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Clinical Trial Results Database

Sponsor

Novartis

Generic Drug Name

LGH447 (PIM447)

Trial Indication(s)

Relapsed and/or refractory multiple myeloma

Protocol Number

CLGH447X1101

Protocol Title

A multi-center, open-label, dose escalation, Phase 1 study of oral LGH447 in Japanese patients with relapsed and/or refractory hematologic malignancies

Clinical Trial Study Phase

Phase I

Study Start/End Dates

08 Sep 2014 to 10 May 2016

Reason for Termination (If applicable)

The study was terminated early because of changes in the development strategy of LGH447.

Study Design/Methodology

This was a Phase 1, open-label, dose-escalation study to determine the MTD and/or RDE of LGH447 in Japanese patients with relapsed and/or refractory MM for which no standard effective treatment options were available. The study design consisted of a dose escalation part and a dose expansion part. Two cohorts of patients received continuous oral LGH447 (250 mg or 300 mg) once daily on a 28-day cycle. Dose levels were to be explored following the recommendations of an adaptive 2-parameter Bayesian logistic regression model guided by overdose control criteria.

Centers

5 centers in Japan

Objectives:

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

Secondary objectives:

- To characterize the safety and tolerability of LGH447
- To evaluate the pharmacokinetics (PK) of LGH447 and its metabolites if appropriate
- To describe any preliminary anti-cancer activity associated with LGH447

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

LGH447 250 mg or 300 mg was orally administered once daily as a combination of 50 mg and 200 mg capsules.

Statistical Methods

Demographic and baseline characteristics, efficacy and safety observations and measurements, and all relevant PK measurements were summarized using descriptive statistics (quantitative data) and contingency tables (qualitative data). All summaries, listings, figures and analyses were performed by treatment group unless otherwise specified (e.g., AEs).

A 2-parameter adaptive Bayesian logistic regression model with overdose control principle guided the dose escalation of treatment with LGH447. The model was fitted on DLT data in the first 28 days of treatment with LGH447 (i.e., absence or presence of DLTs) accumulated throughout the dose escalation part of the study.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria: Male or female patients ≥18 years with confirmed diagnosis of relapsed and/or refractory multiple myeloma for which no standard effective treatment options exist.

Exclusion criteria: Patients with uncontrolled cardiovascular condition, including ongoing cardiac arrhythmias, congestive heart failure, angina, or myocardial infarction within the past 6 months.

Participant Flow Table

Patient disposition by treatment (full analysis set)

Disposition Reason	LGH447 250 mg N=7 n (%)	LGH447 300 mg N=6 n (%)	All patients N=13 n (%)
Patients treated			
End of treatment	7 (100)	6 (100)	13 (100)
Primary reason for end of treatment			
Physician decision	0	2 (33.3)	2 (15.4)
Progressive disease	7 (100)	4 (66.7)	11 (84.6)
Primary reason for study evaluation completion			
Completed	5 (71.4)	6 (100)	11 (84.6)
Death	1 (14.3)	0	1 (7.7)

Disposition Reason	LGH447 250 mg N=7 n (%)	LGH447 300 mg N=6 n (%)	All patients N=13 n (%)
Subject/guardian decision	1 (14.3)	0	1 (7.7)

Percentages are based on N.

Baseline Characteristics

Demographic and baseline characteristics by treatment (full analysis set)

Demographic variable	LGH447 250 mg N=7	LGH447 300 mg N=6	All patients N=13
Age (years)			
n	7	6	13
Mean	55.7	68.5	61.6
SD	11.37	7.48	11.49
Median	54.0	67.0	67.0
Minimum	42	59	42
Maximum	73	82	82
Age category (years)-n (%)			
< 65	5 (71.4)	1 (16.7)	6 (46.2)
≥ 65	2 (28.6)	5 (83.3)	7 (53.8)
Sex - n (%)			
Female	3 (42.9)	2 (33.3)	5 (38.5)
Male	4 (57.1)	4 (66.7)	8 (61.5)

