

Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Administration Volume

Dry weight (kg)	Administered volume (mL)	Dose of Difelikefalin (µg/kg)			
		0.25	0.5	1.0	Placebo
<45.0	0.35	8.75 µg	17.5 µg	35.0 µg	0 µg
≥45.0 to <65.0	0.50	12.50 µg	25.0 µg	50.0 µg	0 µg
≥65.0 to <85.0	0.70	17.50 µg	35.0 µg	70.0 µg	0 µg
≥85.0	0.85	21.25 µg	42.5 µg	85.0 µg	0 µg

eTable 2. Sensitivity Analyses in the Primary Endpoint

Method of analysis - analysis population	Group (n) ^a	n ^b	Adjusted weekly mean (SE)	Two-Sided 95% Confidence Interval	
				Lower	Upper
MMRM - FAS (Primary endpoint)	Difelikefalin 0.25 µg/kg (61)	59	-2.97 (0.29)	-3.54	-2.39
	Difelikefalin 0.5 µg/kg (60)	53	-3.65 (0.30)	-4.24	-3.07
	Difelikefalin 1.0 µg/kg (59)	53	-3.64 (0.30)	-4.22	-3.06
	Placebo (63)	58	-2.86 (0.29)	-3.42	-2.29
MMRM - PPS	Difelikefalin 0.25 µg/kg (52)	52	-3.07 (0.32)	-3.70	-2.44
	Difelikefalin 0.5 µg/kg (48)	48	-3.54 (0.33)	-4.19	-2.90
	Difelikefalin 1.0 µg/kg (41)	40	-3.70 (0.35)	-4.39	-3.02
	Placebo (53)	52	-2.92 (0.32)	-3.54	-2.29
MI-MMRM	Difelikefalin 0.25 µg/kg (61)	59	-2.96 (0.29)	-3.53	-2.38
	Difelikefalin 0.5 µg/kg (60)	53	-3.63 (0.30)	-4.21	-3.05
	Difelikefalin 1.0 µg/kg (59)	53	-3.59 (0.30)	-4.17	-3.01
	Placebo (63)	58	-2.84 (0.29)	-3.40	-2.28
Placebo MI-MMRM	Difelikefalin 0.25 µg/kg (61)	59	-2.96 (0.29)	-3.54	-2.39
	Difelikefalin 0.5 µg/kg (60)	53	-3.59 (0.30)	-4.18	-3.00
	Difelikefalin 1.0 µg/kg (59)	53	-3.62 (0.30)	-4.20	-3.03
	Placebo (63)	58	-2.83 (0.29)	-3.39	-2.27

a. number of patients at week 1, b. number of patients at week 8

Abbreviations: FAS, full analysis set; MI, multiple imputation; MMRM, mixed-effects model for repeated measures; PPS, per protocol set; SE, standard error

eTable 3. Subgroup Analyses in the Primary Endpoint

Subgroup	Group (n) ^a	n ^b	Adjusted weekly mean (SE)	Two-Sided 95% Confidence Interval	
				Lower	Upper
Treatment history with nalfurafine - No	Difelikefalin 0.25 µg/kg (31)	29	-2.65 (0.42)	-3.47	-1.83
	Difelikefalin 0.5 µg/kg (30)	28	-3.66 (0.42)	-4.49	-2.83
	Difelikefalin 1.0 µg/kg (27)	26	-3.23 (0.43)	-4.08	-2.38
	Placebo (29)	26	-3.07 (0.42)	-3.90	-2.25
Treatment history with nalfurafine - Yes	Difelikefalin 0.25 µg/kg (30)	30	-3.34 (0.41)	-4.16	-2.52
	Difelikefalin 0.5 µg/kg (30)	25	-3.68 (0.42)	-4.52	-2.84
	Difelikefalin 1.0 µg/kg (32)	27	-3.95 (0.41)	-4.76	-3.15
	Placebo (34)	32	-2.69 (0.39)	-3.47	-1.92

a. number of patients at week 1, b. number of patients at week 8

Abbreviation: SE, standard error

eTable 4. Skindex-16 Overall Score and 5-D Itch Scale Total Score at Week 4 and 8

