Clinical trial results:
A phase Ib/II, multi-center, study of oral LGH447 in combination with oral BYL719 in patients with relapsed and refractory multiple myeloma

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.novfor complete trial results.

Summary

EudraCT number	2013-004959-21
Trial protocol	DE IT
Global end of trial date	28 October 2015

Results information

Result version number	v1 (current)
This version publication date	18 July 2018
First version publication date	18 July 2018

Trial information

Trial identification

Sponsor protocol code	CLGH447X2103C

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02144038
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH- 4002, Basel, Switzerland,
Public contact	Novartis Pharma AG, NOVARTIS Pharma AG, 41 613241111,
Scientific contact	Clinical

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	28 October 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 October 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Phase Ib: to estimate the maximum tolerated dose (MTD) and/or Recommended Phase 2 Dose (RP2D) for LGH447 in combination with BYL719 in patients with relapsed and refractory multiple myeloma.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 July 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 3
Country: Number of subjects enrolled	Singapore: 3
Country: Number of subjects enrolled	United States: 5

Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Italy: 7
Worldwide total number of subjects	20
EEA total number of subjects	9

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	14
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

It was expected that 20-25 patients were to be enrolled in this Phase Ib portion of the study. The actual number of patients could be adapted by results obtained during the study.

Period 1

Period 1 title	Phase 1b Phase (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	LGH 200mg + BYL 100mg

Arm description:

Patients in this arm received 200 mg qd LGH447 and 100 mg qd BYL719

Arm type	Experimental
Investigational medicinal product name	LGH447
Investigational medicinal product code	LGH477
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

LGH477 was an investigational drug and was supplied as 10 mg, 50 mg, and 200 mg hard gelatin capsules for oral use. LGH477 was dosed prior to BYL719 on a flat scale of mg/day and was not adjusted to body weight or body surface area.

Investigational medicinal product name	BYL719
Investigational medicinal product code	alpelisib
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

BYL719 was an investigational drug and was supplied as 10 mg, 50 mg, and 100 mg film-coated tablets for oral use. BYL719 was dosed immediately following LGH447 on a flat scale of mg/day and was not adjusted to body weight or body surface area.

Arm title	LGH 150mg + BYL 150mg

Arm description:

Patients in this arm received doses of 150 mg qd LGH447 and 150 mg qd BYL719

Arm type	Experimental
Investigational medicinal product name	LGH447
Investigational medicinal product code	LGH477
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

LGH477 was an investigational drug and was supplied as 10 mg, 50 mg, and 150 mg hard gelatin capsules for oral use. LGH477 was dosed prior to BYL719 on a flat scale of mg/day and was not adjusted

to body weight or body surface area.

Investigational medicinal product name	alpelisib
Investigational medicinal product code	BYL719
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

BYL719 was an investigational drug and was supplied as 10 mg, 50 mg, and 150 mg film-coated tablets for oral use. BYL719 was dosed immediately following LGH447 on a flat scale of mg/day and was not adjusted to body weight or body surface area.

Arm title	LGH 200mg + BYL 200mg

Arm description:

Patients in this arm received doses of 200 mg qd LGH447 and 200 mg qd BYL719

Arm type	Experimental
Investigational medicinal product name	LGH447
Investigational medicinal product code	LGH477
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

LGH477 was an investigational drug and was supplied as 10 mg, 50 mg, and 200 mg hard gelatin capsules for oral use. LGH477 was dosed prior to BYL719 on a flat scale of mg/day and was not adjusted to body weight or body surface area.

Investigational medicinal product name	alpelisib
Investigational medicinal product code	BYL719
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

BYL719 was an investigational drug and was supplied as 10 mg, 50 mg, and 200 mg film-coated tablets for oral use. BYL719 was dosed immediately following LGH447 on a flat scale of mg/day and was not adjusted to body weight or body surface area.

Number of subjects in period 1	LGH 200mg + BYL 100mg	LGH 150mg + BYL 150mg	LGH 200mg + BYL 200mg
Started	7	4	9
Completed	0	0	0
Not completed	7	4	9
Subject withdrew consent	1	-	-
Physician decision	-	1	-
Disease progression	2	3	4
Adverse event, non-fatal	3	-	3
Death	-	-	1
Subject/guardian decision	1	-	1

Baseline characteristics

Reporting groups	
Reporting group title	LGH 200mg + BYL 100mg
Reporting group description:	
Patients in this arm received 200 mg qd LGH447 and 100 mg qd BYL719	
Reporting group title	LGH 150mg + BYL 150mg
Reporting group description:	
Patients in this arm received doses of 150 mg qd LGH447 and 150 mg qd BYL719	
Reporting group title	LGH 200mg + BYL 200mg
Reporting group description:	
Patients in this arm received doses of 200 mg qd LGH447 and 200 mg qd BYL719	

Reporting group values	LGH 200mg + BYL 100mg	LGH 150mg + BYL 150mg	LGH 200mg + BYL 200mg
Number of subjects	7	4	9
Age categorical Units: Subjects			
Adults (18-64 years)	4	4	6
From 65-84 years	3	0	3
Age continuous Units: years			
median	58.9	60.8	62.2
standard deviation	± 9.32	± 1.5	± 61
Gender categorical Units: Subjects			
Female	2	3	3
Male	5	1	6

Reporting group values	Total		
Number of subjects	20		
Age categorical Units: Subjects			
Adults (18-64 years)	14		
From 65-84 years	6		
Age continuous Units: years			
median			
standard deviation	-		
Gender categorical Units: Subjects			
Female	8		
Male	12		

End points

End points reporting groups

Reporting group title	LGH 200mg + BYL 100mg
Reporting group description:	
Patients in this arm received 200 mg qd LGH447 and 100 mg qd BYL719	
Reporting group title	LGH 150mg + BYL 150mg
Reporting group description:	
Patients in this arm received doses of 150 mg qd LGH447 and 150 mg qd BYL719	
Reporting group title	LGH 200mg + BYL 200mg
Reporting group description:	
Patients in this arm received doses of 200 mg qd LGH447 and 200 mg qd BYL719	

Primary: Maximum Tolerted dose (MTD) or Recommended Phase 2 Dose (RP2D)

End point title	Maximum Tolerted dose (MTD) or Recommended Phase 2 Dose (RP2D)[1]
End point description:	
The study was terminated prematurely and no maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D) was declared.	
End point type	Primary
End point timeframe:	
Cycle 1 = 28 days	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was planned for this endpoint.

End point values	LGH 200mg + BYL 100mg	LGH 150mg + BYL 150mg	LGH 200mg + BYL 200mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	4	9	
Units: Pariticipants	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Primary PK Paramenter for LGH447: AUC0-24

End point title	Primary PK Paramenter for LGH447: AUC0-24
End point description:	
Pharmacokinetics (PK) parameters were estimated and reported, when feasible, by noncompartmental analysis of LGH447 and BYL719 concentration versus time data. Only PK blood samples with dates and times and for which the dose dates and times were adequately recorded were included in the PK analyses. Samples taken from patients who vomited within 4 hours of dosing were excluded from summary statistics. AUC0-24: Area under the plasma concentration-time curve calculated from time zero to 24 hour.	
End point type	Secondary

End point timeframe:

C1D1, C1D15

End point values	LGH 200mg + BYL 100mg	LGH 150mg + BYL 150mg	LGH 200mg + BYL 200mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	4	8	
Units: h*ng/mL				
arithmetic mean (standard deviation)				
Cycle 1, Day 1 (C1D1)	22700 (± 14000)	14200 (± 14700)	25000 (± 12900)	
Cycle 1, Day 15 (C1, D15)	78100 (± 38600)	32500 (± 15300)	61700 (± 21400)	

Statistical analyses

No statistical analyses for this end point

Secondary: Primary PK parameters for LGH447: Cmax

End point title	Primary PK parameters for LGH447: Cmax

End point description:

Pharmacokinetics (PK) parameters were estimated and reported, when feasible, by noncompartmental analysis of LGH447 and BYL719 concentration versus time data. Only PK blood samples with dates and times and for which the dose dates and times were adequately recorded were included in the PK analyses. Samples taken from patients who vomited within 4 hours of dosing were excluded from summary statistics. Cmax = Maximum (peak) observed plasma drug concentration (mass x volume-1).

