NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

LGH447

Trial Indication(s)

Acute myeloid leukemia or high-risk myelodysplastic syndrome

Protocol Number

CLGH447X2102

Protocol Title

A phase I, multicenter, open-label study of oral LGH447 in patients with acute myeloid leukemia or high risk myelodysplastic syndrome

Clinical Trial Phase

Phase 1

Phase of Drug Development

LGH447: Phase I

Study Start/End Dates

Study Start Date: March 2014 (Actual)
Primary Completion Date: April 2019 (Actual)
Study Completion Date: April 2019 (Actual)

Reason for Termination (If applicable)

The study was terminated after review of the available data showed minimal anti-tumor activity, and PK results demonstrated complex drug-drug interaction between LGH447 and midostaurin, which impeded the ability to achieve consistent and predictable concentrations of both drugs. The termination of the study was not a consequence of safety concerns.

Study Design/Methodology

This was a Phase I, open-label, dose-escalation study to determine maximum tolerated dose (MTD) and/or recommended dose for expansion (RDE) of LGH447 given as a monotherapy in patients with relapsed or refractory AML, AML patients for whom no effective therapy exists or high risk MDS patients who have failed prior therapies, and LGH447 in combination with midostaurin in AML patients harboring either FLT3 wild type or FLT3-ITD/TKD mutations. For each treatment arm of the study, a dose escalation part and a dose expansion part were planned. Enrollment into the dose expansion part was only initiated after MTD and/or RDE was determined. A treatment cycle was defined as 28 days. Patients were treated until disease progression, occurrence of unacceptable toxicity, or withdrawal of informed consent, whichever occurred first.

Centers

9 centers in 7 countries: Australia(1), Germany(1), France(1), Italy(3), Netherlands(1), United States(1), Japan(1)

Objectives:

Primary:

- Estimate the MTD and/or RDE of LGH447 in patients with AML or high risk MDS
- Estimate the MTD and/or RDE of LGH447 in combination with midostaurin in patients with FLT3-ITD/TKD+ AML

Secondary:

- Characterize the safety and tolerability of LGH447
- Characterize the safety and tolerability of LGH447 in combination with midostaurin
- Evaluate the PK of LGH447 (monotherapy arm)
- Evaluate the PK of LGH447, midostaurin and its metabolites (combination arm)
- Assess PD effects of LGH447
- To assess any preliminary anti-tumor activity in AML or high risk MDS associated with LGH447
- To assess any preliminary anti-tumor activity in AML associated with LGH447 in combination with midostaurin

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

Oral capsules of LGH447 50 mg and 200 mg
Oral capsules of PKC412 25 mg

Statistical Methods

The primary variable was the incidence of DLTs in the first treatment cycle (28 days). Estimation of the MTD was based upon the estimation of the probability of a DLT in the first 28 days of dosing for patients in DDS, separately for each arm (monotherapy arm and combination arm). In the monotherapy dose escalation part, a 2-parameter BLRM models the dose-toxicity relationship and it uses all the available dose limiting toxicity information accumulated across all dose cohorts during the 28 days of DLT evaluation period. In the combination dose escalation part, a 5-parameter BLRM models the dose-toxicity relationship and it uses all the available dose limiting toxicity information accumulated across all dose cohorts during the 28 days of DLT evaluation period.

Evaluation of anti-leukemic activity was based on local investigator tumor assessment based on the International Working Group for diagnosis, standardization of response criteria, treatment outcomes, and reporting standards for therapeutic trials in AML and MDS. The variable used to evaluate anti- leukemic activity was Best Overall Response (BOR) using the FAS. BOR was the best response recorded from the start of the treatment until treatment failure/disease progression/relapse. However, any assessments taken more than 30 days after the last dose of study therapy in single therapy arm or 120 days after the last dose of study therapy in the combination arm were not included in the best overall response derivation.

Overall response rate (ORR) was the proportion of patients with a BOR of CR, CRi or PR. ORR and corresponding 95% confidence intervals (CIs) based on the exact binomial distribution was presented.

Biomarker analysis to observe the PD effect of the drugs was not done due to ineffectiveness of the pS6RP and p4EBP1 as suitable biomarkers. Samples were used to support the development of a separate assay. Descriptive statistics were presented for all PK parameters,

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria

-Male or female patients ≥18 years of age who present with one of the following:

LGH447 monotherapy arm
•Refractory/Relapsed AML following no more than 2 prior therapies, or in previously untreated AML patients who are not candidates for standard therapy.
•High and very high risk MDS according to the revised International Prognostic Scoring System (rIPSS) who have failed prior therapies, such as azacitidine and decitabine
•Patients with rIPSS score of > 4.5

LGH447 and midostaurin combination arm
•Refractory/Relapsed AML following no more than 2 prior therapies, or in previously untreated AML patients who are not candidates for standard therapy. AML patients may have either FLT3 wild type or FLT3-ITD/TKD mutant disease, and FLT3 mutation status needs to be defined at study entry.

- For AML patients, peripheral blast counts < 50,000 blasts/mm3

- For MDS patients;
•Platelet count > 25,000/mm3
•Neutrophils > 500/mm3
•Blood transfusions are allowed to maintain clinically adequate hemoglobin and hematocrit levels

- Patients with active central nervous system (CNS) disease are eligible to participate and may be treated concurrently with intrathecal (or intra Ommaya) chemotherapy

- Patients who are maintained on prophylactic antibiotics are eligible to participate as long as agents comply with the list of approved concomitant medications

-Performance status ≤ 2

-Meet other lab criteria

Exclusion Criteria

- Systemic antineoplastic therapy (including unconjugated therapeutic antibodies and toxin immunoconjugates) or any experimental therapy within 7 days or 5 half-lives, whichever is longer, before the first dose of LGH447 monotherapy or LGH447 in combination with midostaurin

- Radiotherapy with a wide field of radiation within 28 days or radiotherapy with a limited field of radiation for palliation within 7 days of the first dose of LGH447 monotherapy or LGH447 in combination with midostaurin

- Patients who received CNS irradiation for meningeal leukemia, except if radiotherapy occurred > 3 months previously

- Major surgery within 4 weeks before the first dose of LGH447 monotherapy or LGH447 in combination with midostaurin

- Ongoing therapy with corticosteroids greater than 10 mg of prednisone or its equivalent per day. Inhaled and topical steroids are permitted

- Patients who are currently receiving hydroxyurea to control peripheral blood leukemic blasts and cannot be discontinued for at least 48 hours prior to obtaining PD biomarkers at screening/baseline and during the study

- Patients who are currently receiving treatment with prohibited medication and that cannot be discontinued at least one week prior to the start of treatment with LGH447 monotherapy or LGH447 in combination with midostaurin

- Active infection requiring systemic therapy or other severe infection, including pneumonia, within 2 weeks before the first dose of LGH447 monotherapy or LGH447 in combination with midostaurin

- Known human immunodeficiency virus (HIV) positive

- Corrected QT interval (QTc) of > 450 milliseconds (ms) in males and > 470 milliseconds (ms) in females on baseline electrocardiogram (ECG) (using corrected QT interval using Fridericia [QTcF] or local standards).

- Uncontrolled cardiovascular condition, including ongoing cardiac arrhythmias, congestive heart failure, angina, or myocardial infarction within the past 6 months

- Pregnant or nursing

Participant Flow Table

Overall Study

	LGH 250mg QD	LGH 300mg QD	LGH 400mg QD	LGH 500mg QD	LGH 100mg QD + MID 50mg BID	LGH 200mg QD + MID 50mg BID	LGH 250mg QD + MID 50mg BID	LGH 300mg QD + MID 50mg BID	Total
Arm/Group Description	Patients were maintained on LGH447 250 mg capsules taken without food once a day (QD) for 28 days unless dose limiting toxicities occurred or other events at which time patient discontinued study or had dose adjustment	Patients were maintained on 300 mg capsules taken without food once a day (QD) for 28 days unless dose limiting toxicities occurred or other events at which time patient discontinued study or had dose adjustment	Patients were maintained on LGH447 400 mg capsules taken without food once a day (QD) for 28 days unless dose limiting toxicities (DLTs) occurred or other events at which time patient discontinued study or had dose adjustment	Patients were maintained on LGH447 500 mg capsules taken without food once a day (QD) for 28 days unless dose limiting toxicities (DLTs) occurred or other events at which time patient discontinued study or had dose adjustment	Patients were maintained on LGH447 100 mg once a day + midostaurin 50 mg twice a day capsules taken with food once a day (QD) for 28 days unless dose limiting toxicities (DLTs) occurred or other events at which time patient discontinued study or had dose adjustment	Patients were maintained on LGH447 200 mg once a day + midostaurin 50 mg twice a day capsules taken with food once a day (QD) for 28 days unless dose limiting toxicities (DLTs) occurred or other events at which time patient discontinued study or had dose adjustment	Patients were maintained on LGH447 250mg once a day + midostaurin 50 mg twice a day capsules taken with food once a day (QD) for 28 days unless dose limiting toxicities (DLTs) occurred or other events at which time patient discontinued study or had dose adjustment	Patients were maintained on LGH447 300 mg once a day + midostaurin 50 mg twice a day capsules taken with food once a day (QD) for 28 days unless dose limiting toxicities (DLTs) occurred or other events at which time patient discontinued study or had dose adjustment	
Started	11	22	5	6	6	6	6	8	70

Completed at least 3 cycles of treatment	3	3	1	0	0	1	0	1	9
Completed	0	0	0	0	0	0	0	0	0
Not Completed	11	22	5	6	6	6	6	8	70
Adverse Event	2	2	1	1	2	0	2	2	12
Protocol Violation	0	1	0	0	0	0	0	0	1
Physician Decision	1	1	0	0	1	1	0	1	5
Withdrawal by Subject	1	1	0	1	0	0	0	1	4
Death	0	0	0	0	1	0	0	0	1
Disease progression	7	12	4	2	2	5	2	4	38
Patient/guardian decision	0	5	0	2	0	0	2	0	9

Baseline Characteristics

	LGH 250mg QD	**LGH 300mg QD**	**LGH 400mg QD**	**LGH 500mg QD**	**LGH 100mg QD + MID 50mg BID**	**LGH 200mg QD + MID 50mg BID**	**LGH 250mg QD + MID 50mg BID**	**LGH 300mg QD + MID 50mg BID**	**Total**
Arm/Group Description	Patients were maintained on LGH447 250 mg capsules taken without food once a day (QD) for	Patients were maintained on 300 mg capsules taken without food once a day (QD) for 28 days	Patients were maintained on LGH447 400 mg capsules taken without food once a day (QD) for	Patients were maintained on LGH447 500 mg capsules taken without food once a day (QD) for	Patients were maintained on LGH447 100 mg once a day + midostaurin 50 mg twice a day	Patients were maintained on LGH447 200 mg once a day + midostaurin 50 mg twice a day	Patients were maintained on LGH447 250mg once a day + midostaurin 50 mg twice a day	Patients were maintained on LGH447 300 mg once a day + midostaurin 50 mg twice a day	

	28 days unless dose limiting toxicities occurred or other events at which time patient discontinued study or had dose adjustment	unless dose limiting toxicities occurred or other events at which time patient discontinued study or had dose adjustment	28 days unless dose limiting toxicities (DLTs) occurred or other events at which time patient discontinued study or had dose adjustment	28 days unless dose limiting toxicities (DLTs) occurred or other events at which time patient discontinued study or had dose adjustment	capsules taken with food once a day (QD) for 28 days unless dose limiting toxicities (DLTs) occurred or other events at which time patient discontinued study or had dose adjustment	capsules taken with food once a day (QD) for 28 days unless dose limiting toxicities (DLTs) occurred or other events at which time patient discontinued study or had dose adjustment	capsules taken with food once a day (QD) for 28 days unless dose limiting toxicities (DLTs) occurred or other events at which time patient discontinued study or had dose adjustment	capsules taken with food once a day (QD) for 28 days unless dose limiting toxicities (DLTs) occurred or other events at which time patient discontinued study or had dose adjustment	
Number of Participants [units: participants]	11	22	5	6	6	6	6	8	70
Age, Customized (units: years) Count of Participants (Not Applicable)									
18 - <65	3	8	1	2	2	4	0	2	22
65 - <85	8	13	4	4	4	2	6	6	47
>= 85	0	1	0	0	0	0	0	0	1
Sex: Female, Male (units: Participants) Count of Participants (Not Applicable)									
Female	5	10	3	5	4	3	1	5	36
Male	6	12	2	1	2	3	5	3	34
Diagnosis of disease: acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS)[1] (units: Participants) Count of Participants (Not Applicable)									
AML	11	19	5	6	6	6	6	8	67

MDS	0	3	0	0	0	0	0	0	3
Race/Ethnicity, Customized (units: Participants) Count of Participants (Not Applicable)									
Caucasian	7	15	3	3	5	6	5	5	49
Black	1	0	0	1	0	0	0	0	2
Asian	1	1	0	1	1	0	1	3	8
Other	0	1	0	0	0	0	0	0	1
Missing	2	5	2	1	0	0	0	0	10
Age Continuous (units:)									

[1] Monotherapy arms (LGH447): refractory/relapsed AML following no more than 2 prior therapies, or untreated AML patients who were not candidates for standard therapy, high and very high risk MDS according to the revised International Prognostic Scoring System (rIPSS) who have failed prior therapies, such as azacitidine and decitabine, patients with rIPSS score of > 4.5. Combination therapy arms: refractory/relapsed AML following no more than 2 prior therapies, or untreated AML patients who were not candidates for standard therapy

Summary of Efficacy

Primary Outcome Result(s)

Incidence rate of dose limiting toxicities (DLTs) of LGH447 in monotherapy arms

(Time Frame: Baseline up to 28 days post study treatment)

	LGH 250mg QD	LGH 300mg QD	LGH 400mg QD	LGH 500mg QD
Arm/Group Description	Patients were maintained on LGH447 250 mg capsules taken without food once a	Patients were maintained on 300 mg capsules taken without food once a	Patients were maintained on LGH447 400 mg capsules taken without food once a	Patients were maintained on LGH447 500 mg capsules taken without food once a

	day (QD) for 28 days unless dose limiting toxicities occurred or other events at which time patient discontinued study or had dose adjustment	day (QD) for 28 days unless dose limiting toxicities occurred or other events at which time patient discontinued study or had dose adjustment	day (QD) for 28 days unless dose limiting toxicities (DLTs) occurred or other events at which time patient discontinued study or had dose adjustment	day (QD) for 28 days unless dose limiting toxicities (DLTs) occurred or other events at which time patient discontinued study or had dose adjustment
Number of Participants Analyzed [units: participants]	10	6	3	4
Incidence rate of dose limiting toxicities (DLTs) of LGH447 in monotherapy arms (units: patient) Count of Units (Not Applicable)				
Dermatitis Bullous - grade 3	0	0	0	1
Erythema Multiforme- grade 3	1	0	0	0
Liver Function Test Increased- grade 3	0	0	1	0
Nausea	0	0	0	1
Abdominal Pain- grade 3	0	0	0	0
Electrocardiogram Qt Prolonged- grade 3	0	0	0	0
Stomatitis- grade 3	0	0	0	0

Incidence rate of dose limiting toxicities (DLTs) in LGH447 + midostaurin combination arms

(Time Frame: Baseline up to 28 days post study treatment)

	LGH 100mg QD + MID 50mg BID	LGH 200mg QD + MID 50mg BID	LGH 250mg QD + MID 50mg BID	LGH 300mg QD + MID 50mg BID
Arm/Group Description	Patients were maintained on LGH447 100 mg once a day + midostaurin 50 mg twice a day capsules taken with food once a day (QD) for 28 days unless dose limiting toxicities (DLTs) occurred or other events at which time patient discontinued study or had dose adjustment	Patients were maintained on LGH447 200 mg once a day + midostaurin 50 mg twice a day capsules taken with food once a day (QD) for 28 days unless dose limiting toxicities (DLTs) occurred or other events at which time patient discontinued study or had dose adjustment	Patients were maintained on LGH447 250mg once a day + midostaurin 50 mg twice a day capsules taken with food once a day (QD) for 28 days unless dose limiting toxicities (DLTs) occurred or other events at which time patient discontinued study or had dose adjustment	Patients were maintained on LGH447 300 mg once a day + midostaurin 50 mg twice a day capsules taken with food once a day (QD) for 28 days unless dose limiting toxicities (DLTs) occurred or other events at which time patient discontinued study or had dose adjustment
Number of Participants Analyzed [units: participants]	6	6	5	7
Incidence rate of dose limiting toxicities (DLTs) in LGH447 + midostaurin combination arms (units: patient with at least one event) Count of Units (Not Applicable)				

Dermatitis Bullous - grade 3	0	0	0	0
Erythema Multiforme- grade 3	0	0	0	0
Liver Function Test Increased- grade 3	0	0	0	0
Nausea	0	0	0	0
Abdominal Pain- grade 3	0	1	0	0
Electrocardiogram Qt Prolonged- grade 3	0	0	0	1
Stomatitis- grade 3	0	0	0	1

Secondary Outcome Result(s)

AUClast (hr*ng/mL) and AUCtau (hr*ng/mL) for LGH447 in monotherapy arms (PAS)

(Time Frame: days 1, 15 of 28 day cycles)

	LGH 250mg QD	LGH 300mg QD	LGH 400mg QD	LGH 500mg QD
Arm/Group Description	Patients were maintained on LGH447 250 mg capsules taken without food once a day (QD) for 28 days unless dose limiting toxicities occurred or other events at which time patient discontinued	Patients were maintained on 300 mg capsules taken without food once a day (QD) for 28 days unless dose limiting toxicities occurred or other events at which time patient discontinued study or had	Patients were maintained on LGH447 400 mg capsules taken without food once a day (QD) for 28 days unless dose limiting toxicities (DLTs) occurred or other events at which time patient discontinued	Patients were maintained on LGH447 500 mg capsules taken without food once a day (QD) for 28 days unless dose limiting toxicities (DLTs) occurred or other events at which time patient discontinued

	study or had dose adjustment	dose adjustment	study or had dose adjustment	study or had dose adjustment
Number of Participants Analyzed [units: participants]	11	22	5	6
AUClast (hr*ng/mL) and AUCtau (hr*ng/mL) for LGH447 in monotherapy arms (PAS) (units: hr*ng/mL) (Geometric Coefficient of Variation)				
AUClast C1, D1 n=11,20,5,6	28600 (60.2%)	27800 (89.2%)	26200 (128.5%)	58300 (65.1%)
AUClast C1, D15 n=8,18,2,4	88800 (25.2%)	78300 (89.1%)	16100 (18.8%)	22100 (39.7%)
AUClast C2, D1 n=9,12,3,1	84400 (39.0%)	60700 (133.2%)	80100 (131.4%)	17400 (NA%)
AUCltau C1, D1 n=10,18,5,5	31100 (55.5%)	2700 (82.6%)	30300 (98.0%)	68100 (54.5%)
AUCltau C1, D15 n=7,17,2,3	86400 (22.4%)	81200 (82.3%)	161000 (17.1%)	220000 (51.1%)
AUCltau C2, D1 n=8,8,2,1	89600 (33.2%)	77800 (81.3%)	48000 (75.4%)	171000 (NA%)

Cmax (ng/mL) for LGH447 monotherapy arms (PAS)

(Time Frame: days 1, 15 of 28 day cycles)

	LGH 250mg QD	LGH 300mg QD	LGH 400mg QD	LGH 500mg QD
Arm/Group Description	Patients were maintained on LGH447 250 mg capsules taken without food once a day (QD) for 28 days unless dose limiting	Patients were maintained on 300 mg capsules taken without food once a day (QD) for 28 days unless dose limiting	Patients were maintained on LGH447 400 mg capsules taken without food once a day (QD) for 28 days unless dose limiting	Patients were maintained on LGH447 500 mg capsules taken without food once a day (QD) for 28 days unless dose limiting

	toxicities occurred or other events at which time patient discontinued study or had dose adjustment	toxicities occurred or other events at which time patient discontinued study or had dose adjustment	toxicities (DLTs) occurred or other events at which time patient discontinued study or had dose adjustment	toxicities (DLTs) occurred or other events at which time patient discontinued study or had dose adjustment
Number of Participants Analyzed [units: participants]	11	22	5	6
Cmax (ng/mL) for LGH447 monotherapy arms (PAS) (units: ng/mL) (Geometric Coefficient of Variation)				
Cycle 1, D1 n=11,20,5,6	1990 (56.5%)	1940 (79.5%)	2220 (74.3%)	4240 (54.7%)
Cycle 1, D15 n=8,18,2,4	4750 (19.2%)	4490 (70.2%)	8530 (1.6%)	11400 (37.3%)
Cycle 2, D1 n=9,12,3,1	4430 (35.4%)	3690 (85.3%)	4220 (118.5%)	9580 (NA%)

T1/2 (hour) for monotherapy LGH447 arms (PAS)

(Time Frame: cycle 1: days 1, 15 and cylce 2: day 1)

	LGH 250mg QD	LGH 300mg QD	LGH 400mg QD	LGH 500mg QD
Arm/Group Description	Patients were maintained on LGH447 250 mg capsules taken without food once a day (QD) for 28 days unless dose limiting toxicities occurred or other events	Patients were maintained on 300 mg capsules taken without food once a day (QD) for 28 days unless dose limiting toxicities occurred or other events	Patients were maintained on LGH447 400 mg capsules taken without food once a day (QD) for 28 days unless dose limiting toxicities (DLTs) occurred or	Patients were maintained on LGH447 500 mg capsules taken without food once a day (QD) for 28 days unless dose limiting toxicities (DLTs) occurred or

	at which time patient discontinued study or had dose adjustment	at which time patient discontinued study or had dose adjustment	other events at which time patient discontinued study or had dose adjustment	other events at which time patient discontinued study or had dose adjustment
Number of Participants Analyzed [units: participants]	11	22	5	6
T1/2 (hour) for monotherapy LGH447 arms (PAS) (units: hour) Median (Full Range)				
Cycle 1, D1 n=6,13,0,3	20.2 (13.8 to 48.7)	17.9 (10.5 to 44.8)		35.0 (26.1 to 39.5)
Cycle 1, D15 n=1,8,0,0	32.0 (32.0 to 32.0)	40.4 (10.3 to 64.0)		
Cycle 2, D1 n=3,4,2,0	49.9 (29.2 to 85.9)	37.7 (35.1 to 49.2)	29.6 (26.1 to 33.0)	

Tmax (hour) for monotherapy LGH447 arms (PAS)

(Time Frame: cycle 1: days 1, 15 and cylce 2: day 1)

	LGH 250mg QD	LGH 300mg QD	LGH 400mg QD	LGH 500mg QD
Arm/Group Description	Patients were maintained on LGH447 250 mg capsules taken without food once a day (QD) for 28 days unless dose limiting toxicities occurred or other events	Patients were maintained on 300 mg capsules taken without food once a day (QD) for 28 days unless dose limiting toxicities occurred or other events	Patients were maintained on LGH447 400 mg capsules taken without food once a day (QD) for 28 days unless dose limiting toxicities (DLTs) occurred or	Patients were maintained on LGH447 500 mg capsules taken without food once a day (QD) for 28 days unless dose limiting toxicities (DLTs) occurred or

	at which time patient discontinued study or had dose adjustment	at which time patient discontinued study or had dose adjustment	other events at which time patient discontinued study or had dose adjustment	other events at which time patient discontinued study or had dose adjustment
Number of Participants Analyzed [units: participants]	11	22	5	6
Tmax (hour) for monotherapy LGH447 arms (PAS) (units: hour) Median (Full Range)				
Cycle 1, D1 n=11,20,5,6	4.00 (2.00 to 6.00)	3.02 (1.88 to 8.00)	7.92 (3.00 to 25.00)	3.00 (2.98 to 5.00)
Cycle 1, D15 n=8,18,2,4	4.00 (2.00 to 24.00)	3.00 (2.00 to 24.00)	4.01 (3.00 to 5.02)	7.00 (5.05 to 24.0)
Cycle 2, D1 n=9,12,3,1	4.00 (1.00 to 6.25)	4.00 (1.00 to 7.77)	4.02 (3.17 to 7.92)	0.967 (0.967 to 0.967)

Accumulation ratio (RACC) for LGH447 monotherapy arms (PAS)

(Time Frame: cycle 1, day 15 and cycle 2, day 1)

	LGH 250mg QD	LGH 300mg QD	LGH 400mg QD	LGH 500mg QD
Arm/Group Description	Patients were maintained on LGH447 250 mg capsules taken without food once a day (QD) for 28 days unless dose limiting	Patients were maintained on 300 mg capsules taken without food once a day (QD) for 28 days unless dose limiting	Patients were maintained on LGH447 400 mg capsules taken without food once a day (QD) for 28 days unless dose limiting	Patients were maintained on LGH447 500 mg capsules taken without food once a day (QD) for 28 days unless dose limiting

	toxicities occurred or other events at which time patient discontinued study or had dose adjustment	toxicities occurred or other events at which time patient discontinued study or had dose adjustment	toxicities (DLTs) occurred or other events at which time patient discontinued study or had dose adjustment	toxicities (DLTs) occurred or other events at which time patient discontinued study or had dose adjustment
Number of Participants Analyzed [units: participants]	11	22	5	6
Accumulation ratio (RACC) for LGH447 monotherapy arms (PAS) (units: geometricc mean ratio)				
Cycle 1, D15 n=6,14,2,2	350	3.36	5.32	1.89
Cycle 2, D1 n=7,8,1,1	3.54	3.01	3.68	2.78

AUClast (hr*ng/mL) and AUCtau (hr*ng/mL) for LGH447 in LGH447 + midostaurin combination arms (PAS)

(Time Frame: cycle 1: days 1 and cylce 2: day 1)

	LGH 100mg QD + MID 50mg BID	LGH 200mg QD + MID 50mg BID	LGH 250mg QD + MID 50mg BID	LGH 300mg QD + MID 50mg BID
Arm/Group Description	Patients were maintained on LGH447 100 mg once a day + midostaurin 50 mg twice a day capsules taken with food once a day (QD) for 28 days unless dose limiting	Patients were maintained on LGH447 200 mg once a day + midostaurin 50 mg twice a day capsules taken with food once a day (QD) for 28 days unless dose limiting	Patients were maintained on LGH447 250mg once a day + midostaurin 50 mg twice a day capsules taken with food once a day (QD) for 28 days unless dose	Patients were maintained on LGH447 300 mg once a day + midostaurin 50 mg twice a day capsules taken with food once a day (QD) for 28 days unless dose limiting

	toxicities (DLTs) occurred or other events at which time patient discontinued study or had dose adjustment	toxicities (DLTs) occurred or other events at which time patient discontinued study or had dose adjustment	limiting toxicities (DLTs) occurred or other events at which time patient discontinued study or had dose adjustment	toxicities (DLTs) occurred or other events at which time patient discontinued study or had dose adjustment
Number of Participants Analyzed [units: participants]	6	6	6	8
AUClast (hr*ng/mL) and AUCtau (hr*ng/mL) for LGH447 in LGH447 + midostaurin combination arms (PAS) (units: hr*ng/mL) (Geometric Coefficient of Variation)				
AUClast Cycle 1, D1 n=6,4,6,8	7570 (59.2%)	18600 (98.9%)	29100 (69.5%)	39800 (97.2%)
AUClast Cycle 2, D1 n=6,4,5,5	13900 (43.2%)	18600 (66.6%)	44600 (63.1%)	76000 (27.9%)
AUCtau Cycle 1, D1 n=4,1,3,3	9600 (52.6%)	24900	39300 (56.5%)	76300 (51.5%)
AUCtau Cycle 2, D1 n=4,2,3,3	15600 (22.0%)	11200 (21.1%)	45800 (84.9%)	71300 (23.9%)

Cmax (ng/mL) for LGH447 + midostaurin combination therapy arms (PAS)

(Time Frame: cycle 1: days 1 and cycle 2: day 1)

	LGH 100mg QD + MID 50mg BID	LGH 200mg QD + MID 50mg BID	LGH 250mg QD + MID 50mg BID	LGH 300mg QD + MID 50mg BID
Arm/Group Description	Patients were maintained on LGH447 100 mg once a	Patients were maintained on LGH447 200 mg once a	Patients were maintained on LGH447 250mg once a	Patients were maintained on LGH447 300 mg once a

	day + midostaurin 50 mg twice a day capsules taken with food once a day (QD) for 28 days unless dose limiting toxicities (DLTs) occurred or other events at which time patient discontinued study or had dose adjustment	day + midostaurin 50 mg twice a day capsules taken with food once a day (QD) for 28 days unless dose limiting toxicities (DLTs) occurred or other events at which time patient discontinued study or had dose adjustment	day + midostaurin 50 mg twice a day capsules taken with food once a day (QD) for 28 days unless dose limiting toxicities (DLTs) occurred or other events at which time patient discontinued study or had dose adjustment	day + midostaurin 50 mg twice a day capsules taken with food once a day (QD) for 28 days unless dose limiting toxicities (DLTs) occurred or other events at which time patient discontinued study or had dose adjustment
Number of Participants Analyzed [units: participants]	6	6	6	8
Cmax (ng/mL) for LGH447 + midostaurin combination therapy arms (PAS) (units: ng/mL) (Geometric Coefficient of Variation)				
Cycle 1, D1 n=6,4,6,8	569 (50.0%)	1080 (97.8%)	1770 (69.8%)	2300 (92.2%)
Cycle 2, D1 n=6,4,5,5	763 (42.7%)	954 (65.3%)	2230 (59.0%)	4000 (25.2%)

T1/2 (hour) for LGH447 + midostaurin combination therapy arms (PAS)

(Time Frame: cycle 1: days 1 and cylce 2: day 1)

	LGH 100mg QD + MID 50mg BID	LGH 200mg QD + MID 50mg BID	LGH 250mg QD + MID 50mg BID	LGH 300mg QD + MID 50mg BID
Arm/Group Description	Patients were maintained on LGH447 100 mg once a	Patients were maintained on LGH447 200 mg once a	Patients were maintained on LGH447 250mg once a	Patients were maintained on LGH447 300 mg once a

	day + midostaurin 50 mg twice a day capsules taken with food once a day (QD) for 28 days unless dose limiting toxicities (DLTs) occurred or other events at which time patient discontinued study or had dose adjustment	day + midostaurin 50 mg twice a day capsules taken with food once a day (QD) for 28 days unless dose limiting toxicities (DLTs) occurred or other events at which time patient discontinued study or had dose adjustment	day + midostaurin 50 mg twice a day capsules taken with food once a day (QD) for 28 days unless dose limiting toxicities (DLTs) occurred or other events at which time patient discontinued study or had dose adjustment	day + midostaurin 50 mg twice a day capsules taken with food once a day (QD) for 28 days unless dose limiting toxicities (DLTs) occurred or other events at which time patient discontinued study or had dose adjustment
Number of Participants Analyzed [units: participants]	6	6	6	8
T1/2 (hour) for LGH447 + midostaurin combination therapy arms (PAS) (units: hour) Median (Full Range)				
Cycle 1, D1 n=2,1,3,0	24.1 (23.2 to 25.0)	64.7 (64.7 to 64.7)	27.5 (18.5 to 42.1)	
Cycle 2, D1 n=1,0,1,3	37.6 (37.6 to 37.6)		71.4 (71.4 to 71.4)	60.1 (23.7 to 64.0)

Tmax (hour) for LGH447 + midostaurin combination therapy arms (PAS)

(Time Frame: cycle 1: days 1 and cylce 2: day 1)

	LGH 100mg QD + MID 50mg BID	LGH 200mg QD + MID 50mg BID	LGH 250mg QD + MID 50mg BID	LGH 300mg QD + MID 50mg BID
Arm/Group Description	Patients were maintained on	Patients were maintained on	Patients were maintained on	Patients were maintained on

	LGH447 100 mg once a day + midostaurin 50 mg twice a day capsules taken with food once a day (QD) for 28 days unless dose limiting toxicities (DLTs) occurred or other events at which time patient discontinued study or had dose adjustment	LGH447 200 mg once a day + midostaurin 50 mg twice a day capsules taken with food once a day (QD) for 28 days unless dose limiting toxicities (DLTs) occurred or other events at which time patient discontinued study or had dose adjustment	LGH447 250mg once a day + midostaurin 50 mg twice a day capsules taken with food once a day (QD) for 28 days unless dose limiting toxicities (DLTs) occurred or other events at which time patient discontinued study or had dose adjustment	LGH447 300 mg once a day + midostaurin 50 mg twice a day capsules taken with food once a day (QD) for 28 days unless dose limiting toxicities (DLTs) occurred or other events at which time patient discontinued study or had dose adjustment
Number of Participants Analyzed [units: participants]	6	6	6	8
Tmax (hour) for LGH447 + midostaurin combination therapy arms (PAS) (units: hour) Median (Full Range)				
Cycle 1, D1 n=6,4,6,8	5.01 (2.00 to 7.87)	6.88 (4.25 to 23.5)	4.11 (2.00 to 8.00)	6.00 (4.00 to 8.05)
Cycle 2, D1 n=6,4,5,5	5.04 (4.02 to 23.3)	13.8 (0 to 23.8)	4.02 (0 to 23.5)	4.00 (0 to 23.4)

Accumulation ratio (RACC) for LGH447 + midostaurin combination therapy arms (PAS)

(Time Frame: cycle 2, day 1)

LGH 100mg QD + MID 50mg BID	LGH 200mg QD + MID 50mg BID	LGH 250mg QD + MID 50mg BID	LGH 300mg QD + MID 50mg BID

Arm/Group Description	Patients were maintained on LGH447 100 mg once a day + midostaurin 50 mg twice a day capsules taken with food once a day (QD) for 28 days unless dose limiting toxicities (DLTs) occurred or other events at which time patient discontinued study or had dose adjustment	Patients were maintained on LGH447 200 mg once a day + midostaurin 50 mg twice a day capsules taken with food once a day (QD) for 28 days unless dose limiting toxicities (DLTs) occurred or other events at which time patient discontinued study or had dose adjustment	Patients were maintained on LGH447 250mg once a day + midostaurin 50 mg twice a day capsules taken with food once a day (QD) for 28 days unless dose limiting toxicities (DLTs) occurred or other events at which time patient discontinued study or had dose adjustment	Patients were maintained on LGH447 300 mg once a day + midostaurin 50 mg twice a day capsules taken with food once a day (QD) for 28 days unless dose limiting toxicities (DLTs) occurred or other events at which time patient discontinued study or had dose adjustment
Number of Participants Analyzed [units: participants]	6	6	6	8
Accumulation ratio (RACC) for LGH447 + midostaurin combination therapy arms (PAS) (units: geometricc mean ratio)				
	0.459	NA	0.486	NA

Changes in levels of pS6RP and p4EBP1 in BMA and p4EBP1 in peripheral blood of LGH447

(Time Frame: screening, days 1 and 29 up to 1.5 years)

	LGH 250mg QD	LGH 300mg QD	LGH 400mg QD	LGH 500mg QD
Arm/Group Description	Patients were maintained on LGH447 250 mg capsules taken without food once a day (QD) for 28 days unless dose limiting toxicities occurred or other events at which time patient discontinued study or had dose adjustment	Patients were maintained on 300 mg capsules taken without food once a day (QD) for 28 days unless dose limiting toxicities occurred or other events at which time patient discontinued study or had dose adjustment	Patients were maintained on LGH447 400 mg capsules taken without food once a day (QD) for 28 days unless dose limiting toxicities (DLTs) occurred or other events at which time patient discontinued study or had dose adjustment	Patients were maintained on LGH447 500 mg capsules taken without food once a day (QD) for 28 days unless dose limiting toxicities (DLTs) occurred or other events at which time patient discontinued study or had dose adjustment
Number of Participants Analyzed [units: participants]	0	0	0	0
Changes in levels of pS6RP and p4EBP1 in BMA and p4EBP1 in peripheral blood of LGH447 (units: biomarker levels) Count of Units (Not Applicable)				

Best overall response (BOR) in the monotherapy arms

(Time Frame: baseline up to 30 days post dose)

	LGH 250mg QD	LGH 300mg QD	LGH 400mg QD	LGH 500mg QD
Arm/Group Description	Patients were maintained on LGH447 250 mg capsules taken without food once a day (QD) for 28 days unless dose limiting toxicities occurred or other events at which time patient discontinued study or had dose adjustment	Patients were maintained on 300 mg capsules taken without food once a day (QD) for 28 days unless dose limiting toxicities occurred or other events at which time patient discontinued study or had dose adjustment	Patients were maintained on LGH447 400 mg capsules taken without food once a day (QD) for 28 days unless dose limiting toxicities (DLTs) occurred or other events at which time patient discontinued study or had dose adjustment	Patients were maintained on LGH447 500 mg capsules taken without food once a day (QD) for 28 days unless dose limiting toxicities (DLTs) occurred or other events at which time patient discontinued study or had dose adjustment
Number of Participants Analyzed [units: participants]	11	22	5	6
Best overall response (BOR) in the monotherapy arms (units: patient) Count of Units (Not Applicable)				
Complete Response (CR)	0	0	0	0
CRi	1	1	0	0
Partial Remission (PR)	2	0	0	0
Relapse from CR, CRi or PR	0	0	0	0
Treatment Failure (TF)	6	15	5	3

Unknown	1	2	0	0

Best overall response (BOR) in the combination arms

(Time Frame: baseline up to 30 days post dose)

	LGH 100mg QD + MID 50mg BID	LGH 200mg QD + MID 50mg BID	LGH 250mg QD + MID 50mg BID	LGH 300mg QD + MID 50mg BID
Arm/Group Description	Patients were maintained on LGH447 100 mg once a day + midostaurin 50 mg twice a day capsules taken with food once a day (QD) for 28 days unless dose limiting toxicities (DLTs) occurred or other events at which time patient discontinued study or had dose adjustment	Patients were maintained on LGH447 200 mg once a day + midostaurin 50 mg twice a day capsules taken with food once a day (QD) for 28 days unless dose limiting toxicities (DLTs) occurred or other events at which time patient discontinued study or had dose adjustment	Patients were maintained on LGH447 250mg once a day + midostaurin 50 mg twice a day capsules taken with food once a day (QD) for 28 days unless dose limiting toxicities (DLTs) occurred or other events at which time patient discontinued study or had dose adjustment	Patients were maintained on LGH447 300 mg once a day + midostaurin 50 mg twice a day capsules taken with food once a day (QD) for 28 days unless dose limiting toxicities (DLTs) occurred or other events at which time patient discontinued study or had dose adjustment
Number of Participants Analyzed [units: participants]	6	6	6	8
Best overall response (BOR) in the combination arms (units: patient)				

Count of Units (Not Applicable)				
Complete Response (CR)	0	0	0	0
CRi	0	1	0	0
Partial Remission (PR)	1	0	0	0
Relapse from CR, CRi or PR	0	0	0	0
Treatment Failure (TF)	5	5	4	4
Unknown	0	0	1	2

Overall response rate (ORR) in the monotherapy arms

(Time Frame: baseline up to 30 days post dose)

	LGH 250mg QD	LGH 300mg QD	LGH 400mg QD	LGH 500mg QD
Arm/Group Description	Patients were maintained on LGH447 250 mg capsules taken without food once a day (QD) for 28 days unless dose limiting toxicities occurred or other events at which time patient discontinued study or had dose adjustment	Patients were maintained on 300 mg capsules taken without food once a day (QD) for 28 days unless dose limiting toxicities occurred or other events at which time patient discontinued study or had dose adjustment	Patients were maintained on LGH447 400 mg capsules taken without food once a day (QD) for 28 days unless dose limiting toxicities (DLTs) occurred or other events at which time patient discontinued study or had dose adjustment	Patients were maintained on LGH447 500 mg capsules taken without food once a day (QD) for 28 days unless dose limiting toxicities (DLTs) occurred or other events at which time patient discontinued study or had dose adjustment

Number of Participants Analyzed [units: participants]	11	22	5	6
Overall response rate (ORR) in the monotherapy arms (units: response rate) Number (95% Confidence Interval)				
	27.3 (6.0 to 61.0)	4.5 (0.1 to 22.8)	0 (0.0 to 52.2)	0 (0.0 to 45.9)

Overall response rate (ORR) in the combination arms

(Time Frame: baseline up to 30 days post dose)

	LGH 100mg QD + MID 50mg BID	**LGH 200mg QD + MID 50mg BID**	**LGH 250mg QD + MID 50mg BID**	**LGH 300mg QD + MID 50mg BID**
Arm/Group Description	Patients were maintained on LGH447 100 mg once a day + midostaurin 50 mg twice a day capsules taken with food once a day (QD) for 28 days unless dose limiting toxicities (DLTs) occurred or other events at which time patient discontinued study or had	Patients were maintained on LGH447 200 mg once a day + midostaurin 50 mg twice a day capsules taken with food once a day (QD) for 28 days unless dose limiting toxicities (DLTs) occurred or other events at which time patient discontinued study or had	Patients were maintained on LGH447 250mg once a day + midostaurin 50 mg twice a day capsules taken with food once a day (QD) for 28 days unless dose limiting toxicities (DLTs) occurred or other events at which time patient discontinued study or had	Patients were maintained on LGH447 300 mg once a day + midostaurin 50 mg twice a day capsules taken with food once a day (QD) for 28 days unless dose limiting toxicities (DLTs) occurred or other events at which time patient discontinued study or had

	dose adjustment	dose adjustment	dose adjustment	dose adjustment
Number of Participants Analyzed [units: participants]	6	6	6	8
Overall response rate (ORR) in the combination arms (units: response rate) Number (95% Confidence Interval)				
	16.7 (0.4 to 64.1)	16.7 (0.4 to 64.1)	0 (0.0 to 36.9)	0 (0.0 to 36.9)

Summary of Safety

Safety Results

All-Cause Mortality

Serious Adverse Events by System Organ Class

Time Frame	Adverse events were collected from first dose of study treatment until end of study treatment plus 30 days for a maximum of 488 days for monotherapy and 120 days for a maximum of 334 days for combination therapy
Additional Description	Any sign or symptom that occurs during the study treatment plus 30 days post treatment for monotherapy and 120 days post treatment for combination therapy
Source Vocabulary for Table Default	MedDRA 21.0
Assessment Type for Table Default	Systematic Assessment

	LGH 250mg QD N = 11	LGH 300mg QD N = 22	LGH 400mg QD N = 5	LGH 500mg QD N = 6	LGH 100mg QD + MID 50mg BID N = 6	LGH 200mg QD + MID 50mg BID N = 6	LGH 250mg QD + MID 50mg BID N = 6	LGH 300mg QD + MID 50mg BID N = 8	All@patients N = 70
Arm/Group Description	Patients were maintained on LGH447 250 mg capsules taken without food once a day (QD) for 28 days unless dose limiting toxicities occurred or other events at which time patient discontinued study or had dose adjustment	Patients were maintained on LGH447 300 mg capsules taken without food once a day (QD) for 28 days unless dose limiting toxicities occurred or other events at which time patient discontinued study or had dose adjustment	Patients were maintained on LGH447 400 mg capsules taken without food once a day (QD) for 28 days unless dose limiting toxicities occurred or other events at which time patient discontinued study or had dose adjustment	Patients were maintained on LGH447 500 mg capsules taken without food once a day (QD) for 28 days unless dose limiting toxicities occurred or other events at which time patient discontinued study or had dose adjustment	Patients were maintained on LGH447 100 mg + midostaurin 50 mg b.i.d. capsules taken with food once a day (QD) for 28 days unless dose limiting toxicities (DLTs) occurred or other events at which time patient discontinued study or had dose adjustment	Patients were maintained on LGH447 200 mg + midostaurin 50 mg b.i.d. capsules taken with food once a day (QD) for 28 days unless dose limiting toxicities (DLTs) occurred or other events at which time patient discontinued study or had dose adjustment	Patients were maintained on LGH447 250 mg + midostaurin 50 mg b.i.d. capsules taken with food once a day (QD) for 28 days unless dose limiting toxicities (DLTs) occurred or other events at which time patient discontinued study or had dose adjustment	Patients were maintained on LGH447 300 mg + midostaurin 50 mg b.i.d. capsules taken with food once a day (QD) for 28 days unless dose limiting toxicities (DLTs) occurred or other events at which time patient discontinued study or had dose adjustment	All@patients
Total participants affected	9 (81.82%)	20 (90.91%)	4 (80.00%)	5 (83.33%)	5 (83.33%)	3 (50.00%)	5 (83.33%)	8 (100.00%)	59 (84.29%)
Blood and lymphatic system disorders									
Anaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Disseminated Intravascular Coagulation	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	1 (1.43%)

Febrile Bone Marrow Aplasia	2 (18.18%)	4 (18.18%)	1 (20.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	8 (11.43%)
Febrile Neutropenia	4 (36.36%)	4 (18.18%)	1 (20.00%)	1 (16.67%)	2 (33.33%)	1 (16.67%)	2 (33.33%)	2 (25.00%)	17 (24.29%)
Splenomegaly	0 (0.00%)	1 (4.55%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Cardiac disorders									
Cardiac Failure	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	1 (1.43%)
Cardiac Flutter	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	1 (1.43%)
Myocarditis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	1 (1.43%)
Gastrointestinal disorders									
Abdominal Pain	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Anal Haemorrhage	0 (0.00%)	1 (4.55%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Colitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Diarrhoea	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (12.50%)	3 (4.29%)
Gastric Haemorrhage	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	2 (2.86%)
Gastritis	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Gastrointestinal Haemorrhage	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Intestinal Perforation	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Nausea	0 (0.00%)	1 (4.55%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.86%)
Stomatitis	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Vomiting	1 (9.09%)	0 (0.00%)	1 (20.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (4.29%)
General disorders and administration site conditions									

Euthanasia	0 (0.00%)	1 (4.55%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
General Physical Health Deterioration	1 (9.09%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	3 (4.29%)
Malaise	0 (0.00%)	1 (4.55%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Multiple Organ Dysfunction Syndrome	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	2 (2.86%)
Pyrexia	1 (9.09%)	2 (9.09%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (16.67%)	1 (16.67%)	1 (12.50%)	7 (10.00%)
Infections and infestations									
Anal Abscess	0 (0.00%)	1 (4.55%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Anal Infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	1 (1.43%)
Anorectal Infection	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Appendicitis	0 (0.00%)	1 (4.55%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Bronchopulmonary Aspergillosis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (12.50%)	2 (2.86%)
Cellulitis	0 (0.00%)	1 (4.55%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.86%)
Clostridial Infection	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Clostridium Difficile Colitis	0 (0.00%)	1 (4.55%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Colonic Abscess	0 (0.00%)	1 (4.55%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Device Related Infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (1.43%)
Encephalitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Listeriosis	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Orchitis	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Pharyngitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	1 (1.43%)

Picornavirus Infection	0 (0.00%)	1 (4.55%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Pleural Infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	1 (1.43%)
Pneumonia	1 (9.09%)	1 (4.55%)	1 (20.00%)	1 (16.67%)	1 (16.67%)	0 (0.00%)	3 (50.00%)	3 (37.50%)	11 (15.71%)
Pneumonia Fungal	0 (0.00%)	1 (4.55%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Respiratory Tract Infection Fungal	0 (0.00%)	1 (4.55%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Sepsis	0 (0.00%)	1 (4.55%)	0 (0.00%)	2 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	4 (5.71%)
Septic Shock	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.86%)
Sinusitis	0 (0.00%)	1 (4.55%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Urinary Tract Infection	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Injury, poisoning and procedural complications									
Fall	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (1.43%)
Febrile Nonhaemolytic Transfusion Reaction	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Femoral Neck Fracture	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	1 (1.43%)
Post Procedural Haemorrhage	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Subarachnoid Haemorrhage	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (1.43%)
Subdural Haematoma	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	2 (2.86%)
Subdural Haemorrhage	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (1.43%)

Investigations									
Blood Pressure Decreased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Human Metapneumovirus Test Positive	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
White Blood Cell Count Increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Metabolism and nutrition disorders									
Dehydration	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Hyperglycaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Hypernatraemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	1 (1.43%)
Hypokalaemia	0 (0.00%)	1 (4.55%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.86%)
Hyponatraemia	0 (0.00%)	1 (4.55%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Musculoskeletal and connective tissue disorders									
Pain In Extremity	0 (0.00%)	1 (4.55%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)									
Rectal Adenoma	0 (0.00%)	1 (4.55%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Nervous system disorders									
Cerebral Haemorrhage	0 (0.00%)	2 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.86%)
Dizziness	0 (0.00%)	1 (4.55%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Headache	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)

Syncope	0 (0.00%)	1 (4.55%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Psychiatric disorders									
Mental Status Changes	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Renal and urinary disorders									
Acute Kidney Injury	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (12.50%)	2 (2.86%)
Haematuria	0 (0.00%)	1 (4.55%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Renal Failure	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.86%)
Respiratory, thoracic and mediastinal disorders									
Acute Respiratory Failure	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	1 (1.43%)
Dyspnoea	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	2 (2.86%)
Epistaxis	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Lung Disorder	0 (0.00%)	1 (4.55%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Pneumonia Aspiration	0 (0.00%)	1 (4.55%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Pneumonitis	0 (0.00%)	1 (4.55%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Pulmonary Mass	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	1 (1.43%)
Respiratory Failure	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Skin and subcutaneous tissue disorders									
Dermatitis Bullous	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)

Dermatitis Exfoliative Generalised	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (1.43%)
Vascular disorders									
Hypotension	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (1.43%)

Other Adverse Events by System Organ Class

Time Frame	Adverse events were collected from first dose of study treatment until end of study treatment plus 30 days for a maximum of 488 days for monotherapy and 120 days for a maximum of 334 days for combination therapy
Additional Description	Any sign or symptom that occurs during the study treatment plus 30 days post treatment for monotherapy and 120 days post treatment for combination therapy
Source Vocabulary for Table Default	MedDRA 21.0
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	5%

	LGH 250mg QD N = 11	**LGH 300mg QD N = 22**	**LGH 400mg QD N = 5**	**LGH 500mg QD N = 6**	**LGH 100mg QD + MID 50mg BID N = 6**	**LGH 200mg QD + MID 50mg BID N = 6**	**LGH 250mg QD + MID 50mg BID N = 6**	**LGH 300mg QD + MID 50mg BID N = 8**	**All@patients N = 70**
Arm/Group Description	Patients were maintained on LGH447 250 mg capsules taken without food once a day (QD) for 28 days unless	Patients were maintained on LGH447 300 mg capsules taken without food once a day (QD) for 28 days unless	Patients were maintained on LGH447 400 mg capsules taken without food once a day (QD) for 28 days	Patients were maintained on LGH447 500 mg capsules taken without food once a day (QD) for 28 days	Patients were maintained on LGH447 100 mg + midostaurin 50 mg b.i.d. capsules taken with food once a day (QD)	Patients were maintained on LGH447 200 mg + midostaurin 50 mg b.i.d. capsules taken with food once a day (QD)	Patients were maintained on LGH447 250 mg + midostaurin 50 mg b.i.d. capsules taken with food once a day (QD)	Patients were maintained on LGH447 300 mg + midostaurin 50 mg b.i.d. capsules taken with food once a day (QD)	All@patients

	dose limiting toxicities occurred or other events at which time patient discontinued study or had dose adjustment	dose limiting toxicities occurred or other events at which time patient discontinued study or had dose adjustment	unless dose limiting toxicities occurred or other events at which time patient discontinued study or had dose adjustment	unless dose limiting toxicities occurred or other events at which time patient discontinued study or had dose adjustment	for 28 days unless dose limiting toxicities (DLTs) occurred or other events at which time patient discontinued study or had dose adjustment	for 28 days unless dose limiting toxicities (DLTs) occurred or other events at which time patient discontinued study or had dose adjustment	for 28 days unless dose limiting toxicities (DLTs) occurred or other events at which time patient discontinued study or had dose adjustment	for 28 days unless dose limiting toxicities (DLTs) occurred or other events at which time patient discontinued study or had dose adjustment	
Total participants affected	11 (100.00%)	22 (100.00%)	4 (80.00%)	6 (100.00%)	6 (100.00%)	6 (100.00%)	6 (100.00%)	8 (100.00%)	69 (98.57%)
Blood and lymphatic system disorders									
Anaemia	5 (45.45%)	1 (4.55%)	0 (0.00%)	0 (0.00%)	3 (50.00%)	0 (0.00%)	0 (0.00%)	2 (25.00%)	11 (15.71%)
Bone Marrow Failure	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Disseminated Intravascular Coagulation	1 (9.09%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.86%)
Febrile Bone Marrow Aplasia	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Febrile Neutropenia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (33.33%)	1 (16.67%)	1 (16.67%)	1 (12.50%)	5 (7.14%)
Haemorrhagic Diathesis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Hypoprothrombinaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Neutropenia	1 (9.09%)	2 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	4 (5.71%)
Thrombocytopenia	2 (18.18%)	3 (13.64%)	0 (0.00%)	0 (0.00%)	2 (33.33%)	1 (16.67%)	1 (16.67%)	1 (12.50%)	10 (14.29%)
Thrombotic Microangiopathy	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)

