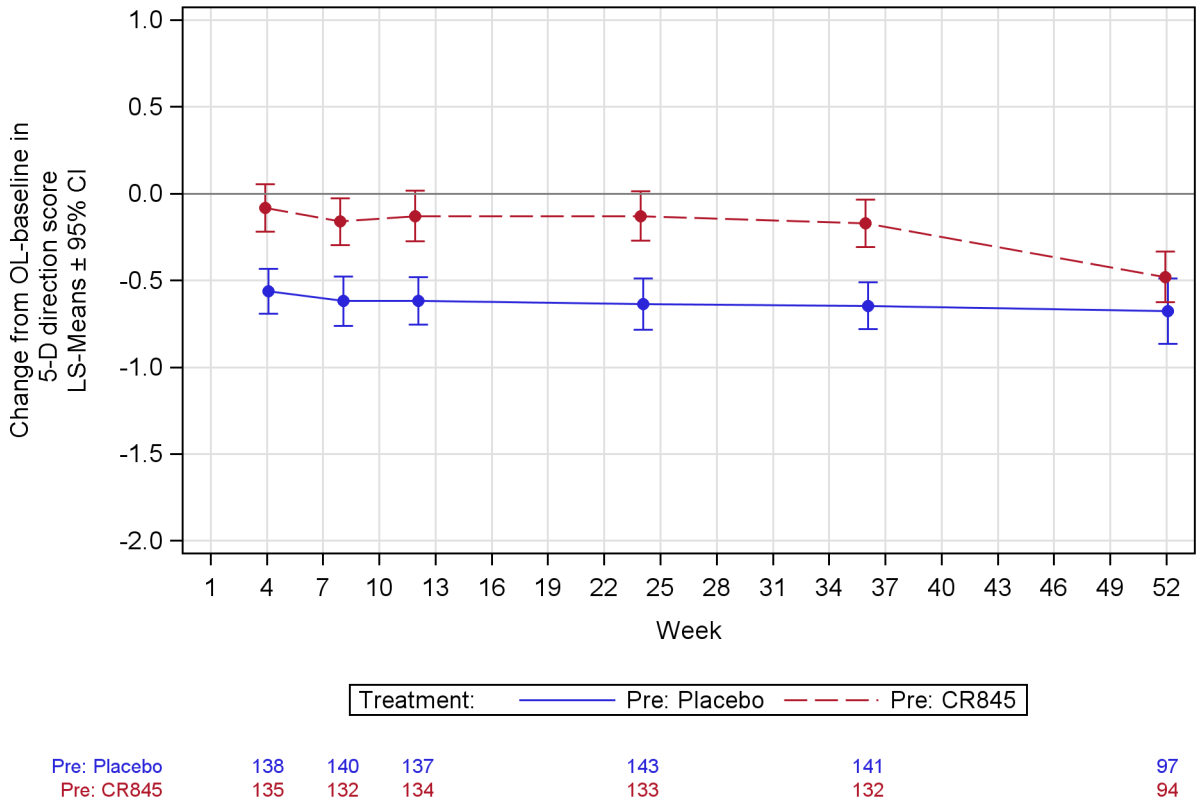
Note: SAF-C = Week 52 Study Completer Set.
N = total number of patients in analysis set. n = number of evaluable values. SD = standard deviation. Q = quantile.
Source Data: afived_p, created on: 07MAR2022

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

Change from OL-baseline in 5-D direction score				Repeated measures analysis	
				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)	(-0.7, -0.4)
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.
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.
Source Data: afived_p, created on: 07MAR2022

Figure PF3DWO_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.
Source Table: PT3DWO_CMD0
Source Data: afived_p, created on: 07MAR2022

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

		Treatment	N	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

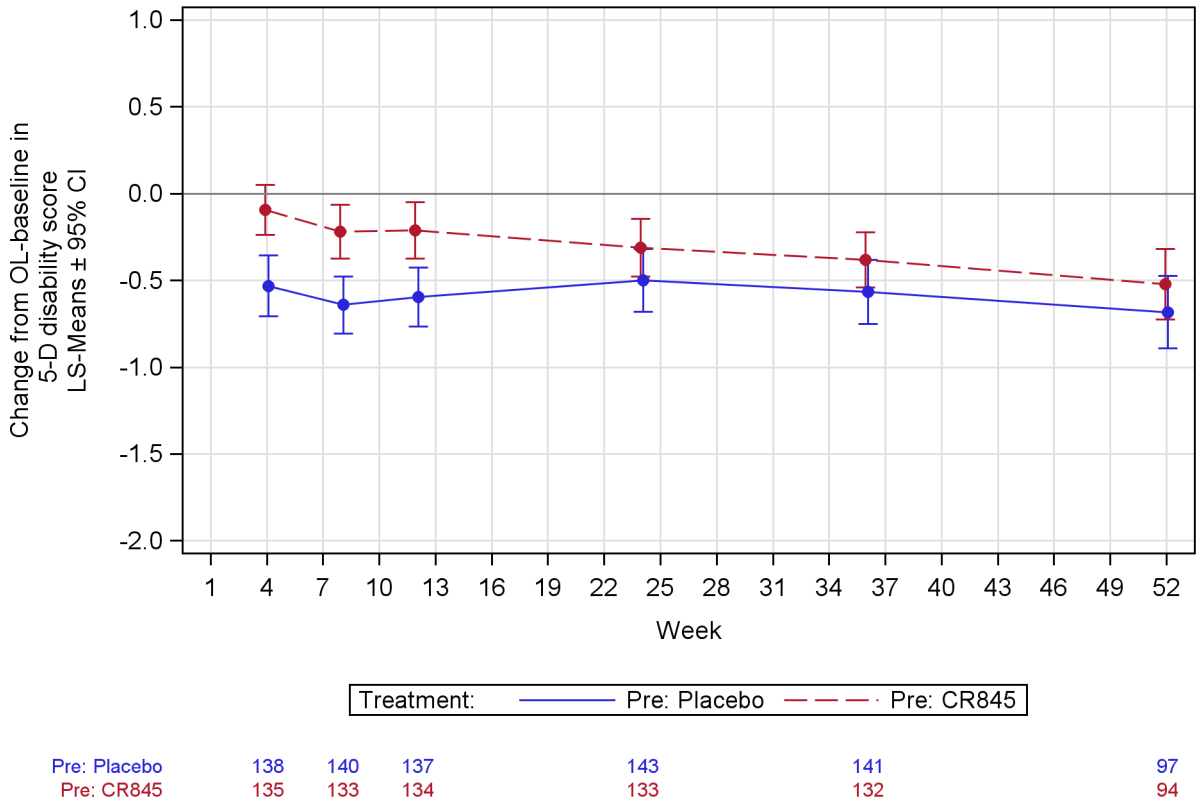
Note: SAF-C = Week 52 Study Completer Set.
N = total number of patients in analysis set. n = number of evaluable values. SD = standard deviation. Q = quantile.
Source Data: afived_p, created on: 07MAR2022

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

Change from OL-baseline in 5-D disability score				Repeated measures analysis	
				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)	-0.5 (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.
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.
Source Data: afived_p, created on: 07MAR2022

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
Source Data: afived_p, created on: 07MAR2022

Table PT3DVO_CMHO: Change from OL-baseline in 5-D distribution score
SAF-C

		Treatment	N	n (%)	Mean (SD)	Min	Q50	Max
5-D distribution score	OL Baseline	Pre: CR845	136	136 (100.0)	2.6 (1.3)	1	3.0	5
		Pre: Placebo	143	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
		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
		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
		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
		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