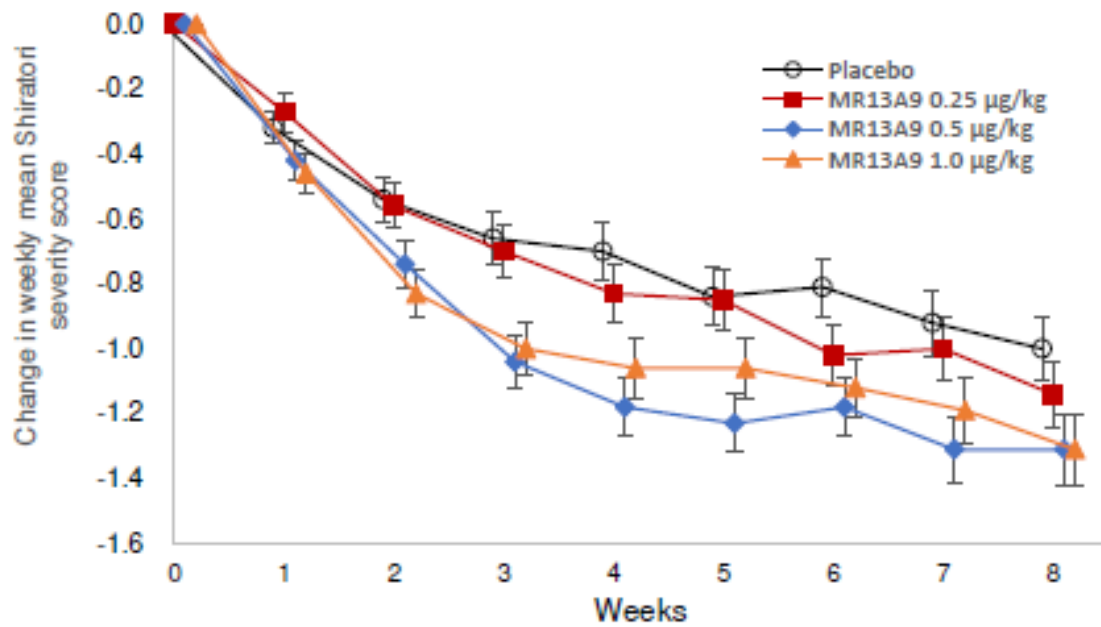
	Group	Weeks	n	Adjusted weekly mean (SE)	Two-Sided 95% Confidence Interval	
					Lower	Upper
Skindex-16 overall score	Difelikefalin 0.25 µg/kg	4	59	-20.25 (1.85)	-23.89	-16.60
		8	59	-24.25 (1.96)	-28.11	-20.39
	Difelikefalin 0.5 µg/kg	4	56	-26.01 (1.91)	-29.76	-22.25
		8	53	-27.79 (2.05)	-31.83	-23.74
	Difelikefalin 1.0 µg/kg	4	55	-19.03 (1.91)	-22.80	-15.25
		8	54	-22.69 (2.04)	-26.71	-18.68
	Placebo	4	61	-19.99 (1.82)	-23.57	-16.41
		8	59	-24.04 (1.94)	-27.87	-20.21
5-D itch scale total score	Difelikefalin 0.25 µg/kg	4	59	-5.3 (0.4)	-6.0	-4.6
		8	59	-6.6 (0.3)	-7.2	-5.9
	Difelikefalin 0.5 µg/kg	4	56	-6.3 (0.4)	-7.0	-5.6
		8	53	-6.5 (0.4)	-7.2	-5.8
	Difelikefalin 1.0 µg/kg	4	55	-5.7 (0.4)	-6.5	-5.0
		8	54	-6.8 (0.3)	-7.5	-6.2
	Placebo	4	61	-4.5 (0.3)	-5.2	-3.9
		8	59	-5.8 (0.3)	-6.5	-5.2

Abbreviation: SE, standard error

eTable 5. Patient Global Impression of Change at the End of the Treatment Period

		Difelikefalin ($\mu\text{g}/\text{kg}$)			Placebo N = 62
		0.25	0.5	1.0	
		N = 61	N = 59	N = 60	
Very much improved	n (%)	12 (19.7)	22 (37.3)	19 (31.7)	11 (17.7)
Much improved	n (%)	21 (34.4)	17 (28.8)	23 (38.3)	15 (24.2)
Minimally improved	n (%)	21 (34.4)	13 (22.0)	11 (18.3)	23 (37.1)
No change	n (%)	7 (11.5)	6 (10.2)	5 (8.3)	11 (17.7)
Minimally worse	n (%)	0 (0.0)	1 (1.7)	1 (1.7)	0 (0.0)
Much worse	n (%)	0 (0.0)	0 (0.0)	1 (1.7)	1 (1.6)
Very much worse	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Two-sample Wilcoxon test		<i>P</i> = .158	<i>P</i> = .005	<i>P</i> = .005	---

eFigure. Time Course of the Adjusted Weekly Mean Change \pm Standard Error in the Shiratori Severity Score



No. of patients								
Placebo	63	62	61	61	61	59	59	58
Difelikefalin 0.25 µg/kg	61	61	60	59	59	59	59	59
Difelikefalin 0.5 µg/kg	60	57	58	56	55	54	53	53
Difelikefalin 1.0 µg/kg	59	59	58	54	55	55	53	53