Sponsor

Novartis

Generic Drug Name

DNK333

Therapeutic Area of Trial

Pruritus in patients with atopic dermatitis

Approved Indication

Investigational

Protocol Number

CDNK333B2103

Title

A multicenter, randomized, double-blinded, placebo and positive controlled study to evaluate the anti-pruritic effect, safety and tolerability, systemic and skin exposure, after 2 weeks of treatment with a microemulsion formulation of DNK333 in atopic dermatitis patients

Phase of Development

Phase II

Study Start/End Dates

22-Nov-2009 to 13-Jul-2011

Study Design/Methodology

A multicenter, randomized, double-blinded, placebo and positive controlled study to evaluate the anti-pruritic effect, safety and tolerability, systemic and skin exposure, after 2 weeks of treatment with a microemulsion formulation of DNK333 in atopic dermatitis patients

Centers

5 centers in Germany (001, 002, 003, 004, 005)

Publication

Not applicable

Outcomes measures

Primary measures:

- Global Itch Assessment using a Visual Analogue Scale (VAS), Actigraphy (noctural movement measurement using an Actiwatch).

Secondary measures

- Collection of all adverse events (AEs), serious adverse events (SAEs), with their severity and relationship to study drug, and pregnancies. Monitoring of hematology, blood chemistry and urine, assessments of vital signs, ECGs, physical condition and body weight.
- Eczema Area Severity Index (EASI),
- Patient Benefit Index for Pruritus (PBIfP)
- Quality of Life for Atopic Dermatitis (QoLIAD)
- Plasma pharmacokinetics and skin exposure data for DNK333
- Comparison of pharmacokinetics of DNK333, oral microemulsion drinking solution to a solid dispersion tablets

Test Product(s), Dose(s), and Mode(s) of Administration

DNK333 00 mg/ml solution 50 ml Batch number: 3298635.001 Y077 0409
DNK333 was supplied to the investigators as a microemulsion for oral intake at dose strengths of 10 mg/mL. These materials were used for patients'treatment from Day 1 to Day 14 of the treatment period. On Day 15, the majority of patients on active treatment received a solid dispersion tablet at the strength of 25 mg DNK333.

- Multiple oral doses of 1 mg DNK333 twice daily over 14 days
- Multiple oral doses of 5 mg DNK333 twice daily over 14 days
- Multiple oral doses of 25 mg DNK333 twice daily over 14 days
- Multiple oral doses of 100 mg DNK333 twice daily over 14 days
- Multiple doses of 4 mg betamethasone once daily (in the morning) over 14 days and multiple oral doses of placebo matching 25mg DNK333 once daily (in the evening) over 14 days

Betamethasone solution was purchased locally by the investigator.

Reference Product(s), Dose(s), and Mode(s) of Administration

Matching placebo to DNK333 was supplied to the investigators as a microemulsion containing the same ingredients as the active microemulsion, except the active agent. These materials were used for patients'treatment from Day 1 to Day 14 of the treatment period. On Day 15 the majority of patients on placebo treatment received a placebo solid dispersion tablet.

- Multiple doses of oral placebo matching 1mg DNK333 twice daily over 14 days
- Multiple doses of oral placebo matching 5mg DNK333 twice daily over 14 days
- Multiple doses of oral placebo matching 25mg DNK333 twice daily over 14 days
- Multiple doses of oral placebo matching 100 mg DNK333 twice daily over 14 days

Criteria for Evaluation

Primary variables

- Global Itch Assessment using a Visual Analogue Scale (VAS)
- Average nocturnal activity intensity (actigraphy)
- Nocturnal activity counts above zero (actigraphy)

Secondary variables

- Collection of all adverse events (AEs), serious adverse events (SAEs), with their severity and relationship to study drug, and pregnancies. Monitoring of hematology, blood chemistry and urine, assessments of vital signs, ECGs, physical condition and body weight.
- Patient Benefit Index for Pruritus (PBIfP)
- Eczema Area Severity Index (EASI)
- Quality of Life for Atopic Dermatitis (QoLIAD)
- Plasma pharmacokinetics and skin exposure data for DNK333
- Comparison of pharmacokinetics of DNK333, oral microemulsion drinking solution to a solid dispersion tablet

Statistical Methods

Primary variables

For the three efficacy primary variables, given the non-normality of these variables, the data was transformed using the natural logarithm and analyzed in this log scale. Following this transformation, the actigraphy and VAS data from the last seven days of treatment (when efficacy steady state is expected to have been achieved) was averaged and this new variable was used to assess efficacy.

The primary statistical analysis was performed for the comparisons of log of the ratio to baseline (log(endpt/baseline)) of the four DNK333 dose groups to placebo. For each of the three efficacy primary variables an Analysis of Variance (ANOVA) was performed with one-sided t-tests for comparisons of DNK333 dose groups to placebo. The resulting 12 p-values were adjusted for multiplicity by the Hochberg procedure with overall one-sided alpha of 20%.

In addition, point estimates for the ratio of log of the ratio to baseline DNK333 means to log of the ratio to baseline placebo means (on the original scale) were provided together with unadjusted two-sided 60% confidence intervals.

The differences between placebo and positive control (betamethasone) for the mean log transformed primary variables were also calculated.

Secondary variables

Vitals signs, ECG data, and standard clinical laboratory data were listed and summarized. All information obtained on adverse events was displayed by treatment and patient, and the number and percentage of patients with adverse events summarized by body system and preferred term.

The Patient Benefit Index for Pruritus (PBIfP) score data, the Eczema Area Severity index (EASI) score data and the Quality of Life for Atopic Dermatitis (QoLIAD) data were summarized by treatment group and visit.

Descriptive statistics of pharmacokinetic data/ parameters were listed and summarized.

Study Population: Inclusion/Exclusion Criteria and Demographics

Key Inclusion Criterion:

• Male and female atopic dermatitis patients,18 to 60 years of age inclusive, who fulfilled the following criteria at Baseline:

- Requirement of systemic therapy
- Itch VAS score higher than 50 mm
- EASI score higher than 8

Key Exclusion Criteria:

- Women of child-bearing potential not willing to use two highly effective methods of contraception. Similarly, men not willing to use two acceptable methods of contraception.
- Any systemic immunosuppressive treatment and/or phototherapy within 4 weeks prior to the first dosing.
- Use of any systemic antihistamines or topical corticosteroids within one week prior to first dosing and for the duration of the treatment period. Any other topical or oral treatment for atopic dermatitis (except emollients prescribed by the investigator) within 2 weeks prior to the first dosing were also excluded.

Demographics:

The demographics evaluation of the patients consisted of: age, weight, height, BMI, sex, predom-

inant race, and ethnicity.

Participant Flow

	DNK333 1 mg b.i.d. N=12 n (%)	DNK333 5 mg b.i.d. N=14 n (%)	DNK333 25 mg b.i.d. N=13 n (%)	DNK333 100 mg b.i.d. N=12 n (%)	Placebo N=17 n (%)	Positive Control N=12 n (%)	Total N=80 n (%)
Patients							
Completed	12 (100.0)	14 (100.0)	12 (92.3)	12 (100.0)	15 (88.2)	12 (0.0)	77 (96.3)
Discontinued	0 (0.0)	0 (0.0)	1 (7.7)	0 (0.0)	2 (11.8)	0 (0.0)	3 (3.8)
Main cause of discontinuation							
Adverse event(s)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.9)	0 (0.0)	1 (1.3)
Subject withdrew consent	0 (0.0)	0 (0.0)	1 (7.7)	0 (0.0)	1 (5.9)	0 (0.0)	2 (2.5)

Baseline Characteristics

		DNK333 1 mg b.i.d. N=12	DNK333 5 mg b.i.d. N=14	DNK333 25 mg b.i.d. N=13	DNK333 100 mg b.i.d. N=12	Placebo N=17	Positive Control N=12
Age (years)	Mean	29.3	30.9	24.8	34.5	30.6	31.2
	SD	9.19	8.80	4.88	9.83	11.78	11.11
	Median	26.5	27.5	25.0	33.0	25.0	28.5
	Range	26.5-50	22-51	18-38	23-49	19-23	20-56
Height (cm)	Mean	175.7	171.0	174.8	171.8	175.5	178.1
	SD	13.34	8.16	7.35	8.45	8.74	8.87
	Median	175.0	170.0	172.0	173.5	173.0	177.0
	Range	157-202	159-187	164-187	160-185	161-190	168-195
Weight	Mean	74.46	70.67	73.39	74.38	73.22	77.31
	SD	17.073	12.692	12.175	16.411	12.625	15.69
	Median	73.45	69.90	73.20	74.75	76.00	75.75
	Range	51.9 - 104.7	51.0-94.2	53.0-97.0	50.0-103.0	52.7-98.6	55.0-108.0
BMI (kg/m^2)	Mean	23.833	24.111	23.962	25.021	23.730	24.365
	SD	2.8153	3.8444	3.3501	4.2009	3.6282	4.7254
	Median	23.200	23.572	23.492	25.515	22.964	23.505

	Range	19.3 - 28.7	19.98-34.60	18.78-29.67	18.42-31.00	17.81-32.56	18.96-34.47
Sex (n %)	Male	5 (41.7)	6 (42.9)	6 (46.2)	3 (25.0)	8 (47.1)	8 (66.7)
	Female	7 (58.3)	8 (57.1)	7 (53.8)	9 (75.0)	9 (52.9)	4 (33.3)
Predominant Race (n %)	Caucasian	12 (100.0)	14 (100.0)	12 (92.3)	12 (100.0)	16 (94.1)	11 (91.7)
	Asian					1 (5.9)	1 (8.3)
	Other			1 (7.7)			
Ethnicity (n %)	Hispanic		3 (21.4)	2 (15.4)	4 (33.3)	1 (5.9)	2 (16.7)
	Japanese					1 (5.9)	1 (8.3)
	Mixed					1 (5.9)	
	Other	12 (100.0)	11 (78.6)	11 (84.6)	8 (66.7)	14 (82.4)	9 (75.0)

Outcome

Primary Outcome Results

Ratio to baseline: DNK333 vs Placebo:

Treatment	n	LS Geo-mean (90% CI)	Ratio DNK333:Placebo (60% CI)	P-value (1-sided)
Nocturnal activity intensity				
DNK333 1 mg b.i.d.	12	1.2 (1.0,1.5)	1.01 (0.89,1.15)	0.5260
DNK333 5 mg b.i.d.	14	0.9 (0.8,1.1)	0.75 (0.67,0.85)	0.0259*
DNK333 25 mg b.i.d.	13	0.9 (0.8,1.1)	0.79 (0.69,0.89)	0.0541*
DNK333 100 mg b.i.d.	10	0.8 (0.7,1.0)	0.70 (0.61,0.80)	0.0129*
Placebo	16	1.2 (1.0,1.4)		
Nocturnal activity counts above zero				
DNK333 1 mg b.i.d.	12	1.3 (1.0,1.5)	1.08 (0.96,1.23)	0.7061
DNK333 5 mg b.i.d.	14	0.9 (0.8,1.1)	0.80 (0.71,0.90)	0.0566*
DNK333 25 mg b.i.d.	13	0.9 (0.7,1.0)	0.74 (0.65,0.83)	0.0191*
DNK333 100 mg b.i.d.	10	0.9 (0.7,1.1)	0.77 (0.67,0.87)	0.0464*
Placebo	16	1.2 (1.0,1.4)		
VAS Score				
DNK333 1 mg b.i.d.	12	0.9 (0.4,2.0)	1.29 (0.76,2.19)	0.6563
DNK333 5 mg b.i.d.	14	0.8 (0.4,1.6)	1.09 (0.66,1.82)	0.5598
DNK333 25 mg b.i.d.	13	0.9 (0.4,1.9)	1.27 (0.76,2.13)	0.6516
DNK333 100 mg b.i.d.	12	0.6 (0.3,1.3)	0.81 (0.48,1.37)	0.3678
Placebo	17	0.7 (0.4,1.4)		

Ratio to baseline: Positive Control vs Placebo:

Treatment	n	LS Geo-mean (90% CI)	Ratio Positive Control:Placebo (60% CI)	P-value (1-sided)
Nocturnal activity intensity				
Positive Control	11	0.8 (0.7,1.0)	0.70 (0.62,0.80)	0.0123
Placebo	16	1.2 (1.0,1.4)		
Nocturnal activity counts above zero				
Positive Control	11	0.9 (0.7,1.1)	0.75 (0.66,0.85)	0.0282
Placebo	16	1.2 (1.0,1.4)		
VAS Score				
Positive Control	12	0.0 (0.0,0.1)	0.06 (0.04,0.11)	< 0.001
Placebo	17	0.7 (0.4,1.4)		

Secondary Outcome Result(s)

Patient Benefit Index for Pruritus (PBIfP)

Summary of the Patient Benefit Index for Pruritus (PBIfP) by treatment group

PBIfP	DNK333 1mg (n=12)	DNK333 5mg (n=14)	DNK333 25mg (n=12)	DNK333 100 mg (n=12)	Placebo (n=15)	Control (n=12)
median	1.61	1.55	1.57	2.08	1.47	3.52
(min, max)	(0.9, 4.6)	(0.6, 4.1)	(0.7, 4.4)	(1.1, 4.3)	(0.7, 3.8)	(1.5, 5.0)

Eczema Area Severity Index (EASI) total score

Summary of the median Eczema Area Severity Index (EASI) total score by treatment group and time point	DNK333 1mg (n=12)	DNK333 5mg (n=14)	DNK333 25mg (n=13)	DNK333 100 mg (n=12)	Placebo (n=17)	Control (n=12)
Screening	15.60	12.60	10.20	9.35	11.20	16.55

Baseline	14.65	12.85	11.40	12.30	14.50	15.10
Day 1	13.70	12.90	10.50	12.35	15.20	15.45
Day 3	10.45	13.15	9.90	9.30	11.65	10.20
Day 8	7.85	12.70	9.50	9.30	11.50	8.20
Day 10	10.20	9.30	10.00	10.60	9.80	5.05
Day 14	10.40	7.50	10.40	7.10	9.50	3.90
Day 15		7.60	11.25	6.75	9.15	2.80
EOS	8.25	7.10	10.20	6.60	8.30	3.40

Quality of life for Atopic Dermatitis (QoLIAD)

No clinically relevant changes could be observed in the Quality of life for atopic dermatitis when comparing the results from baseline to Day 14

Summary statisitics for plasma DNK333 parameters following multiple oral doses of 1 mg to 100 mg DNK333 : Day 1 and Day 14

Day 1

Treatment	Statistic	AUC0-12h (ng.h/mL)	Cmax (ng/mL)	Tmax [1] (h)
1 mg	Mean (SD)	31.9 (12.6)	9.15 (3.31)	1.00
	CV% mean	39.4	36.1	0.50 - 2.00
5 mg	Mean (SD)	316 (193)	81.0 (53.3)	1.02
	CV% mean	61.1	65.7	0.50 - 1.57
25 mg	Mean (SD)	1250 (169)	308 (73.3)	1.00
	CV% mean	13.6	23.8	0.50 – 1.50
100 mg	Mean (SD)	6060 (1480)	1350 (285)	1.50
	CV% mean	24.5	21.2	1.00 -1.52

Day 14

Treat-ment	Statistic	AUCtau,ss (ng.h/mL)	Cmax,ss (ng/mL)	Tmax,ss [1] (h)	CL/F (L/h)	Vz/F (L)	Racc [2]
1 mg	Mean (SD)	57.2 (29.2)	12.8 (4.82)	1.00	25.5 (19.1)	177 (54.1)	1.62/1.36
	CV%	51.1	37.8	0.50 - 2.00	74.9	30.6	
5 mg	Mean (SD)	456 (221)	90.6 (23.3)	0.509	31.1 (5.36)	117 (49.8)	1.47/1.22
	CV%	48.4	25.8	0.47 – 1.50	41.0	42.7	
25 mg	Mean (SD)	1970 (413)	371 (70.2)	1.01	13.4 (3.70)	172 (111)	1.62/1.22
	CV%	21.0	18.9	0.92 – 11.9	27.6	64.5	
100 mg	Mean (SD)	10400 (4200)	1590 (511)	1.50	10.9 (3.96)	139 (72.9)	1.65/1.16
	CV%	40.2	32.2	0.98 – 2.00	36.2	52.4	

1) median and range are given for Tmax, 2) Racc based on ratio of geometric means of Cmax and AUC0-12h (Cmax / AUC0-12h)

Summary statistics of DNK333 skin concentrations at Day 14

Treatment	Sampling time	n	mean (SD) conc. (ng/g)	CV% mean	min; max (ng/g)
1 mg b.i.d.	predose	12	3.05 (2.96)	96.9	0; 7.37
5 mg b.i.d.	predose	14	10.6 (10.5	99.0	0; 30.4
	2 h post morning dose	10	15.5 (16.1)	103.8	0; 42.4
25 mg b.i.d.	predose	12	73.9 (52.2)	70.7	0; 191
	2 h post morning dose	12	95.0 (52.1)	54.8	25.0; 189
100 mg b.i.d.	predose	10	287 (173)	60.3	50.7; 502
	2 h post morning dose	10	513 (276)	53.7	0; 957

Summary statistics for plasma PK parameters following a single dose of 25 mg and 100 mg DNK333 as a solid formulation at steady state

Day 15

Treatment	**Statistic**	**AUCtau,ss** (ng.h/mL)	**Cmax,ss** (ng/mL)	**Tmax,ss** * (h)	**CL/F** (L/h)	**Vz/F** (L)
25 mg	Mean (SD)	1840 (480)	323 (89.4)	1.50	14.9 (5.79)	154 (74.1)
	CV%	26.1	27.7	0.97 – 2.05	38.9	48.1
100 mg	Mean (SD)	9490 (4020)	1450 (557)	1.50	12.0 (4.08)	147 (68.7)
	CV%	42.3	38.4	1.00 – 4.00	34.0	46.8

* median and range are given for Tmax

Safety Results

Incidence of Adverse Events (AEs) by primary system organ class in patients with atopic dermatitis (Safety set)

	DNK333 1 mg N= 12 n (%)	DNK333 5 mg N= 14 n (%)	DNK333 25 mg N=13 n (%)	DNK333 100 mg N=12 n (%)	Placebo N= 17 n (%)	Positive Control N= 12 n (%)
Patients with at least one AE	7 (58.3)	8 (57.1)	9 (69.2)	9 (75.0)	7 (41.2)	9 (75.0)
Primary system organ class						
Nervous system disorders	2 (16.7)	4 (28.6)	3 (23.1)	2 (16.7)	1 (5.9)	17 (21.3)
Infections & infestations	1 (8.3)	4 (28.6)	3 (23.1)	2 (16.7)	3 (17.6)	5 (41.7)
Gastrointestinal disorders	1 (8.3)	0 (0.0)	3 (23.1)	3 (25.0)	1 (5.9)	4 (33.3)
General disorders & administration site conditions	0 (0.0)	1 (7.1)	0 (0.0)	1 (8.3)	1 (5.9)	2 (16.7)
Injury and procedural complications	0 (0.0)	0 (0.0)	0 (0.0)	2 (16.7)	2 (16.7)	0 (0.0)
Skin & subcutaneous tissue disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (11.8)	1 (8.3)
Vascular disorders	0 (0.0)	0 (0.0)	2 (15.4)	0 (0.0)	0 (0.0)	0 (0.0)
Eye disorders	0 (0.0)	1 (7.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Investigations	0 (0.0)	1 (7.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)
Musculoskeletal & connective tissue disorders	1 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory disorders	1 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Immune system disorders	1 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Renal & urinary disorders	0 (0.0)	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Blood and lymphatic system disorders	1 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Reproductive system & breast disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)

Metabolism and nutrition disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)
Sleep disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)	0 (0.0)

Severity of Adverse Events (AE) by preferred term (Safety set)

Preferred Term	Severity	DNK333 1 mg N=12 n (%)	DNK333 5 mg N=14 n (%)	DNK333 25 mg N=13 n (%)	DNK333 100 mg N=12 n (%)	Placebo N=17 n (%)	Control N=12 n (%)
Total AEs							
	Mild	4 (33.3)	3 (21.4)	4 (30.8)	8 (66.7)	4 (23.5)	2 (16.7)
	Moderate	3 (25.0)	5 (35.7)	5 (38.5)	1 (8.3)	3 (17.6)	5 (41.7)
	Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (16.7)
Leukocytosis	Mild	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)
Lymphadenopathy	Mild	1 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Eyelid edema	Mild	0 (0.0)	1 (7.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Abdominal discomfort	Mild	1 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Diarrhea	Moderate	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)
Dry Mouth	Moderate	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)
Dyspepsia	Mild	0 (0.0)	0 (0.0)	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)
Flatulence	Mild	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)	0 (0.0)	0 (0.0)
Gastric disorder	Mild	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)
Gastritis	Moderate	0 (0.0)	0 (0.0)	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea	Mild	0 (0.0)	0 (0.0)	1 (7.7)	2 (16.7)	0 (0.0)	1 (8.3)
Nausea	Moderate	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.9)	0 (0.0)
Toothache	Mild	0 (0.0)	0 (0.0)	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)
	Moderate	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (16.7)
Fatigue	Mild	0 (0.0)	1 (7.1)	0 (0.0)	1 (8.3)	1 (5.9)	0 (0.0)
	Moderate	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (16.7)
Seasonal allergy	Mild	1 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cystitis	Mild	0 (0.0)	0 (0.0)	0 (0.0)	1 (8,3)	0 (0.0)	0 (0.0)
Epstein Barr Virus Infection	Moderate	0 (0.0)	1 (7.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Folliculitis	Mild	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)
Gastroenteritis	Mild	0 (0.0)	1 (7.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nasopharyngitis	Mild	1 (8.3)	0 (0.0)	1 (7.7)	2 (16.7)	2 (11.8)	3 (25.0)
	Moderate	0 (0.0)	1 (7.1)	1 (7.7)	0 (0.0)	1 (5.9)	0 (0.0)
Oral herpes	Mild	0 (0.0)	1 (7.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Otitis media	Moderate	0 (0.0)	0 (0.0)	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)
Wound infection	Moderate	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)
Joint injury	Moderate	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)
Joint sprain	Moderate	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)

Post procedural complication	Mild	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.9.)	0 (0.0)
	Moderate	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)	0 (0.0)	0 (0.0)
Post procedural swelling	Mild	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)	0 (0.0)	0 (0.0)
Blood creatine Phosphokinase increased	Mild	0 (0.0)	1 (7.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Weight increased	Moderate	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)
Decreased appetite	Mild	0 (0.0)	0 (0.0)	2 (15.4)	0 (0.0)	1 (5.9)	0 (0.0)
Increased appetite	Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)
Joint range of motion decreased	Moderate	1 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pain in extremity	Moderate	1 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dysgeusia	Mild	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)
Head ache	Mild	1 (8.3)	2 (14.3)	1 (7.7)	1 (8.3)	1 (5.9)	2 (16.7)
	Moderate	1 (8.3)	2 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)
	Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)
Orthostatic intolerance	Moderate	1 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Somnolence	Mild	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)	0 (0.0)	0 (0.0)
Sleep disorder	Moderate	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)
Renal pain	Mild	0 (0.0)	0 (0.0)	1 (7,7)	0 (0.0)	0 (0.0)	0 (0.0)
Semen discoloration	Mild	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)
Rhinorrhoea	Moderate	1 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Angioedema	Moderate	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.9)	0 (0.0)
Dermatitis atopic	Mild	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)
Urticaria	Mild	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.9)	0 (0.0)
Poor peripheral circulation	Mild	0 (0.0)	0 (0.0)	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)
Thrombophlebitis	Mild	0 (0.0)	0 (0.0)	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)

Serious Adverse Events and Deaths

There were no deaths, other serious adverse events or other significant adverse events.

Other Relevant Findings

None.

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