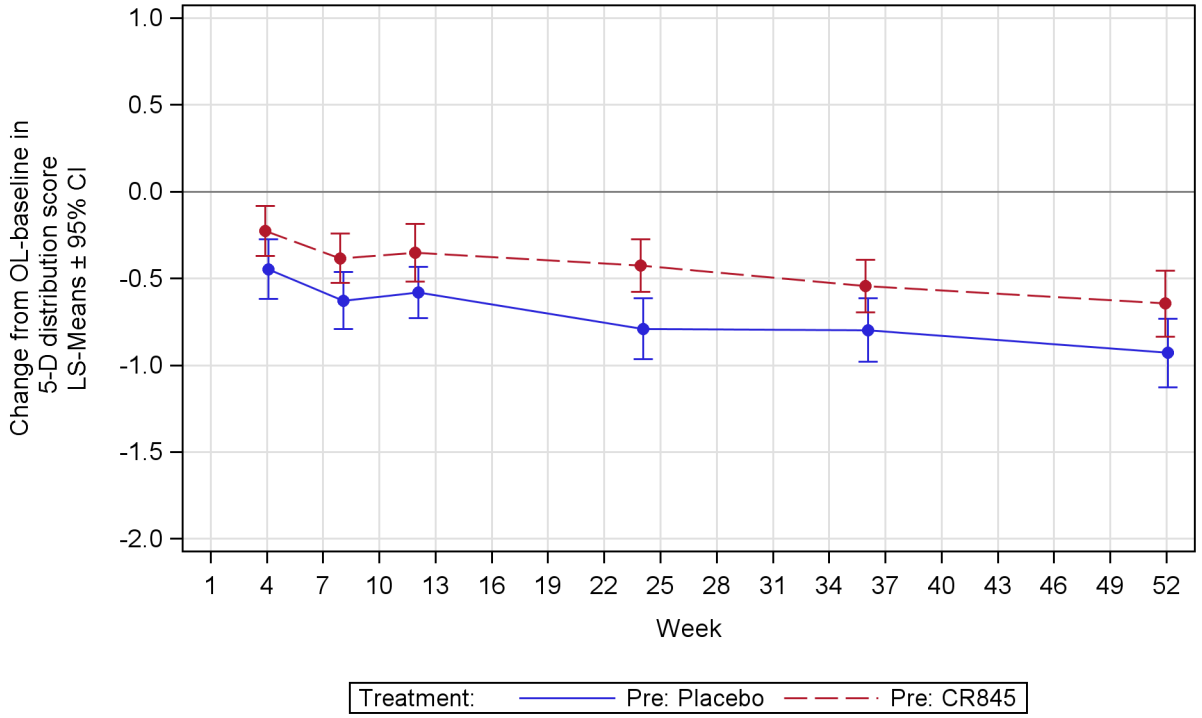
Note: SAF-C = Week 52 Study Completer Set.
N = total number of patients in analysis set. n = number of evaluable values. SD = standard deviation. Q = quantile.
Source Data: afived_p, created on: 07MAR2022

Table PT3DVO_CMD0: Change from OL-baseline in 5-D distribution score - LSMEANS confidence intervals
SAF-C

Change from OL-baseline in 5-D distribution score				Repeated measures analysis	
				Change from 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)	-0.4 (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)	-0.6 (0.1)	(-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)
OL Week 36	Pre: CR845	136	134 (98.5)	-0.5 (0.1)	(-0.7, -0.4)
	Pre: Placebo	143	142 (99.3)	-0.8 (0.1)	(-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.
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.
Source Data: afived_p, created on: 07MAR2022

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
Source Data: afived_p, created on: 07MAR2022

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

	Pre: CR845		Pre: Placebo	
	N	n (%) [95 % CI]	N	n (%) [95 % 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

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

	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]

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

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

TEAEs during OLP	Pre: CR845 N	Pre: CR845 n (%) [95 % CI]	Pre: Placebo N	Pre: Placebo 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]

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

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

TEAEs during OLP	Pre: CR845 N	Pre: CR845 n (%) [95 % CI]	Pre: Placebo N	Pre: Placebo 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]

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

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

TEAEs during OLP	Pre: CR845 N	Pre: CR845 n (%) [95 % CI]	Pre: Placebo N	Pre: Placebo n (%) [95 % CI]
Cough	340	19 (5.6) [3.4, 8.6]	372	18 (4.8) [2.9, 7.5]
Dyspnoea	340	25 (7.4) [4.8, 10.7]	372	21 (5.6) [3.5, 8.5]
Respiratory failure	340	10 (2.9) [1.4, 5.3]	372	16 (4.3) [2.5, 6.9]
SOC: Skin and subcutaneous tissue disorders	340	32 (9.4) [6.5, 13.0]	372	29 (7.8) [5.3, 11.0]
Pruritus	340	10 (2.9) [1.4, 5.3]	372	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	17 (5.0) [2.9, 7.9]	372	14 (3.8) [2.1, 6.2]
Hypotension	340	34 (10.0) [7.0, 13.7]	372	31 (8.3) [5.7, 11.6]

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

TEAEs during OLP	Pre: CR845 N	Pre: CR845 n (%) [95 % CI]	Pre: Placebo N	Pre: Placebo 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]

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

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

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

TEAEs during OLP	Pre: CR845 N	Pre: CR845 n (%) [95 % CI]	Pre: Placebo N	Pre: Placebo 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]

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) [0.0, 1.1]	372	0 (0.0) [0.0, 1.0]

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. AESI = adverse event of special interest.
Source Data: aae_p, created on: 03MAR2022

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

	Pre: CR845		Pre: Placebo	
	N	n (%) [95 % CI]	N	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]

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. AESI = adverse event of special interest.
Source Data: aae_p, created on: 03MAR2022

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]

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. AESI = adverse event of special interest.
Source Data: aae_p, created on: 03MAR2022

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]

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. AESI = adverse event of special interest.
Source Data: aae_p, created on: 03MAR2022