Cardiac disorders									
Atrial Fibrillation	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (25.00%)	2 (2.86%)
Bradycardia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Cardiac Failure	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Cardiac Failure Congestive	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (1.43%)
Pericardial Effusion	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Sinus Bradycardia	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Supraventricular Extrasystoles	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	1 (1.43%)
Tachycardia	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	3 (4.29%)
Congenital, familial and genetic disorders									
Antithrombin Iii Deficiency	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Phimosis	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Ear and labyrinth disorders									
Ear Pain	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
External Ear Inflammation	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Vertigo	1 (9.09%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.86%)
Vertigo Positional	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Eye disorders									
Conjunctivitis Allergic	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Eye Haemorrhage	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Eye Irritation	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (1.43%)

Vision Blurred	0 (0.00%)	2 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.86%)
Gastrointestinal disorders									
Abdominal Pain	5 (45.45%)	6 (27.27%)	1 (20.00%)	0 (0.00%)	2 (33.33%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	15 (21.43%)
Abdominal Pain Upper	3 (27.27%)	1 (4.55%)	0 (0.00%)	1 (16.67%)	1 (16.67%)	2 (33.33%)	1 (16.67%)	2 (25.00%)	11 (15.71%)
Anal Fissure	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Anal Incontinence	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	2 (2.86%)
Anal Ulcer	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Aphthous Ulcer	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	2 (2.86%)
Cheilitis	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Constipation	4 (36.36%)	10 (45.45%)	2 (40.00%)	1 (16.67%)	2 (33.33%)	0 (0.00%)	1 (16.67%)	2 (25.00%)	22 (31.43%)
Diarrhoea	6 (54.55%)	6 (27.27%)	2 (40.00%)	4 (66.67%)	2 (33.33%)	3 (50.00%)	2 (33.33%)	4 (50.00%)	29 (41.43%)
Dry Mouth	0 (0.00%)	2 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.86%)
Dyspepsia	0 (0.00%)	2 (9.09%)	1 (20.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	4 (5.71%)
Dysphagia	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Eructation	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Gastrooesophageal Reflux Disease	1 (9.09%)	1 (4.55%)	1 (20.00%)	1 (16.67%)	2 (33.33%)	1 (16.67%)	0 (0.00%)	1 (12.50%)	8 (11.43%)
Haemorrhoids	1 (9.09%)	1 (4.55%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	4 (5.71%)
Intestinal Pseudo-Obstruction	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Melaena	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Mouth Haemorrhage	0 (0.00%)	2 (9.09%)	0 (0.00%)	0 (0.00%)	2 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	4 (5.71%)
Mouth Ulceration	1 (9.09%)	2 (9.09%)	1 (20.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	5 (7.14%)
Nausea	4 (36.36%)	14 (63.64%)	3 (60.00%)	6 (100.00%)	5 (83.33%)	6 (100.00%)	3 (50.00%)	6 (75.00%)	47 (67.14%)
Oesophagitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)

Oral Disorder	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Oral Pain	0 (0.00%)	1 (4.55%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.86%)
Proctalgia	1 (9.09%)	2 (9.09%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	5 (7.14%)
Rectal Haemorrhage	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Stomatitis	2 (18.18%)	4 (18.18%)	1 (20.00%)	0 (0.00%)	1 (16.67%)	1 (16.67%)	1 (16.67%)	4 (50.00%)	14 (20.00%)
Tongue Ulceration	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Upper Gastrointestinal Haemorrhage	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	1 (1.43%)
Vomiting	4 (36.36%)	12 (54.55%)	1 (20.00%)	3 (50.00%)	6 (100.00%)	6 (100.00%)	2 (33.33%)	5 (62.50%)	39 (55.71%)
General disorders and administration site conditions									
Asthenia	2 (18.18%)	4 (18.18%)	1 (20.00%)	2 (33.33%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	10 (14.29%)
Catheter Site Inflammation	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	1 (1.43%)
Chest Pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (1.43%)
Chills	1 (9.09%)	1 (4.55%)	0 (0.00%)	2 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	4 (5.71%)
Fatigue	5 (45.45%)	5 (22.73%)	2 (40.00%)	2 (33.33%)	2 (33.33%)	0 (0.00%)	3 (50.00%)	3 (37.50%)	22 (31.43%)
General Physical Health Deterioration	0 (0.00%)	1 (4.55%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (16.67%)	1 (16.67%)	0 (0.00%)	4 (5.71%)
Hypothermia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Influenza Like Illness	0 (0.00%)	2 (9.09%)	0 (0.00%)	1 (16.67%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	4 (5.71%)
Injection Site Haematoma	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Localised Oedema	0 (0.00%)	2 (9.09%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (4.29%)
Malaise	1 (9.09%)	1 (4.55%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (16.67%)	1 (12.50%)	5 (7.14%)
Mucosal Inflammation	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	2 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (4.29%)

Non-Cardiac Chest Pain	1 (9.09%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.86%)
Oedema	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Oedema Peripheral	2 (18.18%)	3 (13.64%)	2 (40.00%)	2 (33.33%)	3 (50.00%)	0 (0.00%)	2 (33.33%)	1 (12.50%)	15 (21.43%)
Pain	0 (0.00%)	2 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	3 (4.29%)
Peripheral Swelling	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Pyrexia	2 (18.18%)	7 (31.82%)	0 (0.00%)	0 (0.00%)	2 (33.33%)	3 (50.00%)	1 (16.67%)	5 (62.50%)	20 (28.57%)
Hepatobiliary disorders									
Hepatic Function Abnormal	0 (0.00%)	1 (4.55%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.86%)
Jaundice	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Infections and infestations									
Abscess Jaw	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	2 (2.86%)
Aspergillosis Oral	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Atypical Pneumonia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Bacterial Infection	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Bacterial Sepsis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	1 (1.43%)
Bronchopulmonary Aspergillosis	0 (0.00%)	1 (4.55%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.86%)
Cellulitis	1 (9.09%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.86%)
Clostridium Difficile Infection	1 (9.09%)	1 (4.55%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	3 (4.29%)
Cystitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Diverticulitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (1.43%)
Encephalitis Viral	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Folliculitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	2 (2.86%)

Fungal Infection	1 (9.09%)	1 (4.55%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	3 (4.29%)
Furuncle	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (1.43%)
Herpes Virus Infection	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Lung Infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Nasal Vestibulitis	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Oral Candidiasis	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (33.33%)	0 (0.00%)	0 (0.00%)	3 (4.29%)
Oral Herpes	1 (9.09%)	1 (4.55%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (4.29%)
Paronychia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	1 (1.43%)
Pharyngitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Pneumonia	2 (18.18%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	4 (5.71%)
Respiratory Tract Infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Sepsis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	1 (1.43%)
Upper Respiratory Tract Infection	1 (9.09%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.86%)
Urethritis	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Urinary Tract Infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (12.50%)	2 (2.86%)
Viral Upper Respiratory Tract Infection	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Vulval Abscess	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Injury, poisoning and procedural complications									
Anal Injury	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Fall	1 (9.09%)	1 (4.55%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (16.67%)	3 (37.50%)	7 (10.00%)
Head Injury	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (1.43%)

Infusion Related Reaction	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (4.29%)
Joint Injury	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (1.43%)
Procedural Pain	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Spinal Compression Fracture	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	1 (1.43%)
Tooth Injury	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Transfusion Reaction	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (16.67%)	1 (12.50%)	3 (4.29%)
Investigations									
Alanine Aminotransferase Increased	2 (18.18%)	3 (13.64%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (12.50%)	7 (10.00%)
Amylase Increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	1 (1.43%)
Antithrombin Iii Decreased	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Aspartate Aminotransferase Increased	2 (18.18%)	2 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (12.50%)	6 (8.57%)
Blood Alkaline Phosphatase Increased	1 (9.09%)	2 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	4 (5.71%)
Blood Bilirubin Increased	0 (0.00%)	2 (9.09%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (4.29%)
Blood Creatinine Increased	1 (9.09%)	1 (4.55%)	1 (20.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	5 (7.14%)
Blood Urea Increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	1 (1.43%)
Blood Uric Acid Increased	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Blood Zinc Decreased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	1 (1.43%)

C-Reactive Protein Increased	1 (9.09%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.86%)
Eastern Cooperative Oncology Group Performance Status	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (16.67%)	0 (0.00%)	2 (2.86%)
Eastern Cooperative Oncology Group Performance Status Worsened	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	2 (2.86%)
Electrocardiogram Qt Interval	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	1 (1.43%)
Electrocardiogram Qt Prolonged	1 (9.09%)	1 (4.55%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	2 (33.33%)	4 (50.00%)	9 (12.86%)
Gamma-Glutamyltransferase Increased	0 (0.00%)	2 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.86%)
Liver Function Test Increased	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Lymphocyte Count Decreased	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	3 (4.29%)
Neutrophil Count Decreased	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.86%)
Oxygen Saturation Decreased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Platelet Count Decreased	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	3 (4.29%)
Troponin T Increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (12.50%)	2 (2.86%)
Weight Decreased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (25.00%)	2 (2.86%)
White Blood Cell Count Decreased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	2 (2.86%)
Metabolism and nutrition disorders									
Decreased Appetite	2 (18.18%)	4 (18.18%)	2 (40.00%)	2 (33.33%)	2 (33.33%)	0 (0.00%)	0 (0.00%)	3 (37.50%)	15 (21.43%)

Dehydration	0 (0.00%)	1 (4.55%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	2 (2.86%)
Diabetes Mellitus	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Electrolyte Imbalance	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Fluid Overload	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (16.67%)	1 (12.50%)	4 (5.71%)
Glucose Tolerance Impaired	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Hyperglycaemia	1 (9.09%)	1 (4.55%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	4 (5.71%)
Hyperkalaemia	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	3 (4.29%)
Hypermagnesaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Hypernatraemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	2 (2.86%)
Hyperphosphataemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Hyperuricaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Hypoalbuminaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (33.33%)	0 (0.00%)	1 (16.67%)	2 (25.00%)	5 (7.14%)
Hypocalcaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	1 (1.43%)
Hypoglycaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.86%)
Hypokalaemia	3 (27.27%)	5 (22.73%)	0 (0.00%)	2 (33.33%)	4 (66.67%)	0 (0.00%)	2 (33.33%)	2 (25.00%)	18 (25.71%)
Hypomagnesaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (50.00%)	1 (16.67%)	1 (16.67%)	0 (0.00%)	5 (7.14%)
Hyponatraemia	1 (9.09%)	1 (4.55%)	0 (0.00%)	1 (16.67%)	1 (16.67%)	2 (33.33%)	0 (0.00%)	4 (50.00%)	10 (14.29%)
Hypophosphataemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	2 (33.33%)	1 (16.67%)	3 (37.50%)	7 (10.00%)
Hypovolaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Malnutrition	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Tumour Lysis Syndrome	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Musculoskeletal and connective tissue disorders									
Arthralgia	1 (9.09%)	2 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (33.33%)	1 (16.67%)	1 (12.50%)	7 (10.00%)
Back Pain	2 (18.18%)	2 (9.09%)	0 (0.00%)	0 (0.00%)	2 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	6 (8.57%)

Bone Pain	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	2 (2.86%)
Flank Pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Groin Pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Muscular Weakness	0 (0.00%)	2 (9.09%)	0 (0.00%)	0 (0.00%)	2 (33.33%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	5 (7.14%)
Musculoskeletal Chest Pain	0 (0.00%)	1 (4.55%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	2 (2.86%)
Musculoskeletal Pain	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Myalgia	1 (9.09%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.86%)
Osteonecrosis Of Jaw	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Pain In Extremity	1 (9.09%)	1 (4.55%)	0 (0.00%)	0 (0.00%)	2 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	4 (5.71%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)									
Chloroma	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Nervous system disorders									
Depressed Level Of Consciousness	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Dizziness	2 (18.18%)	3 (13.64%)	1 (20.00%)	1 (16.67%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	8 (11.43%)
Dizziness Postural	2 (18.18%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.86%)
Dysgeusia	1 (9.09%)	2 (9.09%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	5 (7.14%)
Headache	3 (27.27%)	3 (13.64%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (16.67%)	1 (12.50%)	9 (12.86%)
Hypoaesthesia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Lethargy	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
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 (12.50%)	1 (1.43%)
Presyncope	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	1 (1.43%)
Seizure	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (1.43%)

Somnolence	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Syncope	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Tremor	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Psychiatric disorders									
Anxiety	0 (0.00%)	1 (4.55%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.86%)
Confusional State	0 (0.00%)	1 (4.55%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	3 (4.29%)
Delirium	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	1 (1.43%)
Depression	2 (18.18%)	2 (9.09%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	5 (7.14%)
Hallucination	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	1 (1.43%)
Insomnia	3 (27.27%)	1 (4.55%)	0 (0.00%)	1 (16.67%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	6 (8.57%)
Mental Disorder	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	1 (1.43%)
Restlessness	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Renal and urinary disorders									
Acute Kidney Injury	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	2 (2.86%)
Dysuria	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Haematuria	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Nephrolithiasis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Pollakiuria	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	1 (1.43%)
Urinary Incontinence	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (1.43%)
Urinary Retention	0 (0.00%)	1 (4.55%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.86%)
Reproductive system and breast disorders									
Genital Pain	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Menorrhagia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Pelvic Pain	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)

Prostatitis	1 (9.09%)	1 (4.55%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.86%)
Testicular Oedema	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Respiratory, thoracic and mediastinal disorders									
Cough	0 (0.00%)	2 (9.09%)	0 (0.00%)	1 (16.67%)	3 (50.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	7 (10.00%)
Dysphonia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Dyspnoea	3 (27.27%)	3 (13.64%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	7 (10.00%)
Epistaxis	1 (9.09%)	3 (13.64%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	5 (7.14%)
Haemoptysis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Hiccups	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Hypoxia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Nasal Congestion	0 (0.00%)	1 (4.55%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	2 (2.86%)
Oropharyngeal Pain	0 (0.00%)	1 (4.55%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (33.33%)	1 (12.50%)	4 (5.71%)
Pharyngeal Erythema	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Pharyngeal Ulceration	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Pleural Effusion	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	2 (2.86%)
Pulmonary Congestion	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Pulmonary Mass	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	2 (2.86%)
Respiratory Distress	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Rhinorrhoea	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Throat Irritation	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Skin and subcutaneous tissue disorders									
Alopecia	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)

Dermatitis Exfoliative Generalised	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (1.43%)
Drug Eruption	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	1 (1.43%)
Dry Skin	3 (27.27%)	3 (13.64%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	8 (11.43%)
Eczema	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (1.43%)
Erythema	1 (9.09%)	2 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (4.29%)
Erythema Multiforme	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Hyperhidrosis	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Night Sweats	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Palmar-Plantar Erythrodysaesthesia Syndrome	2 (18.18%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.86%)
Petechiae	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	4 (66.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	4 (5.71%)
Pruritus	3 (27.27%)	4 (18.18%)	0 (0.00%)	1 (16.67%)	2 (33.33%)	0 (0.00%)	1 (16.67%)	1 (12.50%)	12 (17.14%)
Rash	2 (18.18%)	3 (13.64%)	0 (0.00%)	1 (16.67%)	1 (16.67%)	1 (16.67%)	2 (33.33%)	1 (12.50%)	11 (15.71%)
Rash Maculo-Papular	0 (0.00%)	1 (4.55%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	2 (2.86%)
Skin Discolouration	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Skin Exfoliation	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Skin Lesion	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Vascular disorders									
Haematoma	2 (18.18%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (33.33%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	5 (7.14%)
Hypertension	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Hypotension	2 (18.18%)	1 (4.55%)	0 (0.00%)	2 (33.33%)	3 (50.00%)	1 (16.67%)	0 (0.00%)	2 (25.00%)	11 (15.71%)
Orthostatic Hypotension	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Pallor	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Phlebitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	1 (1.43%)

Phlebitis Superficial	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)

Other Relevant Findings

N/a

Conclusion:

Based on the findings of this study, LGH447 was found to be safe in patients with acute myeloid leukemia or high-risk myelodysplastic syndrome as a single agent treatment, with recommended dose for expansion declared at 300 mg and no maximum tolerated dose reached. In combination with midostaurin, the safety profile was not determined due to early study termination, related to minimal anti-tumor activity across the treatment arms, as well as a possible pharmacokinetic interaction in the combination arm.

Date of Clinical Trial Report

13-Mar-2020