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Demographic variable	LGH447 250 mg N=7	LGH447 300 mg N=6	All patients N=13
Race - n (%)			
Asian	7 (100)	6 (100)	13 (100)
Ethnicity - n (%)			
Japanese	7 (100)	6 (100)	13 (100)
Weight (kg, at baseline)			
n	7	6	13
Mean	58.94	61.00	59.89
SD	9.671	12.671	10.715
Median	59.80	60.40	59.80
Minimum	41.2	45.4	41.2
Maximum	71.5	78.3	78.3
Height (cm, at baseline)			
n	7	6	13
Mean	160.4	162.3	161.3
SD	8.529	11.291	9.511
Median	159.5	161.5	159.5
Minimum	148.1	149.5	148.1
Maximum	170.0	179.1	179.1
Body mass index (kg/m^2)			
n	7	6	13
Mean	22.98	22.91	22.95
SD	3.842	1.952	2.995
Median	23.36	23.39	23.36
Minimum	16.2	19.4	16.2

Demographic variable	LGH447 250 mg N=7	LGH447 300 mg N=6	All patients N=13
Maximum	27.3	24.6	27.3
ECOG performance status - n (%)			
0	2 (28.6)	3 (50.0)	5 (38.5)
1	2 (28.6)	3 (50.0)	5 (38.5)
2	3 (42.9)	0	3 (23.1)

body mass index = weight in kg at baseline/height in m^2 at Screening

ECOG performance status: 0: fully active, able to carry on all pre-disease performance without restriction; 1: restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work; 2: ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.

Disease history by treatment (full analysis set)

Disease history	LGH447 250 mg N=7	LGH447 300 mg N=6	All patients N=13
Time since initial diagnosis of primary site (months)			
n	7	6	13
Mean	69.40	50.77	60.80
SD	43.806	35.214	39.619
Median	64.49	37.08	52.96
Minimum	23.7	21.9	21.9
Maximum	160.9	118.6	160.9
Number of prior stem cell transplantation-n (%)			
0	2 (28.6)	2 (33.3)	4 (30.8)
1	4 (57.1)	4 (66.7)	8 (61.5)

Disease history	LGH447 250 mg N=7	LGH447 300 mg N=6	All patients N=13
2	1 (14.3)	0	1 (7.7)

Summary of Efficacy

Primary Outcome Result(s)

Refer to Safety Result section for primary outcome result.

Secondary Outcome Result(s)

Summary of primary pharmacokinetic parameters for LGH447 by treatment (pharmacokinetic analysis set)

Treatment	Statistics	AUCtau (hr*ng/mL)	AUClast (hr*ng/mL)	Cmax (ng/mL)	Tmax (hr)
Cycle 1 Day 1					
250 mg (N=7)	n	3	7	7	7
	Mean (SD)	22800 (10700)	26500 (22000)	1610 (1130)	N/A
	CV% mean	47.2	83.1	70.0	N/A
	Geo-mean	21100	20900	1320	N/A
	CV% Geo-mean	51.7	81.7	76.4	N/A
	Median	21100	21000	1320	8.00
	[Min; Max]	[12900; 34200]	[8190; 72600]	[491; 3840]	[4.00; 23.9]
300 mg (N=6)	n	5	6	6	6
	Mean (SD)	26100 (6670)	29700 (10700)	1800 (661)	N/A
	CV% mean	25.5	36.1	36.7	N/A

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Treatment	Statistics	AUCtau (hr*ng/mL)	AUClast (hr*ng/mL)	Cmax (ng/mL)	Tmax (hr)
Cycle 1 Day 1					
	Geo-mean	25400	28200	1700	N/A
	CV% Geo-mean	27.4	36.5	38.9	N/A
	Median	25900	26900	1720	4.58
	[Min; Max]	[16800; 35400]	[16800; 48100]	[976; 2850]	[2.93; 24.1]
Cycle 1 Day 14					
250 mg (N=7)	n	3	5	5	5
	Mean (SD)	105000 (66200)	83800 (55700)	4260 (2200)	N/A
	CV% mean	62.9	66.5	51.8	N/A
	Geo-mean	92300	72700	3920	N/A
	CV% Geo-mean	69.1	61.2	45.0	N/A
	Median	84600	60800	3500	5.97
	[Min; Max]	[51800; 179000]	[42700; 179000]	[2760; 8120]	[4.00; 5.97]
300 mg (N=6)	n	2	4	4	4
	Mean (SD)	88500 (8480)	167000 (99100)	7600 (4370)	N/A
	CV% mean	9.6	59.4	57.5	N/A
	Geo-mean	88300	145000	6710	N/A
	CV% Geo-mean	9.6	66.5	62.8	N/A
	Median	88500	146000	6600	7.03
	[Min; Max]	[82500; 94500]	[81800; 294000]	[3920; 13300]	[2.98; 24.0]
Cycle 1 Day 28					
250 mg (N=7)	n	2	3	3	3