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]

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. AESI = adverse event of special interest.
Source Data: aae_p, created on: 03MAR2022

Table PT3LAEKN_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	340	0 (0.0) [0.0, 1.1]	372	1 (0.3) [0.0, 1.5]

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. AESI = adverse event of special interest.
Source Data: aae_p, created on: 03MAR2022

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

	Pre: CR845		Pre: Placebo	
	N	n (%) [95 % CI]	N	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]

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. AESI = adverse event of special interest.
Source Data: aae_p, created on: 03MAR2022

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 during OLP	340	7 (2.1) [0.8, 4.2]	372	2 (0.5) [0.1, 1.9]

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. AESI = adverse event of special interest.
Source Data: aae_p, created on: 03MAR2022

Table PT3LAEUN_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]
AESI unusual feeling/sensation - non-severe during OLP	340	8 (2.4) [1.0, 4.6]	372	4 (1.1) [0.3, 2.7]

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. AESI = adverse event of special interest.
Source Data: aae_p, created on: 03MAR2022

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 - non-severe during OLP	340	4 (1.2) [0.3, 3.0]	372	4 (1.1) [0.3, 2.7]

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. AESI = adverse event of special interest.
Source Data: aae_p, created on: 03MAR2022

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]

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. AESI = adverse event of special interest.
Source Data: aae_p, created on: 03MAR2022

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 during OLP	340	47 (13.8) [10.3, 18.0]	372	46 (12.4) [9.2, 16.1]

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. AESI = adverse event of special interest.
Source Data: aae_p, created on: 03MAR2022

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]

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. AESI = adverse event of special interest.
Source Data: aae_p, created on: 03MAR2022

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]

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. AESI = adverse event of special interest.
Source Data: aae_p, created on: 03MAR2022

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]

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. AESI = adverse event of special interest.
Source Data: aae_p, created on: 03MAR2022

Table PT3LAEKN_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	340	1 (0.3) [0.0, 1.6]	372	4 (1.1) [0.3, 2.7]

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. AESI = adverse event of special interest.
Source Data: aae_p, created on: 03MAR2022

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

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

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. AESI = adverse event of special interest.
Source Data: aae_p, created on: 03MAR2022

Table PT3LAEEN_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 during OLP	340	10 (2.9) [1.4, 5.3]	372	8 (2.2) [0.9, 4.2]

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. AESI = adverse event of special interest.
Source Data: aae_p, created on: 03MAR2022

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

	Pre: CR845		Pre: Placebo	
	N	n (%) [95 % CI]	N	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]

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. AESI = adverse event of special interest.
Source Data: aae_p, created on: 03MAR2022

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

	Pre: CR845		Pre: Placebo	
	N	n (%) [95 % CI]	N	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]

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. AESI = adverse event of special interest.
Source Data: aae_p, created on: 03MAR2022

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) [0.0, 2.7]	143	1 (0.7) [0.0, 3.8]

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_p, created on: 03MAR2022

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 during OLP	136	22 (16.2) [10.4, 23.5]	143	28 (19.6) [13.4, 27.0]

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_p, created on: 03MAR2022

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]

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_p, created on: 03MAR2022

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]

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_p, created on: 03MAR2022

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]

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_p, created on: 03MAR2022

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]

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_p, created on: 03MAR2022

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

	Pre: CR845		Pre: Placebo	
	N	n (%) [95 % CI]	N	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]

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_p, created on: 03MAR2022

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 during OLP	136	4 (2.9) [0.8, 7.4]	143	3 (2.1) [0.4, 6.0]

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_p, created on: 03MAR2022

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

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

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_p, created on: 03MAR2022

Table PT3LAERN_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	136	9 (6.6) [3.1, 12.2]	143	9 (6.3) [2.9, 11.6]

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_p, created on: 03MAR2022

Anhang 4-I-4:
Zusatzauswertungen der Studie CLIN3101

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

TEAEs during OLP	Pre: CR845 N	Pre: CR845 n (%) [95 % CI]	Pre: Placebo N	Pre: Placebo n (%) [95 % CI]	Pre: De Novo N	Pre: De Novo 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]

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_LMS1: TEAEs during first quarter of 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	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]

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
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: 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
SAF-L

TEAEs during OLP	Pre: CR845 N	Pre: CR845 n (%) [95 % CI]	Pre: Placebo N	Pre: Placebo n (%) [95 % CI]	Pre: De Novo N	Pre: De Novo 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.
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
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
SAF-C

