Clinical trial results:
A phase Ib/II, multicenter, study of LEE011 in combination with LGX818 in adult patients with BRAF mutant melanoma

Summary

EudraCT number	2012-004551-36
Trial protocol	IT ES DE NL GB
Global end of trial date	13 April 2015

Results information

Result version number	v1 (current)
This version publication date	29 April 2016
First version publication date	29 April 2016

Trial information

Trial identification

Sponsor protocol code	CLEE011X2105

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01777776
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Array BioPharma, Inc.
Sponsor organisation address	1865 33rd Street, Boulder, United States, 80301
Public contact	Clinical Operations, Array BioPharma, Inc., 1 303-381-6604, info@arraybiopharma.com
Scientific contact	Clinical Operations, Array BioPharma, Inc., 1 303-381-6604, info@arraybiopharma.com

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	13 April 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 April 2015
Global end of trial reached?	Yes
Global end of trial date	13 April 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Phase Ib:
• To estimate the MTD(s) and/or RP2D of oral ribociclib in combination with oral encorafenib in patients with BRAF mutant melanoma.

Phase II:
• To assess the anti-tumor activity of ribociclib in combination with encorafenib vs. encorafenib alone in patients with metastatic BRAF mutant melanoma who are naïve to prior selective BRAFi treatment.
• To assess the anti-tumor activity of ribociclib in combination with encorafenib in patients with metastatic BRAF mutant melanoma who are resistant to prior selective BRAFi treatment.

Enrollment in this study was halted during the Phase Ib (dose escalation phase) before the determination of MTD(s)/RP2D. All ongoing patients were followed until discontinuation before the study was terminated. The Phase II part of the study was not initiated. Therefore, all Phase II endpoints are not reported on, as no patients were enrolled in the Phase II part of the study.

Protection of trial subjects:

This clinical study was designed, shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

Eligible patients were only included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent.

Informed consent was obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent was documented in the patient source documents. The date when a patient's Informed Consent was actually obtained was captured in their Case Report Forms.

Background therapy:

N/A

Evidence for comparator:

N/A

Actual start date of recruitment	10 July 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 3
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	Netherlands: 1

Country: Number of subjects enrolled	United States: 22
Worldwide total number of subjects	28
EEA total number of subjects	1

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)	18
From 65 to 84 years	10
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment to CLEE011X2105 began on 10-July-2013. The study concluded on 13-April-2015. Participant Flow data is comprised of the Full Analysis Set (FAS), which is all patients who received at least one dose of LGX818 or LEE011.

Not completed subjects represents subjects that stopped treatment early, due to the corresponding reason.

Pre-assignment

Screening details:

In response to developments in the treatment of melanoma, the sponsor reviewed the data from the ongoing study and decided to halt further enrollment of patients in the Phase Ib part of the study. Consequently, the Phase II part of the study was not performed. Early termination of the study was not due to any safety concerns.

Period 1

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

Blinding implementation details:

Blinding implementation details are not applicable, due to study being open-label.

Arms

Arm title	Phase I (Dose Escalation)

Arm description:

Adult patients with locally advanced or metastatic BRAF V600 mutant melanoma who are resistant to selective BRAFi treatment or patients who are naïve to selective BRAFi treatment.

LEE011: Administered orally, once daily for 21 consecutive days followed by a 7-day planned break (28-day cycle).

LGX818: Administered orally, once daily on a continuous dosing schedule (28-day cycle).

Arm type	Experimental
Investigational medicinal product name	Ribociclib
Investigational medicinal product code	LEE011
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Administered orally, once daily for 21 consecutive days followed by a 7-day planned break (28-day cycle).

Investigational medicinal product name	Encorafenib
Investigational medicinal product code	LGX818
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Administered orally, once daily on a continuous dosing schedule (28-day cycle).

Number of subjects in period 1	Phase I (Dose Escalation)
Started	28
Completed	0
Not completed	28
Consent withdrawn by subject	1
Disease progression	21
Adverse event, non-fatal	6

Baseline characteristics

Reporting groups

Reporting group title	Phase I (Dose Escalation)

Reporting group description:

Adult patients with locally advanced or metastatic BRAF V600 mutant melanoma who are resistant to selective BRAFi treatment or patients who are naïve to selective BRAFi treatment.

LEE011: Administered orally, once daily for 21 consecutive days followed by a 7-day planned break (28-day cycle).

LGX818: Administered orally, once daily on a continuous dosing schedule (28-day cycle).

Reporting group values	Phase I (Dose Escalation)	Total	
Number of subjects	28	28	
Age Categorical Units: participants			
<=18 years	0	0	
Between 18 and 65 years	18	18	
>=65 years	10	10	
Age Continuous Units: years			
arithmetic mean	56.6		
standard deviation	± 13.9	-	
Gender, Male/Female Units: participants			
Female	11	11	
Male	17	17	
WHO/ECOG performance status			
Categories: • 0 - Fully active, able to carry on all pre-disease performance without restriction • 1 - Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work • 2 - Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours • 3 - Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours • 4 - Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair			
Units: Subjects			
0:	8	8	
1:	19	19	
2:	1	1	
Weight Units: kilograms			
arithmetic mean	79.44		
standard deviation	± 14.45	-	

Subject analysis sets

Subject analysis set title	Phase Ib: LEE011 200 mg + LGX818 300 mg (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

Full Analysis (FAS) included all patients who received at least one dose of encorafenib or ribociclib.