Treatment	Statistics	AUCtau (hr*ng/mL)	AUClast (hr*ng/mL)	Cmax (ng/mL)	Tmax (hr)
Cycle 1 Day 1					
	Mean (SD)	56100 (11100)	62100 (13600)	3020 (609)	N/A
	CV% mean	19.8	21.8	20.1	N/A
	Geo-mean	55600	61100	2980	N/A
	CV% Geo-mean	20.2	22.4	21.7	N/A
	Median	56100	61600	3250	7.80
	[Min; Max]	[48300; 64000]	[48800; 75900]	[2330; 3480]	[3.08; 7.97]
300 mg (N=6)	n	1	3	3	3
	Mean (SD)	95500	192000 (177000)	9090 (7890)	N/A
	CV% mean		92.4	86.8	N/A
	Geo-mean	95500	147000	7200	N/A
	CV% Geo-mean		104.7	95.6	N/A
	Median	95500	92200	4850	8.00
	[Min; Max]	[95500; 95500]	[86900; 397000]	[4230; 18200]	[5.00; 23.9]

n = number of patients with non-missing values. CV% = coefficient of variation (%) = SD/mean*100, CV% geo-mean = sqrt(exp (variance for log transformed data)-1)*100.

Summary of best overall response by treatment, IMWG criteria as per Investigator (full analysis set)

	LGH447 250 mg N=7		LGH447 300 mg N=6		All patients N=13	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
Best overall response						
Stringent complete response (sCR)	0		0		0	

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	LGH447 250 mg N=7		LGH447 300 mg N=6		All patients N=13	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
Complete response (CR)	0		0		0	
Very good partial response (VGPR)	0		0		0	
Partial response (PR)	1 (14.3)		1 (16.7)		2 (15.4)	
Minor response (MR)	1 (14.3)		0		1 (7.7)	
Stable disease (SD)	4 (57.1)		2 (33.3)		6 (46.2)	
Unknown (UNK)	0		1 (16.7)		1 (7.7)	
Progressive disease (PD)	1 (14.3)		2 (33.3)		3 (23.1)	
Overall response rate (ORR: sCR, CR, VGPR or PR)	1 (14.3)	(0.4-57.9)	1 (16.7)	(0.4 - 64.1)	2 (15.4)	(1.9-45.4)
Disease control rate (DCR: sCR, CR, VGPR, PR, MR or SD)	6 (85.7)	(42.1-99.6)	3 (50.0)	(11.8 - 88.2)	9 (69.2)	(38.6-90.9)
Clinical benefit rate (CBR: sCR, CR, VGPR, PR or MR)	2 (28.6)	(3.7-71.0)	1 (16.7)	(0.4-64.1)	3 (23.1)	(5.0-53.8)

Best overall response is based on Investigator's assessment of disease status using the modified response criteria by the International Myeloma Working Group (IMWG).

Best overall response was unknown if a patient had no post-baseline assessment or assessments with only unknown response.

The 95% confidence intervals were calculated using exact binomial distribution.

Summary of Safety

Safety Results

Determination of MTD/RDE

RDE	Not determined
MTD	Not determined

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Dose-limiting toxicities occurring during the first cycle by primary system organ class, preferred term, maximum grade and treatment (DDS)

Primary system organ class Preferred term Maximum Grade	LGH447 250 mg N=5 n	LGH447 300 mg N=4 n	All patients N=9 n
Any primary system organ class			
Grade 3	0	1	1
Investigations			
-Total			
Grade 3	0	1	1
electrocardiogram QT prolonged			
Grade 3	0	1	1

Summary of adverse event categories (safety set)

	LGH447 250 mg N=7		LGH447 300 mg N=6		All patients N=13	
Category	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
All deaths [a]	1 (14.3)		0		1 (7.7)	
On-treatment deaths [b]	1 (14.3)		0		1 (7.7)	
Adverse events	7 (100)	7 (100)	6 (100)	6 (100)	13 (100)	13 (100)
Suspected to drug related	6 (85.7)	5 (71.4)	6 (100)	6 (100)	12 (92.3)	11 (84.6)
Serious adverse events	3 (42.9)	2 (28.6)	3 (50.0)	1 (16.7)	6 (46.2)	3 (23.1)
Suspected to drug related	2 (28.6)	1 (14.3)	2 (33.3)	0	4 (30.8)	1 (7.7)

Category	LGH447 250 mg N=7		LGH447 300 mg N=6		All patients N=13	
	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
AEs leading to study drug discontinuation	0	0	0	0	0	0
Suspected to drug related	0	0	0	0	0	0
AEs leading to dose reductions and interruptions	5 (71.4)	3 (42.9)	5 (83.3)	5 (83.3)	10 (76.9)	8 (61.5)
Suspected to drug related	3 (42.9)	2 (28.6)	5 (83.3)	5 (83.3)	8 (61.5)	7 (53.8)
AEs requiring additional therapy	7 (100)	7 (100)	6 (100)	4 (66.7)	13 (100)	11 (84.6)
Suspected to drug related	6 (85.7)	4 (57.1)	6 (100)	4 (66.7)	12 (92.3)	8 (61.5)

Categories are not mutually exclusive. Patients with multiple events in the same category were counted only once in that category. Patients with events in more than one category were counted once in each of those categories.

Additional therapy includes all non-drug therapy and concomitant medications. Only AEs occurring during treatment or within 30 days of the last dose of LGH447 are reported.

[a] All deaths including those occurring more than 30 days after end of treatment.

[b] Deaths occurring more than 30 days after end of treatment are not included.

MedDRA version 19.0 and CTCAE version 4.03 have been used for the reporting.

All and grade 3/4 adverse events in at least 2 of all patients, regardless of their relationship to LGH447 by primary system organ class, preferred term, and treatment (safety set)

	LGH447 250 mg N=7		LGH447 300 mg N=6		All patients N=13	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4

Primary system organ class Preferred term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any primary system organ class						
-Total	7 (100)	7 (100)	6 (100)	6 (100)	13 (100)	13 (100)
Blood and lymphatic system disorders						
-Total	5 (71.4)	5 (71.4)	6 (100)	5 (83.3)	11 (84.6)	10 (76.9)
Thrombocytopenia	5 (71.4)	5 (71.4)	5 (83.3)	3 (50.0)	10 (76.9)	8 (61.5)
Leukopenia	4 (57.1)	4 (57.1)	5 (83.3)	4 (66.7)	9 (69.2)	8 (61.5)
Anaemia	3 (42.9)	3 (42.9)	5 (83.3)	4 (66.7)	8 (61.5)	7 (53.8)
Lymphopenia	3 (42.9)	2 (28.6)	3 (50.0)	3 (50.0)	6 (46.2)	5 (38.5)
Neutropenia	3 (42.9)	3 (42.9)	3 (50.0)	3 (50.0)	6 (46.2)	6 (46.2)
Gastrointestinal disorders						
-Total	4 (57.1)	0	5 (83.3)	0	9 (69.2)	0
Nausea	3 (42.9)	0	2 (33.3)	0	5 (38.5)	0
Vomiting	1 (14.3)	0	2 (33.3)	0	3 (23.1)	0
Constipation	1 (14.3)	0	1 (16.7)	0	2 (15.4)	0
Dysphagia	2 (28.6)	0	0	0	2 (15.4)	0
Retching	0	0	2 (33.3)	0	2 (15.4)	0
General disorders and administration site conditions						
-Total	4 (57.1)	1 (14.3)	2 (33.3)	0	6 (46.2)	1 (7.7)
Pyrexia	4 (57.1)	0	1 (16.7)	0	5 (38.5)	0
Hepatobiliary disorders						
-Total	1 (14.3)	0	3 (50.0)	0	4 (30.8)	0
Hepatic function abnormal	1 (14.3)	0	3 (50.0)	0	4 (30.8)	0
Infections and infestations						
-Total	4 (57.1)	2 (28.6)	2 (33.3)	0	6 (46.2)	2 (15.4)

Primary system organ class Preferred term	LGH447 250 mg N=7		LGH447 300 mg N=6		All patients N=13	
	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Influenza	2 (28.6)	0	1 (16.7)	0	3 (23.1)	0
Pharyngitis	1 (14.3)	0	1 (16.7)	0	2 (15.4)	0
Pneumonia	1 (14.3)	1 (14.3)	1 (16.7)	0	2 (15.4)	1 (7.7)
Investigations						
-Total	3 (42.9)	0	4 (66.7)	1 (16.7)	7 (53.8)	1 (7.7)
Blood creatinine increased	1 (14.3)	0	1 (16.7)	0	2 (15.4)	0
Electrocardiogram QT prolonged	0	0	2 (33.3)	1 (16.7)	2 (15.4)	1 (7.7)
Metabolism and nutrition disorders						
-Total	6 (85.7)	4 (57.1)	5 (83.3)	2 (33.3)	11 (84.6)	6 (46.2)
Decreased appetite	2 (28.6)	0	3 (50.0)	0	5 (38.5)	0
Hypophosphataemia	2 (28.6)	1 (14.3)	1 (16.7)	1 (16.7)	3 (23.1)	2 (15.4)
Dehydration	1 (14.3)	0	1 (16.7)	0	2 (15.4)	0
Hyperglycaemia	0	0	2 (33.3)	0	2 (15.4)	0
Hyperuricaemia	2 (28.6)	0	0	0	2 (15.4)	0
Hypokalaemia	1 (14.3)	0	1 (16.7)	1 (16.7)	2 (15.4)	1 (7.7)
Tumour lysis syndrome	1 (14.3)	1 (14.3)	1 (16.7)	1 (16.7)	2 (15.4)	2 (15.4)
Nervous system disorders						
-Total	4 (57.1)	0	2 (33.3)	0	6 (46.2)	0
Dizziness	3 (42.9)	0	0	0	3 (23.1)	0
Somnolence	1 (14.3)	0	1 (16.7)	0	2 (15.4)	0

Primary system organ class Preferred term	LGH447 250 mg N=7		LGH447 300 mg N=6		All patients N=13	
	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Renal and urinary disorders						
-Total	0	0	4 (66.7)	0	4 (30.8)	0
Renal impairment	0	0	3 (50.0)	0	3 (23.1)	0

Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class in descending frequency of 'all grades' column, as reported for 'all patients.
A patient with multiple occurrences of an adverse events under one treatment is counted only once in the AE category for that treatment.
A patient with multiple adverse events within a primary system organ class is counted only once in the total row. Only adverse events occurring during treatment or within 30 days of the last dose of LGH447 are reported. MedDRA version 19.0 and CTCAE version 4.03 have been used for the reporting.

Other Relevant Findings

N/A

Conclusion:

- The maximum tolerated dose/ recommended dose for expansion was not determined.
- LGH447 administered at 250 mg or 300 mg once daily appeared to be safe and tolerated in Japanese patients with multiple myeloma.
- The pharmacokinetics exposure of LGH447 increased with the dose without apparent effect of LGH447 on CYP3A4 activity.
- LGH447 displayed single agent anti-tumor responses administered as a single agent at 250 mg or 300 mg once daily regimen, as judged by an overall response rate of 15.4%, a clinical benefit rate of 23.1%, and a disease control rate of 69.2%.

Date of Clinical Trial Report

21 Dec 2016