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

TEAEs during OLP	Pre: CR845 N	Pre: CR845 n (%) [95 % CI]	Pre: Placebo N	Pre: Placebo n (%) [95 % CI]	Pre: De Novo N	Pre: De Novo 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.
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
SAF-C

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

	Pre: CR845		Pre: Placebo		Pre: De Novo	
TEAEs during OLP	N	n (%) [95 % CI]	N	n (%) [95 % CI]	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]

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

	Pre: CR845		Pre: 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]

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. AESI = adverse event of special interest.
Source Data: aae, created on: 11MAR2022

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

	Pre: CR845		Pre: 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]

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. AESI = adverse event of special interest.
Source Data: aae, created on: 11MAR2022

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

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

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. AESI = adverse event of special interest.
Source Data: aae, created on: 11MAR2022

Table ET1LAEYN_LMI1: AESI syncope - non-severe during first quarter of OLP
SAF-L

	Pre: CR845		Pre: Placebo		Pre: De Novo	
	N	n (%) [95 % CI]	N	n (%) [95 % CI]	N	n (%) [95 % CI]
AESI syncope - 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]

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. AESI = adverse event of special interest.
Source Data: aae, created on: 11MAR2022

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

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

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. AESI = adverse event of special interest.
Source Data: aae, created on: 11MAR2022

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

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

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. AESI = adverse event of special interest.
Source Data: aae, created on: 11MAR2022

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

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

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. AESI = adverse event of special interest.
Source Data: aae, created on: 11MAR2022

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

	Pre: CR845		Pre: 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]

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. AESI = adverse event of special interest.
Source Data: aae, created on: 11MAR2022

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

	Pre: CR845		Pre: Placebo		Pre: 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]

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. AESI = adverse event of special interest.
Source Data: aae, created on: 11MAR2022

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

	Pre: CR845		Pre: 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]

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. AESI = adverse event of special interest.
Source Data: aae, created on: 11MAR2022

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

	Pre: CR845		Pre: 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]

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. AESI = adverse event of special interest.
Source Data: aae, created on: 11MAR2022

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

	Pre: CR845		Pre: 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]

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. AESI = adverse event of special interest.
Source Data: aae, created on: 11MAR2022

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

	Pre: CR845		Pre: 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]

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. AESI = adverse event of special interest.
Source Data: aae, created on: 11MAR2022

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

	Pre: CR845		Pre: Placebo		Pre: De Novo	
	N	n (%) [95 % CI]	N	n (%) [95 % CI]	N	n (%) [95 % CI]
AESI syncope - 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]

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. AESI = adverse event of special interest.
Source Data: aae, created on: 11MAR2022

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

	Pre: CR845		Pre: Placebo		Pre: De Novo	
	N	n (%) [95 % CI]	N	n (%) [95 % CI]	N	n (%) [95 % CI]
AESI somnolence - non-severe during OLP	52	1 (1.9) [0.0, 10.3]	30	0 (0.0) [0.0, 11.6]	206	2 (1.0) [0.1, 3.5]

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. AESI = adverse event of special interest.
Source Data: aae, created on: 11MAR2022

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

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

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. AESI = adverse event of special interest.
Source Data: aae, created on: 11MAR2022

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

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

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. AESI = adverse event of special interest.
Source Data: aae, created on: 11MAR2022

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

	Pre: CR845		Pre: 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]

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. AESI = adverse event of special interest.
Source Data: aae, created on: 11MAR2022

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

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

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. AESI = adverse event of special interest.
Source Data: aae, created on: 11MAR2022

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

	Pre: CR845		Pre: Placebo		Pre: De Novo	
	N	n (%) [95 % CI]	N	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]

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. AESI = adverse event of special interest.
Source Data: aae, created on: 11MAR2022

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

	Pre: CR845		Pre: Placebo		Pre: 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]

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: 11MAR2022

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

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

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: 11MAR2022

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

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

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: 11MAR2022

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

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

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: 11MAR2022

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

	Pre: CR845		Pre: Placebo		Pre: 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]

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: 11MAR2022

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

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

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: 11MAR2022

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

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

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: 11MAR2022

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

	Pre: CR845		Pre: Placebo		Pre: 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]

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: 11MAR2022

Table ET1LAEUN_CMIO: AESI unusual feeling/sensation - non-severe during OLP
SAF-C

	Pre: CR845		Pre: Placebo		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]

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: 11MAR2022

Table ET1LAERN_CMIO: AESI tachycardia/palpitation - non-severe during OLP
SAF-C

	Pre: CR845		Pre: Placebo		Pre: 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]

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: 11MAR2022