Subject analysis set title	Phase Ib: LEE011 300 mg + LGX818 200 mg (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
Full Analysis Set (FAS) included all patients who received at least one dose of encorafenib or ribociclib.	
Subject analysis set title	Phase Ib: LEE011 400 mg + LGX818 100 mg (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
Full Analysis Set (FAS) includes all patients who received at least one dose of encorafenib or ribociclib.	
Subject analysis set title	Phase Ib: LEE011 400 mg + LGX818 200 mg (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
Full Analysis Set (FAS) included all patients who received at least one dose of encorafenib or ribociclib.	

Reporting group values	Phase Ib: LEE011 200 mg + LGX818 300 mg (FAS)	Phase Ib: LEE011 300 mg + LGX818 200 mg (FAS)	Phase Ib: LEE011 400 mg + LGX818 100 mg (FAS)
Number of subjects	6	12	6
Age Categorical			
Units: participants			
<=18 years	0	0	0
Between 18 and 65 years	2	10	4
>=65 years	4	2	2
Age Continuous			
Units: years			
arithmetic mean	65	49.8	58
standard deviation	± 10.71	± 13.66	± 10.55
Gender, Male/Female			
Units: participants			
Female	3	7	1
Male	3	5	5
WHO/ECOG performance status			
Categories: • 0 - Fully active, able to carry on all pre-disease performance without restriction • 1 - Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work • 2 - Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours • 3 - Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours • 4 - Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair			
Units: Subjects			
0:	2	4	1
1:	4	7	5
2:	0	1	0
Weight			
Units: kilograms			
arithmetic mean	84.6	78.08	80.17
standard deviation	± 12.793	± 17.069	± 10.308

Reporting group values	Phase Ib: LEE011 400 mg + LGX818 200 mg (FAS)		
Number of subjects	4		
Age Categorical			
Units: participants			
<=18 years	0		

Between 18 and 65 years	2		
>=65 years	2		

Age Continuous			
Units: years			
arithmetic mean	62		
standard deviation	± 17.63		
Gender, Male/Female			
Units: participants			
Female	0		
Male	4		
WHO/ECOG performance status			
Categories: • 0 - Fully active, able to carry on all pre-disease performance without restriction • 1 - Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work • 2 - Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours • 3 - Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours • 4 - Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair			
Units: Subjects			
0:	1		
1:	3		
2:	0		
Weight			
Units: kilograms			
arithmetic mean	74.7		
standard deviation	± 16.415		

End points

End points reporting groups

Reporting group title	Phase I (Dose Escalation)

Reporting group description:

Adult patients with locally advanced or metastatic BRAF V600 mutant melanoma who are resistant to selective BRAFi treatment or patients who are naïve to selective BRAFi treatment.

LEE011: Administered orally, once daily for 21 consecutive days followed by a 7-day planned break (28-day cycle).

LGX818: Administered orally, once daily on a continuous dosing schedule (28-day cycle).

Subject analysis set title	Phase Ib: LEE011 200 mg + LGX818 300 mg (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

Full Analysis (FAS) included all patients who received at least one dose of encorafenib or ribociclib.

Subject analysis set title	Phase Ib: LEE011 300 mg + LGX818 200 mg (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

Full Analysis Set (FAS) included all patients who received at least one dose of encorafenib or ribociclib.

Subject analysis set title	Phase Ib: LEE011 400 mg + LGX818 100 mg (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

Full Analysis Set (FAS) includes all patients who received at least one dose of encorafenib or ribociclib.

Subject analysis set title	Phase Ib: LEE011 400 mg + LGX818 200 mg (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

Full Analysis Set (FAS) included all patients who received at least one dose of encorafenib or ribociclib.

Primary: Phase Ib - Incidence of Dose Limiting Toxicities (DLTs) in Cycle 1

End point title	Phase Ib - Incidence of Dose Limiting Toxicities (DLTs) in Cycle 1[1]

End point description:

Dose Limiting Toxicities (DLTs) during the first 28 days of the combination treatment of LEE011 and LGX818.

Due to the halt of enrollment, no Maximum Tolerated Dose (MTD) was formally declared during the study.

End point type	Primary

End point timeframe:

Cycle 1 (approximately 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: Not Applicable

End point values	Phase I (Dose Escalation)			
Subject group type	Reporting group			
Number of subjects analysed	28[2]			
Units: Not Applicable				
number (not applicable)				
Elevated Bilirubin	1			
Maculopapular Rash	1			

Myalagia	1			
Neuralgia	1			

Notes:

[2] - Safety Set

Statistical analyses

No statistical analyses for this end point

Secondary: Phase I - Number of subjects experiencing at least one Adverse Event (AE).

End point title	Phase I - Number of subjects experiencing at least one Adverse Event (AE).

End point description:

End point type	Secondary

End point timeframe:

Approximately 23 months after enrollment

End point values	Phase I (Dose Escalation)			
Subject group type	Reporting group			
Number of subjects analysed	28[3]			
Units: participants				
number (not applicable)	28			

Notes:

[3] - Safety Set

Statistical analyses

No statistical analyses for this end point

Secondary: Phase I - Number of Subjects Experiencing at Least One Serious Adverse Event (SAE).

End point title	Phase I - Number of Subjects Experiencing at Least One Serious Adverse Event (SAE).

End point description:

End point type	Secondary

End point timeframe:

Approximately 23 months after enrollment

End point values	Phase I (Dose Escalation)			
Subject group type	Reporting group			
Number of subjects analysed	28[4]			
Units: participants				
number (not applicable)	12			

Notes:

[4] - Safety Set

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib/II - Plasma concentration-time profiles

End point title	Phase Ib/II - Plasma concentration-time profiles

End point description:

Due to the halt of enrollment during the Phase Ib part of the study, all analyses related to plasma concentration time profiles were not performed. Subsequently, Phase II of the study did not enroll any subjects.

As EudraCT only allows numerical data entry, the value of 999 indicates "No Value", as no data was analyzed/ collected for this end point.

End point type	Secondary

End point timeframe:

28-day cycles

End point values	Phase I (Dose Escalation)			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: Not Applicabe				
number (not applicable)	999			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib/II - Overall Response Rate (ORR)

End point title	Phase Ib/II - Overall Response Rate (ORR)

End point description:

ORR is defined as the proportion of patients with a best overall response of complete response or partial response.

Due to the halt of enrollment during the Phase Ib part of the study, this analysis was not performed. Subsequently, Phase II of the study did not enroll any subjects.

As EudraCT only allows numerical data entry, the value of 999 indicates "No Value", as no data was analyzed/ collected for this end point.

End point type	Secondary

End point timeframe:

Approximately 23 months after enrollment

End point values	Phase I (Dose Escalation)			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: Not Applicable				
number (not applicable)	999			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib/II - Progression Free Survival (PFS)

End point title	Phase Ib/II - Progression Free Survival (PFS)

End point description:

PFS is the time from date of randomization/start of treatment to the date of event defined as the first documented progression or death due to any cause.

Due to the halt of enrollment during the Phase Ib part of the study, this analysis was not performed. Subsequently, Phase II of the study did not enroll any subjects.

As EudraCT only allows numerical data entry, the value of 999 indicates "No Value", as no data was analyzed for this end point.

End point type	Secondary

End point timeframe:

Approximately 23 months after enrollment

End point values	Phase I (Dose Escalation)			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: Not Applicable				
number (not applicable)	999			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib/II - Duration Of Response (DOR)

End point title	Phase Ib/II - Duration Of Response (DOR)

End point description:

DOR is calculated as the time from the date of first documented response (complete response (CR) or partial response (PR)) to the first documented date of progression or death due to underlying cancer.

Due to the halt of enrollment during the Phase Ib part of the study, this analysis was not performed. Subsequently, Phase II of the study did not enroll any subjects.

As EudraCT only allows numerical data entry, the value of 999 indicates "No Value", as no data was analyzed for this end point.

End point type	Secondary

End point timeframe:

Approximately 23 months after enrollment

End point values	Phase I (Dose Escalation)			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: Not Applicable				
number (not applicable)	999			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib/II - Pharmacokinetic Parameters: AUCtau

End point title	Phase Ib/II - Pharmacokinetic Parameters: AUCtau

End point description:

Due to the halt of enrollment during the Phase Ib part of the study, all analyses related to pharmacokinetic parameters were not performed. Subsequently, Phase II of the study did not enroll any subjects.

As EudraCT only allows numerical data entry, the value of 999 indicates "No Value", as no data was analyzed for this end point.

End point type	Secondary

End point timeframe:

28-day cycles

End point values	Phase I (Dose Escalation)			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: Not Applicable				
number (not applicable)	999			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib/II - Pharmacokinetic Parameters: Cmin

End point title	Phase Ib/II - Pharmacokinetic Parameters: Cmin

End point description:

Due to the halt of enrollment during the Phase Ib part of the study, all analyses related to pharmacokinetic parameters were not performed. Subsequently, Phase II of the study did not enroll any subjects.

As EudraCT only allows numerical data entry, the value of 999 indicates "No Value", as no data was analyzed for this end point.

End point type	Secondary

End point timeframe:

28-day cycles

End point values	Phase I (Dose Escalation)			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: Not Applicable				
number (not applicable)	999			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib/II - Pharmacokinetic Parameters: Cmax

End point title	Phase Ib/II - Pharmacokinetic Parameters: Cmax

End point description:

Due to the halt of enrollment during the Phase Ib part of the study, all analyses related to pharmacokinetic parameters were not performed. Subsequently, Phase II of the study did not enroll any subjects.