End point type	Secondary

End point timeframe:

C1D1, C1D15

End point values	LGH 200mg + BYL 100mg	LGH 150mg + BYL 150mg	LGH 200mg + BYL 200mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	4	8	
Units: ng/mL				
arithmetic mean (standard deviation)				
C1D1	1580 (± 957)	885 (± 788)	1490 (± 729)	
C1D15	3840 (± 1730)	1810 (± 665)	3160 (± 1050)	

Statistical analyses

No statistical analyses for this end point

Secondary: Primary PK paramenters for LGH447: Tmax

End point title	Primary PK paramenters for LGH447: Tmax

End point description:

Pharmacokinetics (PK) parameters were estimated and reported, when feasible, by noncompartmental analysis of LGH447 and BYL719 concentration versus time data. Only PK blood samples with dates and times and for which the dose dates and times were adequately recorded were included in the PK analyses. Samples taken from patients who vomited within 4 hours of dosing were excluded from summary statistics. Following oral dose of both study drugs, mean peak plasma concentrations were achieved at Tmax ranging from 2 to 5 hr post-dose. Tmax: Time to reach maximum (peak) plasma drug concentration (time).

End point type	Secondary

End point timeframe:

C1D1, C1D15

End point values	LGH 200mg + BYL 100mg	LGH 150mg + BYL 150mg	LGH 200mg + BYL 200mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	4	8	
Units: hr				
median (full range (min-max))				
C1D1	2.51 (1.92 to 6)	4.15 (3.03 to 5.02)	3.96 (2 to 24.3)	
C1D15	4.95 (4 to 6)	2.45 (1.98 to 2.92)	4 (2.98 to 7.75)	

Statistical analyses

No statistical analyses for this end point

Secondary: Primary PK parameter for BYL719: AUC0-24

End point title	Primary PK parameter for BYL719: AUC0-24

End point description:

Pharmacokinetics (PK) parameters were estimated and reported, when feasible, by noncompartmental analysis of LGH447 and BYL719 concentration versus time data. Only PK blood samples with dates and times and for which the dose dates and times were adequately recorded were included in the PK analyses. Samples taken from patients who vomited within 4 hours of dosing were excluded from summary statistics. AUC0-24: Area under the plasma concentration-time curve calculated from time zero to 24 hour.

End point type	Secondary

End point timeframe:

C1D1, C1D15

End point values	LGH 200mg + BYL 100mg	LGH 150mg + BYL 150mg	LGH 200mg + BYL 200mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	3	8	
Units: h*ng/mL				
arithmetic mean (standard deviation)				
Cycle 1, Day 1 (C1D1)	8970 (± 3960)	4970 (± 1730)	12900 (± 4790)	
Cycle 1, Day 15 (C1D15)	6650 (± 3300)	7850 (± 999.99)	17900 (± 5960)	

Statistical analyses

No statistical analyses for this end point

Secondary: Primary PK parameter for BYL719: Cmax

End point title	Primary PK parameter for BYL719: Cmax

End point description:

Pharmacokinetics (PK) parameters were estimated and reported, when feasible, by noncompartmental analysis of LGH447 and BYL719 concentration versus time data. Only PK blood samples with dates and times and for which the dose dates and times were adequately recorded were included in the PK analyses. Samples taken from patients who vomited within 4 hours of dosing were excluded from summary statistics. Cmax = Maximum (peak) observed plasma drug concentration (mass x volume-1).

End point type	Secondary

End point timeframe:

C1D1, C1D15

End point values	LGH 200mg + BYL 100mg	LGH 150mg + BYL 150mg	LGH 200mg + BYL 200mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	3	8	
Units: ng/mL				
arithmetic mean (standard deviation)				
C1D1	1040 (± 483)	439 (± 152)	1230 (± 400)	
C1D15	535 (± 298)	674 (± 99.99)	1500 (± 453)	

Statistical analyses

No statistical analyses for this end point

Secondary: Primary PK parameter for BYL719: Tmax

End point title	Primary PK parameter for BYL719: Tmax

End point description:

Pharmacokinetics (PK) parameters were estimated and reported, when feasible, by noncompartmental analysis of LGH447 and BYL719 concentration versus time data. Only PK blood samples with dates and times and for which the dose dates and times were adequately recorded were included in the PK analyses. Samples taken from patients who vomited within 4 hours of dosing were excluded from

summary statistics. Following oral dose of both study drugs, mean peak plasma concentrations were achieved at Tmax ranging from 2 to 5 hr post-dose. Tmax: Time to reach maximum (peak) plasma drug concentration (time).

End point type	Secondary

End point timeframe:

C1D1, C1D15

End point values	LGH 200mg + BYL 100mg	LGH 150mg + BYL 150mg	LGH 200mg + BYL 200mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	3	8	
Units: hr				
median (full range (min-max))				
C1D1	2.01 (1.92 to 2.92)	3.95 (2.08 to 5.02)	3.46 (2 to 5.08)	
C1D15	4 (1.97 to 5)	2.92 (2.92 to 2.92)	2.96 (2.05 to 6)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
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	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups	
Reporting group title	LGH 200mg + BYL 100mg
Reporting group description:	
LGH 200mg + BYL 100mg	
Reporting group title	LGH 200mg + BYL 200mg
Reporting group description:	
LGH 200mg + BYL 200mg	
Reporting group title	LGH 150mg + BYL 150mg
Reporting group description:	
LGH 150mg + BYL 150mg	

Serious adverse events	LGH 200mg + BYL 100mg	LGH 200mg + BYL 200mg	LGH 150mg + BYL 150mg
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 7 (28.57%)	4 / 9 (44.44%)	2 / 4 (50.00%)
number of deaths (all causes)	0	2	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Platelet count decreased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
White blood cell count decreased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina unstable			

subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Multi-organ failure			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Mania			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Escherichia infection			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			

subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pseudomonas infection			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 7 (0.00%)	2 / 9 (22.22%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	LGH 200mg + BYL 100mg	LGH 200mg + BYL 200mg	LGH 150mg + BYL 150mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 7 (100.00%)	9 / 9 (100.00%)	4 / 4 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Plasmacytoma			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	2
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	0	2	0

General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Chest pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Fatigue			
subjects affected / exposed	5 / 7 (71.43%)	4 / 9 (44.44%)	3 / 4 (75.00%)
occurrences (all)	5	4	3
Non-cardiac chest pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Pyrexia			
subjects affected / exposed	2 / 7 (28.57%)	3 / 9 (33.33%)	2 / 4 (50.00%)
occurrences (all)	5	4	2
Temperature intolerance			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 7 (28.57%)	1 / 9 (11.11%)	1 / 4 (25.00%)
occurrences (all)	3	1	1
Dysphonia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Dyspnoea exertional			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	0	5	0
Epistaxis			

subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
Oropharyngeal pain			
subjects affected / exposed	1 / 7 (14.29%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Insomnia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Investigations			
Blood creatinine increased			
subjects affected / exposed	3 / 7 (42.86%)	3 / 9 (33.33%)	1 / 4 (25.00%)
occurrences (all)	5	9	1
C-reactive protein increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 7 (14.29%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Glutamate dehydrogenase increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	0	3	0
Lipase increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Lymphocyte count decreased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Neutrophil count decreased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Platelet count decreased			

subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
White blood cell count decreased			
subjects affected / exposed	2 / 7 (28.57%)	4 / 9 (44.44%)	0 / 4 (0.00%)
occurrences (all)	5	5	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Spinal compression fracture			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Cardiac disorders			
Atrioventricular block first degree			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	2
Hypersomnia			
subjects affected / exposed	2 / 7 (28.57%)	0 / 9 (0.00%)	2 / 4 (50.00%)
occurrences (all)	2	0	2
Hypogeusia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Lumbar radiculopathy			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Neuropathy peripheral			
subjects affected / exposed	1 / 7 (14.29%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Paraesthesia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Peripheral sensory neuropathy			

subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Sensory loss			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Somnolence			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 7 (28.57%)	6 / 9 (66.67%)	1 / 4 (25.00%)
occurrences (all)	12	14	2
Increased tendency to bruise			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Leukopenia			
subjects affected / exposed	2 / 7 (28.57%)	1 / 9 (11.11%)	1 / 4 (25.00%)
occurrences (all)	2	7	3
Neutropenia			
subjects affected / exposed	2 / 7 (28.57%)	5 / 9 (55.56%)	2 / 4 (50.00%)
occurrences (all)	10	15	7
Thrombocytopenia			
subjects affected / exposed	2 / 7 (28.57%)	6 / 9 (66.67%)	3 / 4 (75.00%)
occurrences (all)	5	10	3
Eye disorders			
Eye pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Photopsia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
Constipation			

subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Diarrhoea			
subjects affected / exposed	3 / 7 (42.86%)	4 / 9 (44.44%)	2 / 4 (50.00%)
occurrences (all)	8	4	2
Dyspepsia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	1 / 7 (14.29%)	4 / 9 (44.44%)	2 / 4 (50.00%)
occurrences (all)	1	4	2
Oesophagitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Oral pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Stomatitis			
subjects affected / exposed	2 / 7 (28.57%)	0 / 9 (0.00%)	1 / 4 (25.00%)
occurrences (all)	2	0	1
Vomiting			
subjects affected / exposed	6 / 7 (85.71%)	4 / 9 (44.44%)	0 / 4 (0.00%)
occurrences (all)	10	6	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 7 (14.29%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Drug eruption			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Dry skin			
subjects affected / exposed	2 / 7 (28.57%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	2	2	0
Erythema			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0

Onychoclasis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Palmar erythema			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 7 (14.29%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Petechiae			
subjects affected / exposed	1 / 7 (14.29%)	1 / 9 (11.11%)	1 / 4 (25.00%)
occurrences (all)	1	1	1
Pruritus			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Rash			
subjects affected / exposed	1 / 7 (14.29%)	3 / 9 (33.33%)	1 / 4 (25.00%)
occurrences (all)	1	3	1
Rash maculo-papular			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
Polyuria			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Proteinuria			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	2 / 7 (28.57%)	0 / 9 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Muscle twitching			

subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Musculoskeletal pain			
subjects affected / exposed	1 / 7 (14.29%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Myalgia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Spinal pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Cholecystitis infective			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Clostridium difficile infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Cystitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	1 / 4 (25.00%)
occurrences (all)	2	0	2
Influenza			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Respiratory tract infection			
subjects affected / exposed	0 / 7 (0.00%)	2 / 9 (22.22%)	0 / 4 (0.00%)
occurrences (all)	0	3	0
Rhinitis			
subjects affected / exposed	2 / 7 (28.57%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	2	1	0
Sinusitis			
subjects affected / exposed	2 / 7 (28.57%)	0 / 9 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0

Tooth abscess			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 7 (14.29%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 7 (14.29%)	1 / 9 (11.11%)	1 / 4 (25.00%)
occurrences (all)	1	1	1
Hyperamylasaemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Hypercalcaemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Hyperglycaemia			
subjects affected / exposed	2 / 7 (28.57%)	4 / 9 (44.44%)	0 / 4 (0.00%)
occurrences (all)	2	6	0
Hypocalcaemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Hypokalaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Hypomagnesaemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Hyponatraemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Hypophosphataemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	0	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 March 2014	Amendment 1 introduced changes to the hematologic dose limiting toxicities (DLT) criteria for multiple myeloma patients.
21 August 2014	Amendment 2 introduced the changes relating to thrombocytopenia, and included the following: To better understand the mechanism of action and kinetics underlying LGH447-associated thrombocytopenia, which is the primary DLT seen to date in the LGH447X2101 study, this amendment adds the measurement of thrombopoietin (TPO) level in the blood to determine if LGH447 interferes with the production and differentiation of megakaryocytes; To update safety information for LGH447 to include a DLT of maculopapular rash and modify the monitoring and dose modification guidelines for skin rash; To update safety information to align with BYL719 Investigator Brochure Version 6; Inhibitors of BCRP were added to the list of medication to use with caution since the co-administration of BYL719 with BCRP inhibitors may increase local or systemic BY L719 exposure. Treatment with BCRP inhibitors should be kept as short as possible or fully avoided; Agents which modify gastric pH (H2 receptor antagonists, proton pump inhibitors and antacids) were added to the list of medication to use with caution since both LGH447 and BYL719 are characterized by pH dependent solubility. Therefore, agents that modify gastric pH may affect the absorption and bioavailability of BYL719 and LGH447.
28 January 2015	Amendment 3 introduced guidelines for management of pneumonitis.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Enrollment to the study was permanently terminated based upon review of the available data and since termination occurred before completion of the dose -escalation part (Phase Ib), any analyses related to Phase II were not conducted.

Notes: