NOVARTIS

Sponsor

Novartis

Generic Drug Name

LGH447 and alpelisib

Trial Indication(s)

Patients with relapsed and refractory multiple myeloma

Protocol Number

CLGH447X2103C

Protocol Title

A Phase Ib/II, multi-center study of oral LGH447 in combination with oral BYL719 in patients with relapsed and refractory multiple myeloma

Clinical Trial Phase

Ib

Phase of Drug Development

Phase I

Study Start/End Dates

23-Jul-2014 / 28-Oct-2015

Reason for Termination (If applicable)

The study was terminated prematurely as treatment with the combination of LGH447 and BYL719 in patients with relapsed and refractory multiple myeloma was not clinically well tolerated. A MTD was not declared and the Phase II portion of the study was not started.

Study Design/Methodology

The Phase Ib portion is a multi-center, open-label, dose-finding study to estimate the maximum tolerated dose (MTD) and/or recommended Phase II dose (RP2D) for LGH447 in combination with BYL719 in patients with relapsed and refractory multiple myeloma. Successive cohorts of patients received oral LGH447 immediately followed by oral BYL719 qd continuously. Both study drugs were administered on a 28 day cycle. The dose-escalation started with 200 mg qd LGH447 and 100 mg qd BYL719. Dose levels were explored following the recommendations of a Bayesian logistic regression model (BLRM) guided by escalation with overdose control (EWOC) principle.

The Phase II portion is a multi-center, randomized study to estimate the overall response rate (ORR) in patients with relapsed and refractory multiple myeloma randomized to LGH447 in combination with BYL719 or LGH447 alone.

Centers

The study was performed in 6 countries at 9 study centers as follows: Australia (1 center), Germany (2 centers), Italy (1 center), Singapore (1 center), US (3 centers)

Objectives:

Primary objective for Phase Ib was to estimate the maximum tolerated dose (MTD) and/or recommended Phase II dose (RP2D) for LGH447 in combination with BYL719 in patients with relapsed and refractory multiple myeloma.

Primary objective for Phase II is not provided as this was not performed.

Secondary objective for Phase Ib was to characterize the safety and tolerability of LGH447 in combination with BYL719.

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

Novartis supplied LGH447 as 10 mg, 50 mg, and 200 mg capsules for daily oral use (28-day cycles).

BYL719 was provided as 10 mg, 50 mg, and 200 mg tablets for daily oral use(28-day cycles).

Statistical Methods

The primary objective for the Phase Ib part was to estimate the MTD and/or the RP2D of LGH447 in combination with BYL719 given in one or more of the proposed dosing regimens in patients with relapsed and refractory multiple myeloma. The dose-detrmining analysis set (DDS) was used.
The primary endpoint was the incidence of DLTs in Cycle 1. Estimation of the MTD and/or RP2D of the combination treatment was based upon the estimation of the probability of DLT in Cycle 1 for patients in the DDS.
DLTs were listed and their incidence summarized by primary system organ class, preferred term and treatment group. The DDS was used.
For the Phase Ib part, patients treated during the dose escalation with the same dose level and schedule of LGH447 and BYL719 were pooled into a single treatment group.
All summaries, listings, figures and analyses were performed by treatment group (unless otherwise specified).
The study data were analyzed and an abbreviated CSR was written based on all patients' data from the Phase Ib portion of the study at the time when all patients discontinued treatment.
Categorical data are presented as frequencies and percentages. For continuous data, mean, standard deviation, median, 25^{th} and 75^{th} percentiles, minimum, and maximum are presented. Details of the statistical analysis and data reporting were provided in the Novartis Report and Analysis Plan (RAP) document finalized prior to database lock.

Summary tables for AEs included only AEs that started or worsened during the on-treatment period, comprising the treatment-emergent AEs. The incidence of treatment-emergent adverse events (new or worsening from baseline) was summarized by system organ class and or preferred term, severity (based on CTCAE grades), type of adverse event, relation to study treatment, and by treatment group in the Phase Ib portion. Deaths reportable as SAEs and non-fatal serious adverse events were tabulated by primary system organ class, preferred term and maximum grade in the Phase Ib portion.

Study Population: Key Inclusion/Exclusion Criteria

Key inclusion criteria

- Must be able to provide written informed consent before any screening procedures.
- Male or female patients ≥ 18 years of age.
- Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2.
- Patients with a confirmed diagnosis of multiple myeloma who had received two or more lines of therapy and were refractory to their most recent line of therapy, as defined as relapse while on therapy or within 60 days from their last line of therapy. If patient had not received either an immunomodulatory drug or proteasome inhibitor as a prior therapy then Investigator had to notify Novartis prior to the patient enrollment. Patients who had received a prior bone marrow transplant and otherwise met the inclusion criteria were eligible for this study.
- All patients must be willing to undergo a mandatory bone marrow aspirate and/or biopsy at baseline for the assessment of biomarker/pharmacodynamics and disease status.

Key exclusion criteria

- Patients eligible for this study must not meet any of the following criteria:
- Systemic antineoplastic therapy (including unconjugated therapeutic antibodies and toxin immunoconjugates) or any experimental therapy within 14 days or 5 half-lives, whichever is shorter, before the first dose of either study drug.
- Radiotherapy within 14 days before the first dose of either study drug except localized radiation therapy for lytic bone lesions and plasmacytomas.
- Major surgery within 2 weeks before the first dose of either study drug.
- Ongoing therapy with chronic or high dose corticosteroids. Low dose steroids (i.e. prednisone dose ≤ 10 mg or an equivalent steroid dose), inhaled and topical steroids are permitted.
- Patients with ≥ grade 3 neuropathy, or other residual toxic effects of ≥ grade 2 from previous therapy.

Participant Flow Table

Patient disposition by treatment (Full analysis set)

	LGH 200mg + BYL 100mg N=7	LGH 150mg + BYL 150mg N=4	LGH 200mg + BYL 200mg N=9	All patients N=20

	n (%)	n (%)	n (%)	n (%)
Patients treated				
End of treatment	7 (100)	4 (100)	9 (100)	20 (100)
Primary reason for end of treatment				
Adverse Event(s)	3 (42.9)	0	3 (33.3)	6 (30.0)
Subject withdrew consent	1 (14.3)	0	0	1 (5.0)
Death	0	0	1 (11.1)	1 (5.0)
Disease progression	2 (28.6)	3 (75.0)	4 (44.4)	9 (45.0)
Physician's decision	0	1 (25.0)	0	1 (5.0)
Subject/guardian decision	1 (14.3)	0	1 (11.1)	2 (10.0)
Primary reason for study evaluation completion				
Subject withdrew consent	2 (28.6)	0	0	2 (10.0)
Death	0	0	3 (33.3)	3 (15.0)
Protocol deviation	0	0	1 (11.1)	1 (5.0)
F/u phase completed as per protocol	5 (71.4)	4 (100)	5 (55.6)	14 (70.0)

- Percentage is based on N

Baseline Characteristics

Demographic summary by treatment (Full analysis set)

Demographic variable	LGH 200mg + BYL 100mg N=7	LGH 150mg + BYL 150mg N=4	LGH 200mg + BYL 200mg N=9	All patients N=20
Age (years)				
n	7	4	9	20
Mean (StD)	58.9 (9.32)	60.8 (1.50)	62.2 (7.48)	60.8 (7.33)
Median	61.0	61.0	61.0	61.0
Minimum, Maximum	45, 67	59, 62	51, 73	45, 73
Age category (years) -n (%)				
<65	4 (57.1)	4 (100)	6 (66.7)	14 (70.0)
≥ 65	3 (42.9)	0	3 (33.3)	6 (30.0)
Sex -n (%)				
Male	5 (71.4)	1 (25.0)	6 (66.7)	12 (60.0)
Female	2 (28.6)	3 (75.0)	3 (33.3)	8 (40.0)
Child bearing potential if female -n (%*)				
Post-menopausal	2 (100)	2 (66.7)	3 (100)	7 (87.5)
Sterile- of child bearing age	0	1 (33.3)	0	1 (12.5)
Race -n (%)				
Caucasian	6 (85.7)	4 (100)	6 (66.7)	16 (80.0)
Black	0	0	1 (11.1)	1 (5.0)

Demographic variable	LGH 200mg + BYL 100mg N=7	LGH 150mg + BYL 150mg N=4	LGH 200mg + BYL 200mg N=9	All patients N=20
Asian	1 (14.3)	0	2 (22.2)	3 (15.0)
Ethnicity -n (%)				
Chinese	0	0	1 (11.1)	1 (5.0)
Other	7 (100)	4 (100)	8 (88.9)	19 (95.0)
Weight (kg)				
n	7	4	9	20
Mean (StD)	70.8 (17.57)	71.1 (13.30)	71.5 (11.11)	71.2 (13.32)
Median	66.3	75.8	69.0	70.4
Minimum, Maximum	46.4, 93.0	51.7, 81.0	61.0, 93.3	46.4, 93.3
Height (cm)				
n	6	4	9	19
Mean (StD)	168.1 (8.64)	165.1 (7.96)	168.0 (9.18)	167.5 (8.38)
Median	168.5	165.5	164.0	165.0
Minimum, Maximum	157.5, 178.0	157.5, 172.0	155.0, 181.0	155.0, 181.0
Body mass index (kg/m^2)				
n	6	4	9	19
Mean (StD)	23.4 (3.42)	26.1 (4.66)	25.4 (3.51)	24.9 (3.67)
Median	22.6	26.1	25.8	24.7
Minimum, Maximum	18.7, 28.5	20.5, 31.6	19.9, 30.9	18.7, 31.6
ECOG performance status -n (%)				
0	5 (71.4)	1 (25.0)	4 (44.4)	10 (50.0)
1	2 (28.6)	2 (50.0)	5 (55.6)	9 (45.0)
2	0	1 (25.0)	0	1 (5.0)

*: For child bearing potential panel, % is based on number of female patients within the treatment group. For all other panels, % is based on N.

Summary of Efficacy

Primary Outcome Result(s)

Efficacy was not powered for analysis

Secondary Outcome Result(s)

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

Treatment	Statistics	AUC0-24 (h*ng/mL)	Cmax (ng/mL)	Tmax (hr)
Cycle 1 Day 1				
LGH 200mg + BYL 100mg (N=7)	n	6	6	6
	Mean (StD)	22700(14000)	1580(957)	
	CV% mean	61.5	60.6	
	Geo-mean	19700	1400	
	CV% geo-mean	63.1	54.6	
	Median	19500	1290	2.51
	[Min; Max]	[9260;48200]	[785;3430]	[1.92;6.00]
LGH 150mg + BYL 150mg (N=4)	n	4	4	4
	Mean (StD)	14200(14700)	885(788)	
	CV% mean	104	89.0	
	Geo-mean	9090	603	
	CV% geo-mean	162	158	
	Median	9480	708	4.15
	[Min; Max]	[2390;35400]	[135;1990]	[3.03;5.02]
LGH 200mg + BYL 200mg (N=9)	n	8	8	8
	Mean (StD)	25000(12900)	1490(729)	
	CV% mean	51.5	48.8	
	Geo-mean	22300	1350	
	CV% geo-mean	54.1	51.7	
	Median	20500	1220	3.96
	[Min; Max]	[12200;47300]	[680;2660]	[2.00;24.3]
Cycle:C1D15				
LGH 200mg + BYL 100mg (N=7)	n	5	5	5
	Mean (StD)	78100(38600)	3840(1730)	

Treatment	Statistics	AUC0-24 (h*ng/mL)	Cmax (ng/mL)	Tmax (hr)
	CV% mean	49.5	45.1	
	Geo-mean	70300	3530	
	CV% geo-mean	55.7	48.5	
	Median	65600	3120	4.95
	[Min; Max]	[37300;121000]	[2070;5720]	[4.00;6.00]
LGH 150mg + BYL 150mg (N=4)	n	2	2	2
	Mean (StD)	32500(15300)	1810(665)	
	CV% mean	47.0	36.7	
	Geo-mean	30600	1750	
	CV% geo-mean	51.9	39.0	
	Median	32500	1810	2.45
	[Min; Max]	[21700;43300]	[1340;2280]	[1.98;2.92]
LGH 200mg + BYL 200mg (N=9)	n	6	6	6
	Mean (StD)	61700(21400)	3160(1050)	
	CV% mean	34.6	33.1	
	Geo-mean	58300	2990	
	CV% geo-mean	39.5	40.4	
	Median	61100	3270	4.00
	[Min; Max]	[32000;84500]	[1510;4280]	[2.98;7.75]

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.

Samples (the whole profile for that day) taken from patients who vomited within 4 hours of dosing are excluded

Summary of primary PK parameters for BYL719 by treatment (Pharmacokinetic analysis set)

Treatment	Statistics	AUC0-24 (h*ng/mL)	Cmax (ng/mL)	Tmax (hr)
Cycle 1 Day 1				

Treatment	Statistics	AUC0-24 (h*ng/mL)	Cmax (ng/mL)	Tmax (hr)
LGH 200mg + BYL 100mg (N=7)	n	6	6	6
	Mean (StD)	8970(3960)	1040(483)	N/A
	CV% mean	44.2	46.6	N/A
	Geo-mean	8240	945	N/A
	CV% geo-mean	48.1	50.5	N/A
	Median	8920	999	2.01
	[Min; Max]	[4850;15300]	[522;1780]	[1.92;2.92]
LGH 150mg + BYL 150mg (N=4)	n	3	3	3
	Mean (StD)	4970(1730)	439(152)	N/A
	CV% mean	34.9	34.6	N/A
	Geo-mean	4730	420	N/A
	CV% geo-mean	41.8	38.4	N/A
	Median	5740	451	3.95
	[Min; Max]	[2980;6180]	[281;584]	[2.08;5.02]
LGH 200mg + BYL 200mg (N=9)	n	8	8	8
	Mean (StD)	12900(4790)	1230(400)	N/A
	CV% mean	37.3	32.5	N/A
	Geo-mean	12000	1150	N/A
	CV% geo-mean	43.8	44.0	N/A
	Median	12300	1230	3.46
	[Min; Max]	[5280;20700]	[448;1800]	[2.00;5.08]
Cycle:C1D15				
LGH 200mg + BYL 100mg (N=7)	n	5	5	5
	Mean (StD)	6650(3300)	535(298)	N/A
	CV% mean	49.6	55.6	N/A
	Geo-mean	6050	480	N/A
	CV% geo-mean	51.2	53.2	N/A
	Median	4940	387	4.00

Treatment	Statistics	AUC0-24 (h*ng/mL)	Cmax (ng/mL)	Tmax (hr)
	[Min; Max]	[3610;11400]	[306;1020]	[1.97;5.00]
LGH 150mg + BYL 150mg (N=4)	n	1	1	1
	Mean (StD)	7850(N/A)	674(N/A)	N/A
	CV% mean	N/A	N/A	N/A
	Geo-mean	7850	674	N/A
	CV% geo-mean	N/A	N/A	N/A
	Median	7850	674	2.92
	[Min; Max]	[7850;7850]	[674;674]	[2.92;2.92]
LGH 200mg + BYL 200mg (N=9)	n	6	6	6
	Mean (StD)	17900(5960)	1500(453)	N/A
	CV% mean	33.2	30.3	N/A
	Geo-mean	17000	1430	N/A
	CV% geo-mean	36.7	33.8	N/A
	Median	17500	1480	2.96
	[Min; Max]	[9690;26400]	[843;2020]	[2.05;6.00]

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.

Samples (the whole profile for that day) taken from patients who vomited within 4 hours of dosing are excluded.

Summary of Safety

Safety Results

Dose limiting toxicities by primary system organ class, preferred term and treatment group (DDS)

	LGH 200mg + BYL 100mg N=5	LGH 150mg + BYL 150mg N=3	LGH 200mg + BYL 200mg N=7	All patients N=15
Primary system organ class **Preferred term**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Any primary system organ class	0	2 (66.7)	2 (28.6)	4 (26.7)
Blood and lymphatic system disorders	0	2 (66.7)	2 (28.6)	4 (26.7)
Thrombocytopenia	0	2 (66.7)	2 (28.6)	4 (26.7)

Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class in descending frequency, as reported in the All Patients.
A patient with multiple occurrences of an DLTs under one treatment is counted only once in the AE category for that treatment.
A patient with multiple DLTs within primary system organ class is counted only once in the total row.

Grade 3/4 and all adverse events, regardless of study drug relationship by primary system organ class and treatment (Safety Set)

	LGH 200mg + BYL 100mg N=7		LGH 150mg + BYL 150mg N=4		LGH 200mg + BYL 200mg N=9		All patients N=20	
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Primary system organ class	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
-Total	7 (100)	6 (85.7)	4 (100)	4 (100)	9 (100)	8 (88.9)	20 (100)	18 (90.0)
General disorders and administration site conditions	5 (71.4)	2 (28.6)	4 (100)	0	8 (88.9)	2 (22.2)	17 (85.0)	4 (20.0)
Blood and lymphatic system disorders	4 (57.1)	3 (42.9)	3 (75.0)	3 (75.0)	8 (88.9)	6 (66.7)	15 (75.0)	12 (60.0)
Gastrointestinal disorders	6 (85.7)	2 (28.6)	3 (75.0)	0	5 (55.6)	0	14 (70.0)	2 (10.0)
Skin and subcutaneous tissue disorders	5 (71.4)	0	2 (50.0)	1 (25.0)	6 (66.7)	0	13 (65.0)	1 (5.0)
Infections and infestations	5 (71.4)	1 (14.3)	2 (50.0)	0	5 (55.6)	3 (33.3)	12 (60.0)	4 (20.0)
Investigations	4 (57.1)	3 (42.9)	1 (25.0)	0	6 (66.7)	2 (22.2)	11 (55.0)	5 (25.0)
Metabolism and nutrition disorders	2 (28.6)	0	2 (50.0)	1 (25.0)	5 (55.6)	3 (33.3)	9 (45.0)	4 (20.0)
Nervous system disorders	5 (71.4)	0	3 (75.0)	0	1 (11.1)	0	9 (45.0)	0
Respiratory, thoracic and mediastinal disorders	3 (42.9)	0	2 (50.0)	0	3 (33.3)	0	8 (40.0)	0
Musculoskeletal and connective tissue disorders	3 (42.9)	0	1 (25.0)	0	1 (11.1)	0	5 (25.0)	0
Renal and urinary disorders	1 (14.3)	1 (14.3)	2 (50.0)	1 (25.0)	2 (22.2)	0	5 (25.0)	2 (10.0)
Psychiatric disorders	0	0	2 (50.0)	1 (25.0)	1 (11.1)	0	3 (15.0)	1 (5.0)
Cardiac disorders	1 (14.3)	1 (14.3)	0	0	1 (11.1)	0	2 (10.0)	1 (5.0)
Eye disorders	0	0	1 (25.0)	0	1 (11.1)	0	2 (10.0)	0
Reproductive system and breast disorders	0	0	1 (25.0)	0	1 (11.1)	0	2 (10.0)	0
Injury, poisoning and procedural complications	0	0	1 (25.0)	0	0	0	1 (5.0)	0
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	0	0	1 (25.0)	0	0	0	1 (5.0)	0
Vascular disorders	0	0	0	0	1 (11.1)	0	1 (5.0)	0

	LGH 200mg + BYL 100mg N=7		LGH 150mg + BYL 150mg N=4		LGH 200mg + BYL 200mg N=9		All patients N=20	
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Primary system organ class	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)

- Primary system organ class are sorted in descending frequency of All Grades column, as reported in the All Patients.
- A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
- A patient with multiple adverse events is counted only once in the total row.

Grade 3/4 and all adverse events (more than one occurrence in the All patients group), regardless of study drug relationship by preferred term and treatment (Safety Set)

	LGH 200mg + BYL 100mg N=7		LGH 150mg + BYL 150mg N=4		LGH 200mg + BYL 200mg N=9		All patients N=20	
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
-Total	7 (100)	6 (85.7)	4 (100)	4 (100)	9 (100)	8 (88.9)	20 (100)	18 (90.0)
Fatigue	5 (71.4)	2 (28.6)	3 (75.0)	0	4 (44.4)	0	12 (60.0)	2 (10.0)
Thrombocytopenia	2 (28.6)	2 (28.6)	3 (75.0)	3 (75.0)	6 (66.7)	4 (44.4)	11 (55.0)	9 (45.0)
Vomiting	6 (85.7)	0	0	0	4 (44.4)	0	10 (50.0)	0
Anaemia	2 (28.6)	2 (28.6)	1 (25.0)	1 (25.0)	6 (66.7)	3 (33.3)	9 (45.0)	6 (30.0)
Diarrhoea	3 (42.9)	2 (28.6)	2 (50.0)	0	4 (44.4)	0	9 (45.0)	2 (10.0)
Neutropenia	2 (28.6)	2 (28.6)	2 (50.0)	2 (50.0)	5 (55.6)	4 (44.4)	9 (45.0)	8 (40.0)
Blood creatinine increased	3 (42.9)	0	1 (25.0)	0	3 (33.3)	0	7 (35.0)	0
Nausea	1 (14.3)	0	2 (50.0)	0	4 (44.4)	0	7 (35.0)	0
Pyrexia	2 (28.6)	0	2 (50.0)	0	3 (33.3)	0	7 (35.0)	0
White blood cell count decreased	3 (42.9)	3 (42.9)	0	0	4 (44.4)	1 (11.1)	7 (35.0)	4 (20.0)
Hyperglycaemia	2 (28.6)	0	0	0	4 (44.4)	2 (22.2)	6 (30.0)	2 (10.0)
Rash	1 (14.3)	0	1 (25.0)	0	3 (33.3)	0	5 (25.0)	0
Cough	2 (28.6)	0	1 (25.0)	0	1 (11.1)	0	4 (20.0)	0
Hypersomnia	2 (28.6)	0	2 (50.0)	0	0	0	4 (20.0)	0
Leukopenia	2 (28.6)	0	1 (25.0)	1 (25.0)	1 (11.1)	0	4 (20.0)	1 (5.0)
Acute kidney injury	0	0	2 (50.0)	1 (25.0)	1 (11.1)	0	3 (15.0)	1 (5.0)
Decreased appetite	1 (14.3)	0	1 (25.0)	0	1 (11.1)	0	3 (15.0)	0

	LGH 200mg + BYL 100mg N=7		LGH 150mg + BYL 150mg N=4		LGH 200mg + BYL 200mg N=9		All patients N=20	
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Dry skin	2 (28.6)	0	0	0	1 (11.1)	0	3 (15.0)	0
Petechiae	1 (14.3)	0	1 (25.0)	0	1 (11.1)	0	3 (15.0)	0
Rhinitis	2 (28.6)	0	0	0	1 (11.1)	0	3 (15.0)	0
Stomatitis	2 (28.6)	0	1 (25.0)	0	0	0	3 (15.0)	0
Abdominal pain upper	0	0	1 (25.0)	0	1 (11.1)	0	2 (10.0)	0
Alopecia	1 (14.3)	0	0	0	1 (11.1)	0	2 (10.0)	0
Cystitis	1 (14.3)	0	1 (25.0)	0	0	0	2 (10.0)	0
Electrocardiogram QT prolonged	1 (14.3)	0	0	0	1 (11.1)	0	2 (10.0)	0
Epistaxis	0	0	1 (25.0)	0	1 (11.1)	0	2 (10.0)	0
Muscle spasms	2 (28.6)	0	0	0	0	0	2 (10.0)	0
Musculoskeletal pain	1 (14.3)	0	0	0	1 (11.1)	0	2 (10.0)	0
Neuropathy peripheral	1 (14.3)	0	0	0	1 (11.1)	0	2 (10.0)	0
Oropharyngeal pain	1 (14.3)	0	0	0	1 (11.1)	0	2 (10.0)	0
Palmar-plantar erythrodysaesthesia syndrome	1 (14.3)	0	0	0	1 (11.1)	0	2 (10.0)	0
Pelvic pain	0	0	1 (25.0)	0	1 (11.1)	0	2 (10.0)	0
Rash maculo-papular	1 (14.3)	0	1 (25.0)	1 (25.0)	0	0	2 (10.0)	1 (5.0)
Respiratory tract infection	0	0	0	0	2 (22.2)	0	2 (10.0)	0
Sinusitis	2 (28.6)	0	0	0	0	0	2 (10.0)	0
Upper respiratory tract infection	1 (14.3)	0	0	0	1 (11.1)	0	2 (10.0)	0

	LGH 200mg + BYL 100mg N=7		LGH 150mg + BYL 150mg N=4		LGH 200mg + BYL 200mg N=9		All patients N=20	
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Preferred term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)

Preferred terms are sorted in descending frequency of All Grades column, as reported in the All Patients.
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
A patient with multiple adverse events is counted only once in the total row.

Deaths by preferred term and treatment (Safety Set)

Primary cause of death Preferred term	LGH 200mg + BYL 100mg N=7	LGH 150mg + BYL 150mg N=4	LGH 200mg + BYL 200mg N=9	All patients N=20
Total	0	0	2 (22.2)	2 (10.0)
Study indication	0	0	1 (11.1)	1 (5.0)
Plasma cell myeloma recurrent	0	0	1 (11.1)	1 (5.0)
Other	0	0	1 (11.1)	1 (5.0)
Multi-organ failure	0	0	1 (11.1)	1 (5.0)

Deaths up to 30 days after the last dose are all included.

SAE, regardless of study drug relationship by preferred term, maximum grade and treatment (Safety Set)

	LGH 200mg + BYL 100mg N=7		LGH 150mg + BYL 150mg N=4		LGH 200mg + BYL 200mg N=9		All patients N=20	
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
-Total	2 (28.6)	2 (28.6)	2 (50.0)	2 (50.0)	4 (44.4)	4 (44.4)	8 (40.0)	8 (40.0)
Hyperglycaemia	0	0	0	0	2 (22.2)	2 (22.2)	2 (10.0)	2 (10.0)
Acute kidney injury	0	0	1 (25.0)	1 (25.0)	0	0	1 (5.0)	1 (5.0)
Angina unstable	1 (14.3)	1 (14.3)	0	0	0	0	1 (5.0)	1 (5.0)
Escherichia infection	1 (14.3)	1 (14.3)	0	0	0	0	1 (5.0)	1 (5.0)
Febrile neutropenia	1 (14.3)	1 (14.3)	0	0	0	0	1 (5.0)	1 (5.0)
Hyponatraemia	0	0	0	0	1 (11.1)	1 (11.1)	1 (5.0)	1 (5.0)
Mania	0	0	1 (25.0)	1 (25.0)	0	0	1 (5.0)	1 (5.0)
Multi-organ failure	0	0	0	0	1 (11.1)	1 (11.1)	1 (5.0)	1 (5.0)
Platelet count decreased	0	0	0	0	1 (11.1)	1 (11.1)	1 (5.0)	1 (5.0)
Pneumonia	0	0	0	0	1 (11.1)	1 (11.1)	1 (5.0)	1 (5.0)
Pseudomonas infection	1 (14.3)	1 (14.3)	0	0	0	0	1 (5.0)	1 (5.0)
Rash maculo-papular	0	0	1 (25.0)	1 (25.0)	0	0	1 (5.0)	1 (5.0)
Sepsis	1 (14.3)	1 (14.3)	0	0	0	0	1 (5.0)	1 (5.0)
White blood cell count decreased	1 (14.3)	1 (14.3)	0	0	0	0	1 (5.0)	1 (5.0)

Preferred terms are sorted in descending frequency of All Grades column, as reported in the All Patients.
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
A patient with multiple adverse events is counted only once in the total row.

Conclusion:

The treatment with the combination of LGH447 and BYL719 was clinically not well tolerated. Four patients (26.7%) experienced a dose-limiting toxicity event of thrombocytopenia; two patients during treatment with LGH447 150 mg + BYL719 150 mg and two patients during treatment with LGH447 200 mg + BYL719 200 mg. According to the DLT criteria, two of these events were grade 3 thrombocytopenia with clinically significant bleeding and two of these events were grade 4 thrombocytopenia lasting more than 7 consecutive days. Due to the lack of clinical tolerability of the combination and as a result of project development considerations, the Sponsor terminated the study prematurely after 20 patients were treated, with nine patients treated at the maximum dose of 200 mg LGH447 combined with 200 mg BYL417.

The only efficacy result reported was response, which showed stable disease as best response for nine patients and minor response for one patient.

This abbreviated clinical study report describes the PK parameters and the safety of the 20 patients that completed the study. Two deaths were reported due to progression of disease and multi organ failure deemed not related to study drug treatment. The SOC most affected by the drugs was blood and lymphatic disorders as shown by the DLTs of thrombocytopenia and discontinuation of study drug due to thrombocytopenia.

Date of Clinical Trial Report

10-May-2016