As EudraCT only allows numerical data entry, the value of 999 indicates "No Value", as no data was analyzed for this end point.

End point type	Secondary

End point timeframe:

28-day cycles

End point values	Phase I (Dose Escalation)			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: Not Applicable				
number (not applicable)	999			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib/II - Pharmacokinetic Parameters: Tmax

End point title	Phase Ib/II - Pharmacokinetic Parameters: Tmax

End point description:

Due to the halt of enrollment during the Phase Ib part of the study, all analyses related to pharmacokinetic parameters were not performed. Subsequently, Phase II of the study did not enroll any subjects.

As EudraCT only allows numerical data entry, the value of 999 indicates "No Value", as no data was analyzed for this end point.

End point type	Secondary

End point timeframe:

28-day cycles

End point values	Phase I (Dose Escalation)			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: Not Applicable				
number (not applicable)	999			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib/II - Pharmacokinetic Parameters: Racc

End point title	Phase Ib/II - Pharmacokinetic Parameters: Racc

End point description:

Due to the halt of enrollment during the Phase Ib part of the study, all analyses related to pharmacokinetic parameters were not performed. Subsequently, Phase II of the study did not enroll any subjects.

As EudraCT only allows numerical data entry, the value of 999 indicates "No Value", as no data was analyzed for this end point.

End point type	Secondary

End point timeframe:

28-day cycles

End point values	Phase I (Dose Escalation)			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: Not Applicable				
number (not applicable)	999			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AEs) were collected during the study, which began recruitment on 10-July-2013 and concluded on 13-April-2015.

Adverse event reporting additional description:

An AE is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after patient's signed informed consent has been

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	MedDRA

Reporting groups

Reporting group title	Phase Ib: LEE011 200 mg + LGX818 300 mg (SS)

Reporting group description:

Ribociclib (LEE011) was provided in capsule form for oral use and was to be taken orally, once a day for 21 consecutive days followed by a 7-day planned break as part of each 28-day cycle of treatment.

Encorafenib (LGX818) was to be provided in capsule form for oral use and taken orally, once a day for 28 consecutive days as part of each 28-day cycle of treatment.

Reporting group title	Phase Ib: LEE011 300 mg + LGX818 200 mg (SS)

Reporting group description:

Ribociclib (LEE011) was provided in capsule form for oral use and was to be taken orally, once a day for 21 consecutive days followed by a 7-day planned break as part of each 28-day cycle of treatment.

Encorafenib (LGX818) was to be provided in capsule form for oral use and taken orally, once a day for 28 consecutive days as part of each 28-day cycle of treatment.

Reporting group title	Phase Ib: LEE011 400 mg + LGX818 100 mg (SS)

Reporting group description:

Ribociclib (LEE011) was provided in capsule form for oral use and was to be taken orally, once a day for 21 consecutive days followed by a 7-day planned break as part of each 28-day cycle of treatment.

Encorafenib (LGX818) was to be provided in capsule form for oral use and taken orally, once a day for 28 consecutive days as part of each 28-day cycle of treatment.

Reporting group title	Phase Ib: LEE011 400 mg + LGX818 200 mg (SS)

Reporting group description:

Ribociclib (LEE011) was provided in capsule form for oral use and was to be taken orally, once a day for 21 consecutive days followed by a 7-day planned break as part of each 28-day cycle of treatment.

Encorafenib (LGX818) was to be provided in capsule form for oral use and taken orally, once a day for 28 consecutive days as part of each 28-day cycle of treatment.

Serious adverse events	Phase Ib: LEE011 200 mg + LGX818 300 mg (SS)	Phase Ib: LEE011 300 mg + LGX818 200 mg (SS)	Phase Ib: LEE011 400 mg + LGX818 100 mg (SS)
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 6 (50.00%)	5 / 12 (41.67%)	3 / 6 (50.00%)
number of deaths (all causes)	1	0	1
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			

Brain oedema			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 6 (0.00%)	0 / 12 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Syncope			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	0 / 6 (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
Nervous system disorders			
Memory impairment			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	0 / 6 (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
Seizure			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	0 / 6 (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
Simple partial seizures			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 6 (0.00%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	0 / 6 (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
Immune system disorders			
Systemic inflammatory response syndrome			

alternative assessment type: Systematic			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	0 / 6 (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
Gastrointestinal disorders			
Nausea			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	0 / 6 (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
Hepatobiliary disorders			
Transaminases increased			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	0 / 6 (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
Skin and subcutaneous tissue disorders			
Dermatitis bullous			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	0 / 6 (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
Psychiatric disorders			
Confusional state			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	0 / 6 (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
Mental status changes			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	0 / 6 (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
Renal and urinary disorders			

Urinary tract infection			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 6 (0.00%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Chest wall abscess			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	0 / 6 (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
Failure to thrive			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	0 / 6 (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
Neck pain			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	0 / 6 (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
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Sepsis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 6 (0.00%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Phase Ib: LEE011 400 mg + LGX818 200 mg (SS)		

Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 4 (25.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Brain oedema			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Syncope			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Memory impairment			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Seizure			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Simple partial seizures			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Spinal cord compression			
alternative assessment type: Systematic			

subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Systemic inflammatory response syndrome			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Nausea			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Transaminases increased			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Dermatitis bullous			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Confusional state			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Mental status changes			

alternative assessment type: Systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Urinary tract infection			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Chest wall abscess			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Failure to thrive			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neck pain			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sepsis			
alternative assessment type: Systematic			

subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Phase Ib: LEE011 200 mg + LGX818 300 mg (SS)	Phase Ib: LEE011 300 mg + LGX818 200 mg (SS)	Phase Ib: LEE011 400 mg + LGX818 100 mg (SS)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)	11 / 12 (91.67%)	6 / 6 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acrochordon			
subjects affected / exposed	0 / 6 (0.00%)	2 / 12 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Skin papilloma			
subjects affected / exposed	1 / 6 (16.67%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Melanocytic naevus			
subjects affected / exposed	1 / 6 (16.67%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Acanthoma			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Infected neoplasm			
subjects affected / exposed	0 / 6 (0.00%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Neoplasm			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Seborrhoeic keratosis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0

Vascular disorders			
Flushing			
subjects affected / exposed	3 / 6 (50.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	3	1	0
Hot flush			
subjects affected / exposed	0 / 6 (0.00%)	2 / 12 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Hypotension			
subjects affected / exposed	0 / 6 (0.00%)	0 / 12 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Embolism			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Hypertension			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 6 (33.33%)	6 / 12 (50.00%)	4 / 6 (66.67%)
occurrences (all)	2	6	4
Oedema peripheral			
subjects affected / exposed	0 / 6 (0.00%)	2 / 12 (16.67%)	2 / 6 (33.33%)
occurrences (all)	0	2	2
Chills			
subjects affected / exposed	1 / 6 (16.67%)	2 / 12 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	2	0
Pyrexia			
subjects affected / exposed	0 / 6 (0.00%)	2 / 12 (16.67%)	1 / 6 (16.67%)
occurrences (all)	0	2	1
Localised oedema			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Non-cardiac chest pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Peripheral swelling			

subjects affected / exposed	0 / 6 (0.00%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Xerosis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast disorders			
Penile oedema			
subjects affected / exposed	0 / 6 (0.00%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Scrotal oedema			
subjects affected / exposed	0 / 6 (0.00%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Scrotal pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Scrotal swelling			
subjects affected / exposed	0 / 6 (0.00%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	0 / 6 (0.00%)	2 / 12 (16.67%)	1 / 6 (16.67%)
occurrences (all)	0	2	1
Cough			
subjects affected / exposed	1 / 6 (16.67%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Dyspnoea			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Pulmonary embolism			
subjects affected / exposed	1 / 6 (16.67%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Rhinorrhoea			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Dry throat			

subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Dysphonia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Dyspnoea exertional			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Pleural effusion			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Upper-airway cough syndrome			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Wheezing			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Mood swings			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Anger			
subjects affected / exposed	0 / 6 (0.00%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Confusional state			
subjects affected / exposed	0 / 6 (0.00%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Irritability			
subjects affected / exposed	0 / 6 (0.00%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Mental status changes			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0

Sleep disorder			
subjects affected / exposed	0 / 6 (0.00%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Investigations			
Blood creatinine increased			
subjects affected / exposed	4 / 6 (66.67%)	1 / 12 (8.33%)	1 / 6 (16.67%)
occurrences (all)	4	1	1
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	2 / 6 (33.33%)
occurrences (all)	0	1	2
Weight decreased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Alanine aminotransferase increased			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Blood sodium decreased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
White blood cell count decreased			
subjects affected / exposed	0 / 6 (0.00%)	2 / 12 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Blood bilirubin increased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Blood glucose increased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Blood iron decreased			

subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Blood phosphorus decreased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Blood potassium decreased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Blood thyroid stimulating hormone increased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Cardiac murmur			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Lymphocyte count decreased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Neutrophil count decreased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Troponin increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 6 (16.67%)	1 / 12 (8.33%)	1 / 6 (16.67%)
occurrences (all)	1	1	1
Arthropod bite			
subjects affected / exposed	0 / 6 (0.00%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Laceration			
subjects affected / exposed	0 / 6 (0.00%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Muscle strain			

subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Post procedural complication			
subjects affected / exposed	0 / 6 (0.00%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Post procedural discharge			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Sunburn			
subjects affected / exposed	0 / 6 (0.00%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Palpitations			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 6 (0.00%)	2 / 12 (16.67%)	1 / 6 (16.67%)
occurrences (all)	0	2	1
Dysgeusia			
subjects affected / exposed	2 / 6 (33.33%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	2	1	0
Dizziness			
subjects affected / exposed	0 / 6 (0.00%)	2 / 12 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Neuralgia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 6 (16.67%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Somnolence			

subjects affected / exposed	0 / 6 (0.00%)	0 / 12 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	2
Balance disorder			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Hyperaesthesia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Hypoaesthesia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Neuropathy peripheral			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Paraesthesia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Partial seizures			
subjects affected / exposed	0 / 6 (0.00%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Peripheral motor neuropathy			
subjects affected / exposed	0 / 6 (0.00%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Sciatica			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Syncope			
subjects affected / exposed	0 / 6 (0.00%)	0 / 12 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 6 (16.67%)	1 / 12 (8.33%)	2 / 6 (33.33%)
occurrences (all)	1	1	2
Lymphopenia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0

Neutropenia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Thrombocytopenia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Disseminated intravascular coagulation			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Increased tendency to bruise			
subjects affected / exposed	0 / 6 (0.00%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Leukopenia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Lymphadenopathy			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
Ear pruritus			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Eye pruritus			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Vision blurred			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Blepharospasm			
subjects affected / exposed	0 / 6 (0.00%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Dry eye			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Eye discharge			

subjects affected / exposed	0 / 6 (0.00%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Photophobia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	2 / 6 (33.33%)	6 / 12 (50.00%)	4 / 6 (66.67%)
occurrences (all)	2	6	4
Vomiting			
subjects affected / exposed	1 / 6 (16.67%)	3 / 12 (25.00%)	3 / 6 (50.00%)
occurrences (all)	1	3	3
Constipation			
subjects affected / exposed	3 / 6 (50.00%)	3 / 12 (25.00%)	1 / 6 (16.67%)
occurrences (all)	3	3	1
Diarrhoea			
subjects affected / exposed	2 / 6 (33.33%)	2 / 12 (16.67%)	1 / 6 (16.67%)
occurrences (all)	2	2	1
Stomatitis			
subjects affected / exposed	1 / 6 (16.67%)	4 / 12 (33.33%)	1 / 6 (16.67%)
occurrences (all)	1	4	1
Abdominal distension			
subjects affected / exposed	0 / 6 (0.00%)	2 / 12 (16.67%)	1 / 6 (16.67%)
occurrences (all)	0	2	1
Abdominal pain			
subjects affected / exposed	0 / 6 (0.00%)	2 / 12 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Dyspepsia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Abdominal discomfort			
subjects affected / exposed	0 / 6 (0.00%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Oral pain			
subjects affected / exposed	0 / 6 (0.00%)	2 / 12 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	2	0

Abdominal pain upper			
subjects affected / exposed	0 / 6 (0.00%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Cheilitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Dysphagia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Gingival discolouration			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Gingival ulceration			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Glossitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Glossodynia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Haemorrhoids			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Retching			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	2 / 6 (33.33%)	7 / 12 (58.33%)	3 / 6 (50.00%)
occurrences (all)	2	7	3
Pruritus			

subjects affected / exposed	2 / 6 (33.33%)	7 / 12 (58.33%)	1 / 6 (16.67%)
occurrences (all)	2	7	1
Alopecia			
subjects affected / exposed	3 / 6 (50.00%)	2 / 12 (16.67%)	1 / 6 (16.67%)
occurrences (all)	3	2	1
Dry skin			
subjects affected / exposed	1 / 6 (16.67%)	4 / 12 (33.33%)	2 / 6 (33.33%)
occurrences (all)	1	4	2
Rash			
subjects affected / exposed	4 / 6 (66.67%)	2 / 12 (16.67%)	0 / 6 (0.00%)
occurrences (all)	4	2	0
Rash maculo-papular			
subjects affected / exposed	0 / 6 (0.00%)	2 / 12 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Hyperkeratosis			
subjects affected / exposed	0 / 6 (0.00%)	2 / 12 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Dermatitis acneiform			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Erythema			
subjects affected / exposed	1 / 6 (16.67%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Hyperhidrosis			
subjects affected / exposed	0 / 6 (0.00%)	2 / 12 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Night sweats			
subjects affected / exposed	0 / 6 (0.00%)	2 / 12 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Palmoplantar keratoderma			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Photosensitivity reaction			
subjects affected / exposed	0 / 6 (0.00%)	2 / 12 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Pruritus generalised			

subjects affected / exposed	0 / 6 (0.00%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Skin exfoliation			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Skin hyperpigmentation			
subjects affected / exposed	1 / 6 (16.67%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Skin sensitisation			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Transient acantholytic dermatosis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Actinic keratosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Cold sweat			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Ephelides			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Intertrigo			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Leukoplakia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Pain of skin			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Psoriasis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Rash erythematous			

subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Rash papular			
subjects affected / exposed	0 / 6 (0.00%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Rash pruritic			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Skin hypopigmentation			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Skin lesion			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Vitiligo			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Dysuria			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Renal impairment			
subjects affected / exposed	0 / 6 (0.00%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Urinary retention			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Cushingoid			

subjects affected / exposed	0 / 6 (0.00%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	2 / 6 (33.33%)	4 / 12 (33.33%)	1 / 6 (16.67%)
occurrences (all)	2	4	1
Arthralgia			
subjects affected / exposed	1 / 6 (16.67%)	3 / 12 (25.00%)	1 / 6 (16.67%)
occurrences (all)	1	3	1
Pain in extremity			
subjects affected / exposed	1 / 6 (16.67%)	3 / 12 (25.00%)	2 / 6 (33.33%)
occurrences (all)	1	3	2
Neck pain			
subjects affected / exposed	1 / 6 (16.67%)	2 / 12 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	2	0
Musculoskeletal pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Back pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Muscle spasms			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Musculoskeletal chest pain			
subjects affected / exposed	0 / 6 (0.00%)	2 / 12 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Musculoskeletal stiffness			
subjects affected / exposed	1 / 6 (16.67%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Flank pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Groin pain			

subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Joint swelling			
subjects affected / exposed	0 / 6 (0.00%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Muscular weakness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Osteoporosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Periarthritis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Infections and infestations			
Oral candidiasis			
subjects affected / exposed	0 / 6 (0.00%)	2 / 12 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Skin candida			
subjects affected / exposed	1 / 6 (16.67%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Cellulitis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Conjunctivitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Dermatitis infected			
subjects affected / exposed	0 / 6 (0.00%)	0 / 12 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Fungal infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Furuncle			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0

Lower respiratory tract infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Skin abrasion			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Hypoalbuminaemia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	3 / 6 (50.00%)
occurrences (all)	1	0	3
Decreased appetite			
subjects affected / exposed	1 / 6 (16.67%)	2 / 12 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	2	0
Hypophosphataemia			
subjects affected / exposed	1 / 6 (16.67%)	1 / 12 (8.33%)	1 / 6 (16.67%)
occurrences (all)	1	1	1
Hypokalaemia			
subjects affected / exposed	1 / 6 (16.67%)	1 / 12 (8.33%)	1 / 6 (16.67%)
occurrences (all)	1	1	1
Dehydration			
subjects affected / exposed	2 / 6 (33.33%)	0 / 12 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Hyperglycaemia			
subjects affected / exposed	2 / 6 (33.33%)	0 / 12 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Hypermagnesaemia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Hyponatraemia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Hyperkalaemia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Hypocalcaemia			

subjects affected / exposed	0 / 6 (0.00%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1

Non-serious adverse events	Phase Ib: LEE011 400 mg + LGX818 200 mg (SS)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 4 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acrochordon			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Skin papilloma			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Melanocytic naevus			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Acanthoma			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Infected neoplasm			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Neoplasm			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Seborrhoeic keratosis			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Vascular disorders			
Flushing			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Hot flush			

subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Hypotension			
subjects affected / exposed	2 / 4 (50.00%)		
occurrences (all)	2		
Embolism			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Hypertension			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 4 (75.00%)		
occurrences (all)	3		
Oedema peripheral			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Chills			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Pyrexia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Localised oedema			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Non-cardiac chest pain			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Peripheral swelling			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Xerosis			

subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Reproductive system and breast disorders			
Penile oedema			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Scrotal oedema			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Scrotal pain			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Scrotal swelling			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Cough			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Dyspnoea			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Pulmonary embolism			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Rhinorrhoea			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Dry throat			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Dysphonia			

subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Dyspnoea exertional			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Pleural effusion			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Upper-airway cough syndrome			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Wheezing			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Mood swings			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Anger			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Confusional state			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Irritability			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Mental status changes			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Sleep disorder			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		

Investigations			
Blood creatinine increased			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Weight decreased			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Alanine aminotransferase increased			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Blood sodium decreased			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
White blood cell count decreased			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Blood bilirubin increased			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Blood glucose increased			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Blood iron decreased			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Blood phosphorus decreased			

subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Blood potassium decreased			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Blood thyroid stimulating hormone increased			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Cardiac murmur			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Lymphocyte count decreased			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Neutrophil count decreased			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Troponin increased			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Arthropod bite			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Laceration			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Muscle strain			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Post procedural complication			

subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Post procedural discharge			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Sunburn			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Tachycardia			
subjects affected / exposed	2 / 4 (50.00%)		
occurrences (all)	2		
Palpitations			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Dysgeusia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Dizziness			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Neuralgia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Somnolence			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Balance disorder			

subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Hyperaesthesia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Hypoaesthesia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Neuropathy peripheral			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Paraesthesia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Partial seizures			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Peripheral motor neuropathy			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Sciatica			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Syncope			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Lymphopenia			
subjects affected / exposed	2 / 4 (50.00%)		
occurrences (all)	2		
Neutropenia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		

Thrombocytopenia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Increased tendency to bruise			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Leukopenia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Lymphadenopathy			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Ear and labyrinth disorders			
Ear pruritus			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Eye disorders			
Eye pruritus			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Vision blurred			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Blepharospasm			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Dry eye			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Eye discharge			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Photophobia			

subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	4 / 4 (100.00%)		
occurrences (all)	4		
Vomiting			
subjects affected / exposed	2 / 4 (50.00%)		
occurrences (all)	2		
Constipation			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Diarrhoea			
subjects affected / exposed	2 / 4 (50.00%)		
occurrences (all)	2		
Stomatitis			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Abdominal distension			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Abdominal pain			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Dyspepsia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Abdominal discomfort			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Oral pain			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Abdominal pain upper			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		

Cheilitis subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
Dysphagia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
Gingival discolouration subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
Gingival ulceration subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
Glossitis subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
Glossodynia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
Haemorrhoidal haemorrhage subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
Haemorrhoids subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
Retching subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
Skin and subcutaneous tissue disorders Palmar-plantar erythrodysaesthesia syndrome subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1		
Pruritus subjects affected / exposed occurrences (all)	2 / 4 (50.00%) 2		
Alopecia			

subjects affected / exposed	1 / 4 (25.00%)			
occurrences (all)	1			
Dry skin				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
Rash				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
Rash maculo-papular				
subjects affected / exposed	2 / 4 (50.00%)			
occurrences (all)	2			
Hyperkeratosis				
subjects affected / exposed	2 / 4 (50.00%)			
occurrences (all)	2			
Dermatitis acneiform				
subjects affected / exposed	1 / 4 (25.00%)			
occurrences (all)	1			
Erythema				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
Hyperhidrosis				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
Night sweats				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
Palmoplantar keratoderma				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
Photosensitivity reaction				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
Pruritus generalised				
subjects affected / exposed	1 / 4 (25.00%)			
occurrences (all)	1			
Skin exfoliation				

subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
Skin hyperpigmentation				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
Skin sensitisation				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
Transient acantholytic dermatosis				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
Actinic keratosis				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
Cold sweat				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
Ephelides				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
Intertrigo				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
Leukoplakia				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
Pain of skin				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
Psoriasis				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
Rash erythematous				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
Rash papular				

subjects affected / exposed occurrences (all) Rash pruritic subjects affected / exposed occurrences (all) Skin hypopigmentation subjects affected / exposed occurrences (all) Skin lesion subjects affected / exposed occurrences (all) Vitiligo subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0 0 / 4 (0.00%) 0 0 / 4 (0.00%) 0 0 / 4 (0.00%) 0 0 / 4 (0.00%) 0		
Renal and urinary disorders Acute kidney injury subjects affected / exposed occurrences (all) Dysuria subjects affected / exposed occurrences (all) Renal impairment subjects affected / exposed occurrences (all) Urinary retention subjects affected / exposed occurrences (all)	 0 / 4 (0.00%) 0 0 / 4 (0.00%) 0 0 / 4 (0.00%) 0 0 / 4 (0.00%) 0		
Endocrine disorders Adrenal insufficiency subjects affected / exposed occurrences (all) Cushingoid subjects affected / exposed occurrences (all)	 0 / 4 (0.00%) 0 0 / 4 (0.00%) 0		
Musculoskeletal and connective tissue disorders			

Myalgia				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
Arthralgia				
subjects affected / exposed	1 / 4 (25.00%)			
occurrences (all)	1			
Pain in extremity				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
Neck pain				
subjects affected / exposed	1 / 4 (25.00%)			
occurrences (all)	1			
Musculoskeletal pain				
subjects affected / exposed	1 / 4 (25.00%)			
occurrences (all)	1			
Back pain				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
Muscle spasms				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
Musculoskeletal chest pain				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
Musculoskeletal stiffness				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
Flank pain				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
Groin pain				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
Joint swelling				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			

Muscular weakness			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Osteoporosis			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Periarthritis			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Oral candidiasis			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Skin candida			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Cellulitis			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Conjunctivitis			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Dermatitis infected			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Fungal infection			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Furuncle			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Lower respiratory tract infection			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Skin abrasion			

subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			
Hypoalbuminaemia			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Decreased appetite			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Hypophosphataemia			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Hypokalaemia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Dehydration			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Hyperglycaemia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Hypermagnesaemia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Hyponatraemia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Hyperkalaemia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Hypocalcaemia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 March 2013	Protocol Amendment 1 primarily addressed changes to the protocol required as a result of Health Authority feedback. In addition, minor administrative changes to the protocol were also included.
30 September 2013	Protocol Amendment 2 introduced the following changes based on emerging safety data: • Additional time points were added to the ECG monitoring schedule to assess the safety and tolerability of ribociclib. • Hematological toxicity regimen was no longer pursued. All references to this alternate dosing regimen were removed from the protocol. Only the 21 consecutive days dosing followed by a 7-day planned break regimen was used in this study.
20 December 2013	Protocol Amendment 3 introduced new safety monitoring for visual toxicities, including routine ophthalmic examinations, in order to monitor for the potential risk of retinal/ocular changes and included recommendations for encorafenib dose modifications for visual toxicity. In addition, definitions of ophthalmologic DLTs were provided.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
07 August 2014	Study recruitment was halted on 07-Aug-2014 during the Phase Ib part of the study. The Phase II part of the study was not performed. Subsequently, no subjects were enrolled in the Phase II part of the study. Early termination of the study was not due to any safety concerns.	-

Notes:

Limitations and caveats

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

N/A

Notes: