



Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Trial Indication(s)

Relapsed or refractory multiple myeloma

Protocol Number

CLGH447X2101

Protocol Title

A Multi-Center, Open-Label, Dose Escalation, Phase 1 Study of Oral LGH447 in Patients with Relapsed and/or Refractory Multiple Myeloma

Clinical Trial Phase

Phase 1

Phase of Drug Development

Phase I

Study Start/End Dates

Study Start Date: April 2012 (Actual)

Primary Completion Date: June 2019 (Actual)

Study Completion Date: June 2019 (Actual)

Study Design/Methodology

This was a Phase I, open-label, dose escalation study to determine MTD and/or recommended dose for expansion (RDE) of LGH447 in patients with relapsed or refractory multiple myeloma (MM) for which no effective treatment options exist. Following MTD/RDE declaration, additional patients will be enrolled and treated at this dose level and regimen to further assess safety and preliminary anti –tumor activity of LGH447 and its effect on the pharmacokinetics (PK) of midazolam (expansion part).

Centers

8 centers in 4 countries: United States(4), Singapore(1), Spain(1), Germany(2)

Objectives:

Primary objective:

To estimate the maximum tolerated dose (MTD) and/or recommended dose for expansion (RDE) of LGH447 in patients with relapsed or refractory MM.

Secondary objectives:

- To characterize the safety and tolerability of LGH447
- To evaluate the PK of LGH447 and its metabolites, if appropriate
- To evaluate the effect of multiple-doses of LGH447 on the PK of midazolam
- To assess the pharmacodynamics effects of LGH447
- To describe any preliminary anti-myeloma activity associated with LGH447

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

LGH447 was provided as hard gelatin capsules, and was orally dosed on a flat scale of mg/day once daily (not adjusted to body weight or body surface area). During the dose expansion part, midazolam was administered as an oral solution (2 mg/mL) for use on specified days: Day -7 and Cycle 1, Day 14.

Statistical Methods

A 2-parameter adaptive Bayesian Logistic Regression Model (BLRM) guided by the Escalation with Overdose Control (EWOC) principle was the guide for the dose-escalation of treatment with LGH447 to the MTD (maximum tolerated dose). The model was fitted on the Cycle 1 dose-limiting toxicity data (i.e. absence or presence of DLT [dose limiting toxicities]). The Bayesian approach required the specification of prior distributions for the model parameters. After patients in each cohort had completed at least one Cycle of LGH447 treatment, the prior distribution was updated with the cumulated DLT data from Cycle 1. Posterior probabilities for the rate of DLT were summarized; the recommendation for the next dose level was based on these probabilities.

Dose recommendations were based on posterior summaries for each dose, primarily the posterior probabilities for the following three (3) intervals:

1. (0, 16%) under-dosing
2. (16%, 33%) targeted toxicity
3. (33%, 100%) excessive/unacceptable toxicity

Following the principle of EWOC, after each cohort of patients the recommended dose was the one with the highest posterior probability of the DLT rate falling in the target interval (16%, 33%) among the doses fulfilling EWOC, such that it was unlikely (<25% posterior probability) that the DLT rate at the dose was either excessively or unacceptably toxic (DLT rate $\geq 33\%$).

The final recommended dose was based on the dose estimated by the logistic model, and on an overall assessment of safety taking into consideration tolerability, disease responses and PK data available from all cycles at all different dose levels tested and PD data on the biologic activity of LGH447.

The posterior distribution of model parameters and posterior distribution of DLT rates based on the DLT data from all patients enrolled in the study and included in the DDS were presented graphically.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

- Confirmed diagnosis of multiple myeloma that is relapsed or refractory for which no curative option exists.
- Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2.

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- During the dose expansion part of the study patients must have measurable disease defined by at least 1 of the following 2 measurements:

o Serum M-protein ≥ 0.5 g/dL

o Urine M-protein ≥ 200 mg/24 hours OR Serum free light chain (FLC) > 100 mg/L of involved FLC

Exclusion Criteria:

- Patients who are currently receiving treatment with medications that meet one of the following criteria and that cannot be discontinued at least one week prior to the start of treatment with LGH447:

o Strong inhibitors or inducers of CYP3A4 and CYP2D6

o CYP3A4, CYP2B6 and CYP2D6 substrates with narrow therapeutic index

Other protocol-defined inclusion/exclusion criteria applied.

Participant Flow Table

Overall Study

	LGH447 70 mg	LGH447 150 mg	LGH447 200 mg	LGH447 250 mg	LGH447 300 mg	LGH447 350 mg	LGH447 400 mg	LGH447 500 mg	LGH447 700 mg	Total
Arm/Group Description	escalation	escalation	escalation	escalation	escalation and expansion	escalation	escalation	escalation	escalation	
Started	5	6	6	7	24	10	5	10	6	79
Completed	5	6	5	7	16	5	4	8	4	60
Not Completed	0	0	1	0	8	5	1	2	2	19
protocol deviation	0	0	0	0	0	0	0	1	0	1
disease progression	0	0	0	0	1	1	0	1	1	4
Death	0	0	0	0	0	0	1	0	1	2
Lost to Follow-up	0	0	0	0	1	0	0	0	0	1

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Withdrawal by Subject	0	0	1	0	4	3	0	0	0	8
missing	0	0	0	0	2	1	0	0	0	3

Baseline Characteristics

	LGH447 70 mg	LGH447 150 mg	LGH447 200 mg	LGH447 250 mg	LGH447 300 mg	LGH447 350 mg	LGH447 400 mg	LGH447 500 mg	LGH447 700 mg	Total
Arm/Group Description	escalation	escalation	escalation	escalation	escalation and expansion	escalation	escalation	escalation	escalation	
Number of Participants [units: participants]	5	6	6	7	24	10	5	10	6	79
Age Continuous (units: years) Mean \pm Standard Deviation	59.6 \pm 13.03	60.7 \pm 10.01	69.2 \pm 9.83	71.3 \pm 4.50	65.8 \pm 5.77	60.6 \pm 11.94	57.0 \pm 11.11	65.3 \pm 8.35	63.5 \pm 7.01	64.3 \pm 9.02
Sex: Female, Male (units: participants) Count of Participants (Not Applicable)										
Female	2	2	5	4	7	4	4	4	2	34
Male	3	4	1	3	17	6	1	6	4	45
Race/Ethnicity, Customized^[1] (units: participants) Count of Participants (Not Applicable)										
Asian	1	2	0	1	1	2	1	0	0	8
Black	0	2	1	0	0	2	0	0	0	5
Caucasian	4	2	5	6	23	6	4	10	6	66

[1] race

Summary of Efficacy

Primary Outcome Result(s)

Estimate the MTD and/or RDE : number of participants with dose limiting toxicity in escalation phase

(Time Frame: 12 months)

	LGH447 70 mg	LGH447 150 mg	LGH447 200 mg	LGH447 250 mg	LGH447 300 mg	LGH447 350 mg	LGH447 400 mg	LGH447 500 mg	LGH447 700 mg
Arm/Group Description	escalation	escalation	escalation	escalation	escalation and expansion	escalation	escalation	escalation	escalation
Number of Participants Analyzed [units: participants]	4	5	6	7	7	10	5	10	6
Estimate the MTD and/or RDE : number of participants with dose limiting toxicity in escalation phase (units: participants) Count of Participants (Not Applicable)	0 (%)	0 (%)	1 (16.67%)	1 (14.29%)	2 (28.57%)	1 (10%)	2 (40%)	2 (20%)	2 (33.33%)

Secondary Outcome Result(s)

Pharmacokinetic (PK) effects of LGH447: AUC and Cmax

(Time Frame: day 1)

	LGH447 70 mg	LGH447 150 mg	LGH447 200 mg	LGH447 250 mg	LGH447 300 mg	LGH447 350 mg	LGH447 400 mg	LGH447 500 mg	LGH447 700 mg
Arm/Group Description	escalation	escalation	escalation	escalation	escalation and expansion	escalation	escalation	escalation	escalation
Number of Participants Analyzed [units: participants]	5	6	5	7	24	10	5	10	6
Pharmacokinetic (PK) effects of LGH447: AUC and Cmax (units: ng/ml; hr*ng/ml) Geometric Mean (Geometric Coefficient of Variation)									
Cmax (ng/ml) day 1	510 (32.3%)	623 (60.2%)	1270 (63.9%)	1630 (50.6%)	1480 (52.6%)	2610 (55.6%)	1960 (28.2%)	2990 (48.8%)	3350 (34.2%)
AUC0-24h (hr*ng/ml) day 1	5770 (23.7%)	10300 (38.7%)	26000 (39.9%)	23500 (44.0%)	22100 (53.7%)	42700 (60.3%)	23300 (19.1%)	48700 (48.6%)	61100 (17.3%)
AUClast (hr*ng/ml) day 1	4770 (33.5%)	9280 (44.1%)	19400 (65.0%)	25400 (49.9%)	21400 (60.6%)	23000 (284.4%)	26600 (48.8%)	32700 (87.2%)	46600 (77.7%)
Cmax (ng/ml) day 14	1900 (12.0%)	2300 (35.1%)	4000 (27.6%)	4180 (54.4%)	4220 (43.4%)	4030 (33.2%)	3350 (32.4%)	6570 (24.1%)	6090 (22.7%)
AUC0-24h (hr*ng/ml) day 14	33500 (16.4%)	43800 (31.7%)	76600 (39.9%)	89700 (50.5%)	84400 (50.0%)	75100 (34.2%)	63900 (33.5%)	117000 (29.0%)	102000 (25.1%)
AUClast (hr*ng/ml) day 14	33500 (16.6%)	43600 (31.5%)	76100 (41.2%)	81500 (50.2%)	77700 (54.8%)	75100 (34.3%)	66800 (39.9%)	108000 (43.8%)	89500 (47.3%)

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C _{max} (ng/ml) day 28	1770 (41.2%)	2240 (27.2%)	4080 (63.1%)	3000 (67.6%)	3560 (38.4%)	4060 (29.2%)	4140 (27.3%)	5880 (46.4%)	5710 (28.4%)
AUC _{0-24h} (hr*ng/ml) day 28	29400 (21.2%)	45800 (33.5%)	133000 (42.9%)	65600 (82.9%)	71700 (47.5%)	75300 (25.8%)	69300 (22.5%)	103000 (14.2%)	101000 (34.3%)
AUC _{last} (hr*ng/ml) day 28	27500 (18.4%)	46000 (34.0%)	78300 (75.0%)	61400 (62.1%)	63100 (54.1%)	66200 (30.1%)	69100 (20.9%)	98400 (53.4%)	85900 (66.0%)

Anti-Myeloma activity associated with LGH447 : Overall Response Rate (ORR), Duration of Response (DOR), and Progression Free Survival (PFS) based on International Myeloma Working Group Response Criteria.

(Time Frame: 18 months)

	LGH447 70 mg	LGH447 150 mg	LGH447 200 mg	LGH447 250 mg	LGH447 300 mg	LGH447 350 mg	LGH447 400 mg	LGH447 500 mg	LGH447 700 mg
Arm/Group Description	escalation	escalation	escalation	escalation	escalation and expansion	escalation	escalation	escalation	escalation
Number of Participants Analyzed [units: participants]	5	6	6	7	24	10	5	10	6

Anti-Myeloma activity associated with LGH447 : Overall Response Rate (ORR), Duration of Response (DOR), and Progression Free Survival (PFS) based on International Myeloma Working Group Response Criteria.

(units: participants)

Count of Participants (Not Applicable)

Stringent complete response	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)
Complete response	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)
Very good partial response	0 (%)	0 (%)	1 (16.67%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)
Partial response	0 (%)	1 (16.67%)	0 (%)	0 (%)	1 (4.17%)	2 (20%)	0 (%)	1 (10%)	1 (16.67%)

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Minor response	0 (%)	0 (%)	0 (%)	2 (28.57%)	8 (33.33%)	2 (20%)	0 (%)	1 (10%)	0 (%)
Stable disease	2 (40%)	4 (66.67%)	4 (66.67%)	3 (42.86%)	7 (29.17%)	4 (40%)	2 (40%)	6 (60%)	5 (83.33%)
Progressive disease	3 (60%)	1 (16.67%)	1 (16.67%)	2 (28.57%)	4 (16.67%)	2 (20%)	1 (20%)	1 (10%)	0 (%)
Unknown	0 (%)	0 (%)	0 (%)	0 (%)	1 (4.17%)	0 (%)	0 (%)	0 (%)	0 (%)
not done	0 (%)	0 (%)	0 (%)	0 (%)	3 (12.5%)	0 (%)	2 (40%)	1 (10%)	0 (%)

Effect of multiple-doses of LGH447 on the PK of midazolam (ratio of geometric mean)

(Time Frame: 6 months)

LGH447 300 mg	
Arm/Group Description	escalation and expansion
Number of Participants Analyzed [units: participants]	11
Effect of multiple-doses of LGH447 on the PK of midazolam (ratio of geometric mean) (units: ng/ml; h*ng/ml; h) Geometric Mean (Other Confidence Interval Level)	
AUC(0-24h) (h*ng/ml)	1.09 (0.934 to 1.27)
AUCinf (h*ng/ml)	1.14 (0.946 to 1.36)

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Cmax (ng/ml)	0.857 (0.695 to 1.06)
Tmax (h)	0.017 (0 to 0.083)

Pharmacodynamic (PD) effects of LGH447 - change from baseline

(Time Frame: baseline, day 28)

	LGH447 70 mg	LGH447 150 mg	LGH447 200 mg	LGH447 250 mg	LGH447 300 mg	LGH447 350 mg	LGH447 400 mg	LGH447 500 mg	LGH447 700 mg
Arm/Group Description	escalation	escalation	escalation	escalation	escalation and expansion	escalation	escalation	escalation	escalation
Number of Participants Analyzed [units: participants]	5	6	5	7	24	10	5	10	6
Pharmacodynamic (PD) effects of LGH447 - change from baseline (units: percentage) Median (Full Range)	9.92 (-77.2 to 250.0)	-36.03 (-59.5 to 539.5)	-33.05 (-71.7 to 62.6)	-61.24 (-92.7 to -11.7)	-73.98 (-73.98 to -73.98)	-27.15 (-83.8 to -1.4)	-69.59 (-90.7 to -48.5)	-20.19 (-70.7 to 223.1)	-43.67 (-96.5 to 75.5)

summary of PK parameters for midazolam

(Time Frame: 6 months)

	LGH447 300 mg
Arm/Group Description	escalation and expansion

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**Number of Participants
Analyzed [units:
participants]** 11

**summary of PK parameters for
midazolam**

(units: ng/ml; h*ng/ml;)

Geometric Mean (Geometric Coefficient of
Variation)

Day -7 Cmax (ng/ml)	10200 (45.0%)
Day -7 AUCinf (h*ng/ml)	30800 (60.3%)
Day -7 AUC(0-24h) (h*ng/ml)	29400 (50.3%)
Day 14 Cmax (ng/ml)	8760 (52.8%)
Day 14 AUCinf (h*ng/ml)	32900 (49.1%)
Day 14 AUC(0-24h) (h*ng/ml)	32000 (42.5%)

Summary of Safety

Safety Results

All-Cause Mortality

	70 mg N = 5	150 mg N = 6	200 mg N = 6	250 mg N = 7	300 mg N = 24	350 mg N = 10	400 mg N = 5	500 mg N = 10	700 mg N = 6	All@patients N = 79
Arm/Group Description	70 mg	150 mg	200 mg	250 mg	300 mg	350 mg	400 mg	500 mg	700 mg	All@patients

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Total participants affected	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	1 (16.67%)	2 (2.53%)
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Serious Adverse Events by System Organ Class

Time Frame	7 years									
Additional Description	Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse Events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit.									
Source Vocabulary for Table Default	MedDRA (22.0)									
Assessment Type for Table Default	Systematic Assessment									
	70 mg N = 5	150 mg N = 6	200 mg N = 6	250 mg N = 7	300 mg N = 24	350 mg N = 10	400 mg N = 5	500 mg N = 10	700 mg N = 6	All@patients N = 79
Arm/Group Description	70 mg	150 mg	200 mg	250 mg	300 mg	350 mg	400 mg	500 mg	700 mg	All@patients
Total participants affected	1 (20.00%)	1 (16.67%)	2 (33.33%)	4 (57.14%)	8 (33.33%)	2 (20.00%)	2 (40.00%)	4 (40.00%)	1 (16.67%)	25 (31.65%)
Cardiac disorders										
Congestive cardiomyopathy	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.17%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Palpitations	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Ear and labyrinth disorders										
Vertigo	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Eye disorders										

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Cataract	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.17%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Gastrointestinal disorders										
Diarrhoea	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Gingival disorder	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.17%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
General disorders and administration site conditions										
Pyrexia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Infections and infestations										
Gastroenteritis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Gastrointestinal infection	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Neutropenic sepsis	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Pneumonia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	3 (12.50%)	0 (0.00%)	0 (0.00%)	2 (20.00%)	0 (0.00%)	6 (7.59%)
Respiratory tract infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	2 (2.53%)
Upper respiratory tract infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Urinary tract infection	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.17%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.53%)
Injury, poisoning and procedural complications										
Medication error	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	1 (1.27%)
Tooth fracture	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)

Investigations

C-reactive protein increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Metabolism and nutrition disorders										
Hyperglycaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	1 (1.27%)
Musculoskeletal and connective tissue disorders										
Arthralgia	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Bone pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.17%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Osteoarthritis	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Osteonecrosis of jaw	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)										
Plasmacytoma	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.17%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Nervous system disorders										
Syncope	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (1.27%)
Renal and urinary disorders										
Renal impairment	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Respiratory, thoracic and										

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mediastinal disorders

Pneumonitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.17%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
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Skin and subcutaneous tissue disorders

Photosensitivity reaction	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
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Other Adverse Events by System Organ Class

Time Frame 7 years

Additional Description Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse Events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit.

Source Vocabulary for Table Default MedDRA (22.0)

Assessment Type for Table Default Systematic Assessment

Frequent Event Reporting Threshold 5%

	70 mg N = 5	150 mg N = 6	200 mg N = 6	250 mg N = 7	300 mg N = 24	350 mg N = 10	400 mg N = 5	500 mg N = 10	700 mg N = 6	All@patients N = 79
Arm/Group Description	70 mg	150 mg	200 mg	250 mg	300 mg	350 mg	400 mg	500 mg	700 mg	All@patients
Total participants affected	5 (100.00%)	6 (100.00%)	6 (100.00%)	7 (100.00%)	23 (95.83%)	10 (100.00%)	5 (100.00%)	10 (100.00%)	6 (100.00%)	78 (98.73%)
Blood and lymphatic system disorders										
Anaemia	3 (60.00%)	6 (100.00%)	3 (50.00%)	4 (57.14%)	15 (62.50%)	9 (90.00%)	5 (100.00%)	9 (90.00%)	4 (66.67%)	58 (73.42%)

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Eosinophilia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Leukopenia	0 (0.00%)	2 (33.33%)	0 (0.00%)	1 (14.29%)	4 (16.67%)	1 (10.00%)	0 (0.00%)	2 (20.00%)	2 (33.33%)	12 (15.19%)
Lymphopenia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	3 (12.50%)	1 (10.00%)	0 (0.00%)	1 (10.00%)	3 (50.00%)	9 (11.39%)
Neutropenia	1 (20.00%)	3 (50.00%)	2 (33.33%)	1 (14.29%)	6 (25.00%)	1 (10.00%)	1 (20.00%)	2 (20.00%)	1 (16.67%)	18 (22.78%)
Thrombocytopenia	3 (60.00%)	5 (83.33%)	2 (33.33%)	4 (57.14%)	13 (54.17%)	4 (40.00%)	2 (40.00%)	5 (50.00%)	4 (66.67%)	42 (53.16%)
Cardiac disorders										
Atrial fibrillation	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	2 (2.53%)
Bradycardia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Palpitations	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Sinus bradycardia	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.53%)
Tachycardia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (8.33%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (3.80%)
Ear and labyrinth disorders										
Cerumen impaction	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Ear canal erythema	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Hypoacusis	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	1 (4.17%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.53%)
Tinnitus	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Vertigo	0 (0.00%)	1 (16.67%)	2 (33.33%)	1 (14.29%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	5 (6.33%)

Clinical Trial Results Website
Endocrine disorders

Hypothyroidism	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	1 (1.27%)
Oestrogen deficiency	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)

Eye disorders

Conjunctivitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Conjunctivitis allergic	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Diplopia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.17%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.53%)
Dry eye	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (4.17%)	1 (10.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	4 (5.06%)
Eye pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Eyelid oedema	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Lacrimation increased	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	2 (20.00%)	0 (0.00%)	4 (5.06%)
Photophobia	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Vision blurred	1 (20.00%)	1 (16.67%)	1 (16.67%)	2 (28.57%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	2 (20.00%)	0 (0.00%)	8 (10.13%)
Visual impairment	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.17%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.53%)
Vitreous floaters	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)

Gastrointestinal disorders

Abdominal discomfort	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Abdominal distension	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	2 (2.53%)

Clinical Trial Results Website

Abdominal pain	0 (0.00%)	1 (16.67%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (33.33%)	4 (5.06%)
Abdominal pain upper	0 (0.00%)	1 (16.67%)	1 (16.67%)	2 (28.57%)	1 (4.17%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	2 (33.33%)	8 (10.13%)
Anal fissure	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Anorectal discomfort	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.17%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.53%)
Aphthous ulcer	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Colitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Constipation	0 (0.00%)	1 (16.67%)	2 (33.33%)	2 (28.57%)	3 (12.50%)	3 (30.00%)	0 (0.00%)	2 (20.00%)	0 (0.00%)	13 (16.46%)
Diarrhoea	0 (0.00%)	2 (33.33%)	3 (50.00%)	2 (28.57%)	10 (41.67%)	4 (40.00%)	1 (20.00%)	7 (70.00%)	3 (50.00%)	32 (40.51%)
Dry mouth	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	1 (4.17%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	1 (16.67%)	4 (5.06%)
Dyspepsia	0 (0.00%)	1 (16.67%)	0 (0.00%)	3 (42.86%)	8 (33.33%)	2 (20.00%)	1 (20.00%)	2 (20.00%)	1 (16.67%)	18 (22.78%)
Dysphagia	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (4.17%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (3.80%)
Flatulence	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (8.33%)	0 (0.00%)	0 (0.00%)	2 (20.00%)	0 (0.00%)	4 (5.06%)
Gastrointestinal haemorrhage	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Gastrooesophageal reflux disease	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (12.50%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	5 (6.33%)
Gingival recession	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Haemorrhoidal haemorrhage	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Haemorrhoids	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	2 (2.53%)

Clinical Trial Results Website

Intra-abdominal haematoma	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Nausea	2 (40.00%)	3 (50.00%)	4 (66.67%)	6 (85.71%)	13 (54.17%)	6 (60.00%)	3 (60.00%)	6 (60.00%)	6 (100.00%)	49 (62.03%)
Oesophagitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Oral dysaesthesia	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (14.29%)	2 (8.33%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	5 (6.33%)
Oral pain	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	3 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	4 (5.06%)
Salivary hypersecretion	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	1 (1.27%)
Stomatitis	0 (0.00%)	2 (33.33%)	1 (16.67%)	1 (14.29%)	1 (4.17%)	1 (10.00%)	0 (0.00%)	2 (20.00%)	0 (0.00%)	8 (10.13%)
Tongue discolouration	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.17%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.53%)
Toothache	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	1 (10.00%)	1 (16.67%)	4 (5.06%)
Vomiting	1 (20.00%)	1 (16.67%)	2 (33.33%)	3 (42.86%)	7 (29.17%)	4 (40.00%)	1 (20.00%)	4 (40.00%)	2 (33.33%)	25 (31.65%)
General disorders and administration site conditions										
Asthenia	2 (40.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	4 (16.67%)	1 (10.00%)	0 (0.00%)	2 (20.00%)	2 (33.33%)	12 (15.19%)
Chills	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (1.27%)
Facial pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	1 (1.27%)
Fatigue	1 (20.00%)	2 (33.33%)	2 (33.33%)	5 (71.43%)	12 (50.00%)	4 (40.00%)	0 (0.00%)	5 (50.00%)	2 (33.33%)	33 (41.77%)
Feeling cold	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)

Clinical Trial Results Website

Impaired healing	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Influenza like illness	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Mucosal dryness	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	2 (2.53%)
Non-cardiac chest pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (8.33%)	1 (10.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	4 (5.06%)
Oedema peripheral	0 (0.00%)	1 (16.67%)	1 (16.67%)	2 (28.57%)	4 (16.67%)	2 (20.00%)	0 (0.00%)	1 (10.00%)	1 (16.67%)	12 (15.19%)
Pyrexia	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (42.86%)	0 (0.00%)	2 (20.00%)	0 (0.00%)	2 (20.00%)	1 (16.67%)	8 (10.13%)
Temperature intolerance	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Thirst	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	2 (2.53%)
Immune system disorders										
Hypersensitivity	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Infections and infestations										
Bronchitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	2 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (3.80%)
Candida infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	1 (1.27%)
Cellulitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Clostridium difficile colitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Conjunctivitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.17%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.53%)
Cystitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)

Clinical Trial Results Website

Escherichia urinary tract infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	1 (1.27%)
Gastroenteritis	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.53%)
Gastrointestinal infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Gingival infection	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Gingivitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.53%)
Herpes simplex	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Herpes zoster	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.53%)
Infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (1.27%)
Nasopharyngitis	0 (0.00%)	0 (0.00%)	2 (33.33%)	1 (14.29%)	9 (37.50%)	1 (10.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	14 (17.72%)
Oesophageal candidiasis	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Onychomycosis	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Oral herpes	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (14.29%)	2 (8.33%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	5 (6.33%)
Otitis media	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	1 (1.27%)
Paronychia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	1 (4.17%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (3.80%)
Pneumonia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.53%)
Rash pustular	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.53%)

Clinical Trial Results Website

Respiratory tract infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (42.86%)	4 (16.67%)	1 (10.00%)	0 (0.00%)	1 (10.00%)	2 (33.33%)	11 (13.92%)
Rhinitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.17%)	2 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (3.80%)
Soft tissue infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Tonsillitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.17%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	2 (2.53%)
Tooth infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Upper respiratory tract infection	0 (0.00%)	1 (16.67%)	1 (16.67%)	3 (42.86%)	3 (12.50%)	3 (30.00%)	1 (20.00%)	3 (30.00%)	1 (16.67%)	16 (20.25%)
Urinary tract infection	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (14.29%)	4 (16.67%)	1 (10.00%)	1 (20.00%)	1 (10.00%)	0 (0.00%)	9 (11.39%)
Urinary tract infection bacterial	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	1 (1.27%)
Injury, poisoning and procedural complications										
Arthropod bite	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Back injury	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Bone contusion	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Concussion	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Contusion	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Fall	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	0 (0.00%)	2 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (3.80%)
Foot fracture	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Infusion related reaction	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Limb injury	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	2 (2.53%)

Clinical Trial Results Website

Muscle strain	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Neck injury	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Post-traumatic pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	2 (2.53%)
Procedural pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.17%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.53%)
Road traffic accident	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Scratch	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Sedation complication	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Skeletal injury	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Thoracic vertebral fracture	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Traumatic haematoma	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Investigations										
Alanine aminotransferase increased	0 (0.00%)	0 (0.00%)	2 (33.33%)	1 (14.29%)	5 (20.83%)	1 (10.00%)	1 (20.00%)	4 (40.00%)	1 (16.67%)	15 (18.99%)
Aspartate aminotransferase increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	4 (16.67%)	1 (10.00%)	1 (20.00%)	2 (20.00%)	1 (16.67%)	10 (12.66%)
Blood alkaline phosphatase increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	1 (4.17%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.53%)
Blood cholinesterase decreased	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)

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Blood creatine phosphokinase increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	2 (8.33%)	1 (10.00%)	0 (0.00%)	2 (20.00%)	1 (16.67%)	7 (8.86%)
Blood creatinine increased	2 (40.00%)	1 (16.67%)	2 (33.33%)	3 (42.86%)	5 (20.83%)	2 (20.00%)	0 (0.00%)	4 (40.00%)	2 (33.33%)	21 (26.58%)
Blood glucose increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	1 (4.17%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.53%)
Blood insulin increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (1.27%)
Blood lactate dehydrogenase increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	1 (4.17%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	4 (5.06%)
Blood phosphorus decreased	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	1 (4.17%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.53%)
Blood phosphorus increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Blood pressure systolic increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Blood urea increased	0 (0.00%)	1 (16.67%)	1 (16.67%)	3 (42.86%)	2 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	8 (10.13%)
Blood uric acid increased	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
CD4 lymphocytes decreased	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
C-reactive protein increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (42.86%)	2 (8.33%)	1 (10.00%)	0 (0.00%)	1 (10.00%)	2 (33.33%)	9 (11.39%)
Electrocardiogram QT prolonged	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	4 (16.67%)	0 (0.00%)	0 (0.00%)	2 (20.00%)	1 (16.67%)	7 (8.86%)
Eosinophil count decreased	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Fibrin D dimer increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	1 (4.17%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.53%)

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Gamma-glutamyltransferase increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	1 (4.17%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	3 (3.80%)
Glomerular filtration rate decreased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (20.00%)	0 (0.00%)	2 (2.53%)
Glutamate dehydrogenase increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	1 (4.17%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	3 (3.80%)
Glycosylated haemoglobin increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	1 (1.27%)
Lymphocyte count	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	1 (1.27%)
Lymphocyte count decreased	0 (0.00%)	1 (16.67%)	1 (16.67%)	3 (42.86%)	8 (33.33%)	3 (30.00%)	3 (60.00%)	4 (40.00%)	0 (0.00%)	23 (29.11%)
Neutrophil count	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	1 (1.27%)
Neutrophil count decreased	0 (0.00%)	1 (16.67%)	1 (16.67%)	0 (0.00%)	5 (20.83%)	2 (20.00%)	3 (60.00%)	3 (30.00%)	0 (0.00%)	15 (18.99%)
Platelet count decreased	0 (0.00%)	1 (16.67%)	2 (33.33%)	3 (42.86%)	8 (33.33%)	4 (40.00%)	3 (60.00%)	3 (30.00%)	1 (16.67%)	25 (31.65%)
Procalcitonin increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (1.27%)
Protein total increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Protein urine present	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Sperm concentration decreased	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Weight decreased	0 (0.00%)	0 (0.00%)	0 (0.00%)	4 (57.14%)	1 (4.17%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	6 (7.59%)
Weight increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	3 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	4 (5.06%)

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White blood cell count decreased	0 (0.00%)	1 (16.67%)	2 (33.33%)	3 (42.86%)	11 (45.83%)	2 (20.00%)	3 (60.00%)	4 (40.00%)	0 (0.00%)	26 (32.91%)
Metabolism and nutrition disorders										
Acidosis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	1 (1.27%)
Decreased appetite	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (28.57%)	1 (4.17%)	1 (10.00%)	0 (0.00%)	2 (20.00%)	1 (16.67%)	7 (8.86%)
Dehydration	1 (20.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	2 (20.00%)	0 (0.00%)	5 (6.33%)
Diabetes mellitus	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	1 (4.17%)	1 (10.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	4 (5.06%)
Diabetes mellitus inadequate control	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	2 (2.53%)
Fluid overload	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Hypercalcaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Hyperglycaemia	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (14.29%)	5 (20.83%)	0 (0.00%)	0 (0.00%)	2 (20.00%)	1 (16.67%)	10 (12.66%)
Hyperinsulinaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Hyperkalaemia	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	3 (12.50%)	1 (10.00%)	0 (0.00%)	2 (20.00%)	0 (0.00%)	7 (8.86%)
Hyperphosphataemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	2 (8.33%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	5 (6.33%)
Hyperuricaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	1 (1.27%)
Hypoalbuminaemia	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	1 (4.17%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	4 (5.06%)
Hypocalcaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (8.33%)	1 (10.00%)	0 (0.00%)	2 (20.00%)	1 (16.67%)	6 (7.59%)
Hypokalaemia	0 (0.00%)	2 (33.33%)	1 (16.67%)	1 (14.29%)	1 (4.17%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	1 (16.67%)	7 (8.86%)

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Hypomagnesaemia	0 (0.00%)	1 (16.67%)	1 (16.67%)	0 (0.00%)	1 (4.17%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	2 (33.33%)	6 (7.59%)
Hyponatraemia	1 (20.00%)	0 (0.00%)	0 (0.00%)	2 (28.57%)	1 (4.17%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	1 (16.67%)	6 (7.59%)
Hypophosphataemia	1 (20.00%)	1 (16.67%)	0 (0.00%)	1 (14.29%)	4 (16.67%)	4 (40.00%)	0 (0.00%)	2 (20.00%)	2 (33.33%)	15 (18.99%)
Increased appetite	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	1 (4.17%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.53%)
Metabolic disorder	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Vitamin D deficiency	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Musculoskeletal and connective tissue disorders										
Arthralgia	0 (0.00%)	1 (16.67%)	1 (16.67%)	2 (28.57%)	2 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (33.33%)	8 (10.13%)
Arthritis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Back pain	0 (0.00%)	0 (0.00%)	2 (33.33%)	4 (57.14%)	4 (16.67%)	1 (10.00%)	0 (0.00%)	2 (20.00%)	3 (50.00%)	16 (20.25%)
Bone pain	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	2 (8.33%)	2 (20.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	6 (7.59%)
Exposed bone in jaw	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Flank pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Groin pain	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Joint noise	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Joint swelling	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (1.27%)

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Muscle spasms	1 (20.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	1 (10.00%)	1 (16.67%)	5 (6.33%)
Muscular weakness	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	1 (10.00%)	1 (16.67%)	3 (3.80%)
Musculoskeletal chest pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	1 (1.27%)
Musculoskeletal pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.17%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	2 (2.53%)
Myalgia	0 (0.00%)	0 (0.00%)	2 (33.33%)	0 (0.00%)	2 (8.33%)	1 (10.00%)	1 (20.00%)	2 (20.00%)	1 (16.67%)	9 (11.39%)
Neck pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (28.57%)	1 (4.17%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (3.80%)
Osteoarthritis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Osteonecrosis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Osteonecrosis of jaw	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.53%)
Pain in extremity	0 (0.00%)	1 (16.67%)	2 (33.33%)	1 (14.29%)	4 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	8 (10.13%)
Pain in jaw	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Pathological fracture	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)										
Basal cell carcinoma	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Benign renal neoplasm	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Plasmacytoma	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)

Nervous system disorders

Aphasia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Burning sensation	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.53%)
Cognitive disorder	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Dizziness	0 (0.00%)	2 (33.33%)	1 (16.67%)	3 (42.86%)	3 (12.50%)	4 (40.00%)	0 (0.00%)	2 (20.00%)	2 (33.33%)	17 (21.52%)
Dizziness postural	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (14.29%)	1 (4.17%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (3.80%)
Dysaesthesia	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (14.29%)	2 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	4 (5.06%)
Dysgeusia	1 (20.00%)	1 (16.67%)	0 (0.00%)	1 (14.29%)	2 (8.33%)	2 (20.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	8 (10.13%)
Dyskinesia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.17%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	2 (2.53%)
Headache	1 (20.00%)	0 (0.00%)	0 (0.00%)	2 (28.57%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	2 (20.00%)	1 (16.67%)	7 (8.86%)
Hyperaesthesia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Hypersomnia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Hypoaesthesia	1 (20.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (3.80%)
Hyposmia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Lethargy	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (3.80%)
Memory impairment	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (20.00%)	0 (0.00%)	2 (2.53%)
Neuralgia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)

Clinical Trial Results Website

Neuropathy peripheral	0 (0.00%)	1 (16.67%)	1 (16.67%)	1 (14.29%)	2 (8.33%)	1 (10.00%)	0 (0.00%)	2 (20.00%)	0 (0.00%)	8 (10.13%)
Paraesthesia	0 (0.00%)	1 (16.67%)	1 (16.67%)	0 (0.00%)	5 (20.83%)	2 (20.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	10 (12.66%)
Peripheral sensory neuropathy	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	1 (1.27%)
Presyncope	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	1 (4.17%)	0 (0.00%)	0 (0.00%)	2 (20.00%)	0 (0.00%)	4 (5.06%)
Somnolence	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	1 (1.27%)
Syncope	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (28.57%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.53%)
Taste disorder	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.17%)	1 (10.00%)	0 (0.00%)	1 (10.00%)	1 (16.67%)	4 (5.06%)
Tremor	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (42.86%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (33.33%)	5 (6.33%)
Psychiatric disorders										
Anxiety	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Bulimia nervosa	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (33.33%)	2 (2.53%)
Confusional state	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	2 (2.53%)
Depressed mood	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	1 (1.27%)
Insomnia	1 (20.00%)	1 (16.67%)	2 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	4 (5.06%)
Mental status changes	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (20.00%)	0 (0.00%)	2 (2.53%)
Mood altered	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)

Clinical Trial Results Website

Sleep disorder	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	2 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	4 (5.06%)
Substance-induced psychotic disorder	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Renal and urinary disorders										
Acute kidney injury	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (14.29%)	2 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	4 (5.06%)
Chromaturia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	1 (1.27%)
Dysuria	0 (0.00%)	1 (16.67%)	0 (0.00%)	2 (28.57%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (3.80%)
Pollakiuria	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	1 (1.27%)
Renal failure	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.17%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	2 (2.53%)
Urinary incontinence	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	2 (2.53%)
Reproductive system and breast disorders										
Breast pain	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Respiratory, thoracic and mediastinal disorders										
Asthma	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Catarrh	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	2 (2.53%)
Cough	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (28.57%)	3 (12.50%)	0 (0.00%)	1 (20.00%)	2 (20.00%)	0 (0.00%)	8 (10.13%)

Clinical Trial Results Website

Dysphonia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	3 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	4 (5.06%)
Dyspnoea	0 (0.00%)	1 (16.67%)	1 (16.67%)	0 (0.00%)	3 (12.50%)	3 (30.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	9 (11.39%)
Dyspnoea exertional	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	3 (12.50%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	2 (33.33%)	7 (8.86%)
Epistaxis	0 (0.00%)	0 (0.00%)	1 (16.67%)	2 (28.57%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	4 (5.06%)
Hiccups	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (4.17%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.53%)
Nasal congestion	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Nasal dryness	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	3 (3.80%)
Nasal inflammation	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	2 (2.53%)
Oropharyngeal pain	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (14.29%)	2 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	4 (5.06%)
Productive cough	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Sinus pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Sneezing	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Throat irritation	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	2 (2.53%)
Skin and subcutaneous tissue disorders										
Acne	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Alopecia	0 (0.00%)	1 (16.67%)	1 (16.67%)	0 (0.00%)	1 (4.17%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (3.80%)

Clinical Trial Results Website

Dermatitis exfoliative generalised	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (1.27%)
Dry skin	0 (0.00%)	1 (16.67%)	1 (16.67%)	6 (85.71%)	8 (33.33%)	2 (20.00%)	2 (40.00%)	1 (10.00%)	1 (16.67%)	22 (27.85%)
Ecchymosis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Hyperhidrosis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	1 (1.27%)
Nail dystrophy	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (1.27%)
Neurodermatitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Night sweats	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Onychoclasia	0 (0.00%)	0 (0.00%)	1 (16.67%)	2 (28.57%)	5 (20.83%)	1 (10.00%)	0 (0.00%)	3 (30.00%)	0 (0.00%)	12 (15.19%)
Palmar-plantar erythrodysesthesia syndrome	0 (0.00%)	1 (16.67%)	3 (50.00%)	3 (42.86%)	4 (16.67%)	4 (40.00%)	3 (60.00%)	3 (30.00%)	2 (33.33%)	23 (29.11%)
Petechiae	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (4.17%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.53%)
Pruritus	0 (0.00%)	1 (16.67%)	2 (33.33%)	2 (28.57%)	2 (8.33%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	1 (16.67%)	9 (11.39%)
Rash	1 (20.00%)	0 (0.00%)	1 (16.67%)	1 (14.29%)	4 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	8 (10.13%)
Rash erythematous	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.17%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.53%)
Rash macular	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (28.57%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.53%)
Rash maculopapular	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (4.17%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.53%)
Skin erosion	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)

Clinical Trial Results Website

Skin exfoliation	0 (0.00%)	0 (0.00%)	2 (33.33%)	1 (14.29%)	4 (16.67%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	8 (10.13%)
Skin hyperpigmentation	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Skin plaque	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Skin ulcer	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	1 (1.27%)
Vascular disorders										
Arteritis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.27%)
Deep vein thrombosis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	2 (2.53%)
Haematoma	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.53%)
Hypertension	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	3 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	4 (5.06%)
Hypotension	0 (0.00%)	2 (33.33%)	1 (16.67%)	3 (42.86%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	7 (8.86%)

Other Relevant Findings

NA

Conclusion:

The primary objective of this study was to estimate the MTD and/or RDE of LGH447 as a single agent when administered orally once daily to adult patients with MM. The MTD was established at 500 mg once daily and RDE at 300 mg once daily due to the available data on safety, PK, disease responses and the PK/PD modeling efforts.

Overall, LGH447 was well tolerated at the RDE of 300 mg once daily and displayed preliminary evidence of single agent activity in heavily pretreated patients with relapsed and/or refractory MM.

The most frequently observed DLTs of LGH447 ($\geq 2\%$) were thrombocytopenia (6.7%), platelet count decreased and fatigue (3.3% each).

The ORR was 8.9% [95% CI: 3.6%, 17.4%]. One patient achieved a VGPR and six patients achieved a PR. The DCR was 72.2% [95% CI: 60.9%, 81.7%], and the rate of clinical benefit was 25.3% [95% CI: 16.2%, 36.4%].

The drug exposure (AUC and C_{max}), following a single oral dosing of LGH447 (C1D1), showed approximately dose-proportionality across the dose range tested (70 mg to 700 mg), whereas the exposure became less than dose proportional following multiple daily oral dosing (C1D14 and C1D28). The steady state levels were reached by approximately Day 14 following oral daily dose.

LGH447 is not expected to affect the pharmacokinetics of sensitive CYP3A4 substrates and endogenous 4- β -hydroxycholesterol concentration, thus indicating limited drug-drug interaction potential of LGH447 with CYP3A4 substrates through inhibition of CYP3A4 activity in clinical.

Overall, LGH447 was well tolerated at the RDE of 300 mg once daily and displayed preliminary evidence of single agent activity in heavily pretreated patients with relapsed and/or refractory MM.

Date of Clinical Trial Report

21-Nov-2019