Clinical trial results:
A phase II, multi-center, open-label study of single-agent LGX818 followed by a rational combination with targeted agents after progression on LGX818, to overcome resistance in adult patients with locally advanced or metastatic BRAF V600 melanoma

Summary

EudraCT number	2012-004798-17
Trial protocol	ES DE
Global end of trial date	23 March 2015

Results information

Result version number	v1 (current)
This version publication date	08 April 2016
First version publication date	08 April 2016

Trial information

Trial identification

Sponsor protocol code	CLGX818X2102

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01820364
WHO universal trial number (UTN)	-
Other trial identifiers	ClinicalTrials.gov: NCT01820364

Notes:

Sponsors

Sponsor organisation name	Array BioPharma, Inc.
Sponsor organisation address	3200 Walnut 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	23 March 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 March 2015
Global end of trial reached?	Yes
Global end of trial date	23 March 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

This was a phase II, two-part, multi-center, open-label study in adult patients with locally advanced unresectable or metastatic BRAFV600-mutant melanoma.

Part I: LGX818 single-agent treatment in BRAF inhibitor-naive patients.

Part II: Combination treatments of LGX818 + MEK162, or BKM120, or BGJ398, or INC280, or LEE011 to assess the clinical efficacy and to further evaluate the safety of the drug combinations in patients with locally advanced or metastatic BRAF-mutant melanoma after relapse on LGX818. These drug combinations were selected based on documentation of molecular resistance mechanism. Patients with BRAF-mutant melanoma treated with single agent LGX818 in other studies could be enrolled directly in part II of CLGX818X2102 after relapse and documentation of progression.

Protection of trial subjects:

Patients had to provide a signed molecular pre-screening informed consent form (ICF) for any study-related molecular pre-screening procedure.

After the mutational status of BRAF was known or determined, the patient was allowed to sign the main study ICF prior to any study-specific screening evaluations. The study was described by the Investigator or designee, who answered any questions, and written information was also provided.

Background therapy:

N/A

Evidence for comparator:

N/A

Actual start date of recruitment	24 June 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	Germany: 1
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	Switzerland: 6
Country: Number of subjects enrolled	United States: 2
Worldwide total number of subjects	15
EEA total number of subjects	4

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)	12
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment began on 24-Jun-2013 to the CLGX818X2102 (LOGIC 1) study. A total of 15 subjects were enrolled. The last subject's last visit occurred on 23-Mar-2015.

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

Pre-assignment

Screening details:

N/A

Period 1

Period 1 title	Part I: LGX818
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

This was an open-label study. Therefore, blinding implementation details are not applicable.

Arms

Arm title	Part I: LGX818 - single agent

Arm description:

Subjects in Part I of the study received LGX818 as a single agent.

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

Dosage and administration details:

300 mg QD, (21-day cycles)

Number of subjects in period 1	Part I: LGX818 - single agent
Started	15
Completed	1
Not completed	14
Disease progression	4
Adverse event, non-fatal	6
Death	1
Administrative problems	3

Period 2

Period 2 title	Part II: LGX818 + MEK162
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

This was an open-label study. Therefore, blinding implementation details are not applicable.

Arms

Arm title	Part II: CLGX818 + MEK162

Arm description:

As per the original study design, Part II was to have five arms corresponding to the five potential combination treatments; however, only one patient was treated in this part of the study and received LGX818 in combination with MEK162.

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

Dosage and administration details:

450 mg QD, (21-day cycles)

Investigational medicinal product name	Binimetinib
Investigational medicinal product code	MEK162
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

45 mg QD, (21-day cycles)

Number of subjects in period 2	Part II: CLGX818 + MEK162
Started	1
Completed	0
Not completed	1
Study termination	1

Baseline characteristics

Reporting groups	
Reporting group title	Part I: LGX818
Reporting group description:	
Subjects in Part I of the study received LGX818 - single agent.	

Reporting group values	Part I: LGX818	Total	
Number of subjects	15	15	
Age categorical Units: Subjects			
Adults (18-64 years)	12	12	
From 65-84 years	3	3	
Age continuous Units: years			
arithmetic mean	52.3		
standard deviation	± 16.53	-	
Gender categorical Units: Subjects			
Female	7	7	
Male	8	8	
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 self-care, 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			
Category 0	14	14	
Category 1	1	1	
Weight Units: kilograms			
arithmetic mean	80.3		
standard deviation	± 19.11	-	
Height Units: centimeters			
arithmetic mean	171.8		
standard deviation	± 9.51	-	

End points

End points reporting groups

Reporting group title	Part I: LGX818 - single agent
Reporting group description:	
Subjects in Part I of the study received LGX818 as a single agent.	
Reporting group title	Part II: CLGX818 + MEK162
Reporting group description:	
As per the original study design, Part II was to have five arms corresponding to the five potential combination treatments; however, only one patient was treated in this part of the study and received LGX818 in combination with MEK162.	

Primary: Tumor Response (Overall Response Rate) per Response Evaluation Criteria In Solid Tumors (RECIST) v1.1 (Part I & Part II)

End point title	Tumor Response (Overall Response Rate) per Response Evaluation Criteria In Solid Tumors (RECIST) v1.1 (Part I & Part II)[1]
End point description:	
Objective response rate (ORR) was not evaluated due to an inadequate number of patients enrolled in part II prior to the permanent recruitment halt of this study. As EudraCT only allows numerical data entry, the value of 999 indicates "No Value", as no data was collected for this end point.	
End point type	Primary
End point timeframe:	
Baseline through study completion (approximately 3 years)	
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: Objective response rate (ORR) was not evaluated due to an inadequate number of patients enrolled in part II prior to the permanent recruitment halt of this study.	

End point values	Part I: LGX818 - single agent	Part II: CLGX818 + MEK162		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	1		
Units: Percentage of Subjects				
Not Applicable	999	999		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of Dose Limiting Toxicities (DLTs) (Part II)

End point title	Incidence of Dose Limiting Toxicities (DLTs) (Part II)
End point description:	
Incidence of DLTs in Part II of the study was not evaluated due to an inadequate number of patients enrolled in Part II prior to the permanent recruitment halt of this study.	

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

End point type	Secondary

End point timeframe:

Baseline through study completion (approximately 3 years)

End point values	Part II: CLGX818 + MEK162			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: DLTs				
Not Applicable	999			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration and Derived Pharmacokinetic Parameters

End point title	Plasma Concentration and Derived Pharmacokinetic Parameters

End point description:

Assessment of pharmacokinetic (PK) parameters and plasma concentration was not done due to an inadequate number of patients enrolled in Part II prior to the permanent recruitment halt of this study.

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

End point type	Secondary

End point timeframe:

Baseline through study completion (approximately 3 years)

End point values	Part I: LGX818 - single agent	Part II: CLGX818 + MEK162		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	1		
Units: N/A				
arithmetic mean (standard deviation)				
Not Applicable	999 (± 999)	999 (± 999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Tumor Response (Overall Response Rate) via Response Evaluation Criteria In Solid Tumors (RECIST) v1.1 (Part I)

End point title	Tumor Response (Overall Response Rate) via Response Evaluation Criteria In Solid Tumors (RECIST) v1.1 (Part I)

End point description:

Response Evaluation Criteria In Solid Tumors (RECIST) is a set of published rules that define the status of tumors in cancer patients during a specific treatment.

The Overall Response Rate was calculated according to the RECIST criteria, as per investigator assessment.

Per RECIST guidelines:
- Complete Response (CR) is the Disappearance of all target lesions.
- Partial Response (PR) is at least a 30% decrease in the sum of diameters of target lesions.
- Progressive Disease (PD) is the at least a 20% increase in the sum of diameters of target lesions.
- Stable Disease (SD) is neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

End point type	Secondary

End point timeframe:

Baseline through completion of Part I of the study

End point values	Part I: LGX818 - single agent			
Subject group type	Reporting group			
Number of subjects analysed	15[2]			
Units: Subjects				
Complete Response	1			
Partial Response	8			
Progressive Disease	1			
Stable Disease	2			
Unknown	3			

Notes:

[2] - Full Analysis Set, which consists of all patients who received at least one dose of LGX818.

Statistical analyses

No statistical analyses for this end point

Secondary: Tumor Response (Overall Response Rate) via Response Evaluation Criteria In Solid Tumors (RECIST) v1.1 (Part II)

End point title	Tumor Response (Overall Response Rate) via Response Evaluation Criteria In Solid Tumors (RECIST) v1.1 (Part II)

End point description:

Response Evaluation Criteria In Solid Tumors (RECIST) is a set of published rules that define the status of tumors in cancer patients during a specific treatment.

The Overall Response Rate was calculated according to the RECIST criteria, as per investigator assessment.

Per RECIST guidelines:
- Complete Response (CR) is the Disappearance of all target lesions.
- Partial Response (PR) is at least a 30% decrease in the sum of diameters of target lesions.
- Progressive Disease (PD) is the at least a 20% increase in the sum of diameters of target lesions.
- Stable Disease (SD) is neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

One patient with documented PD at study Day 146 entered into Part II of the study and received combination treatment of LGX818 450 mg plus MEK162 45 mg for two weeks. The patient experienced disease progression on Day 22 of Part II and discontinued the study.

End point type	Secondary

End point timeframe:

Entry to Part II of the study through study completion (approximately 22 days)

End point values	Part II: CLGX818 + MEK162			
Subject group type	Reporting group			
Number of subjects analysed	1[3]			
Units: Subjects				
Progressive Disease	1			

Notes:

[3] - Full Analysis Set, which consists of all patients who received at least one dose of LGX818.

Statistical analyses

No statistical analyses for this end point

Secondary: Molecular Status of Markers Relevant to the RAP/MEK/ERK and PI3K/AKT Pathways

End point title	Molecular Status of Markers Relevant to the RAP/MEK/ERK and PI3K/AKT Pathways

End point description:

Molecular status was not evaluated due to an inadequate number of patients enrolled in Part II prior to the permanent recruitment halt of this study.

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

End point type	Secondary

End point timeframe:

Baseline and at progression with LGX818 single agent treatment

End point values	Part I: LGX818 - single agent	Part II: CLGX818 + MEK162		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	1		
Units: N/A				
arithmetic mean (standard deviation)				
Not Applicable	999 (± 999)	999 (± 999)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events, Serious Adverse Events, and Non-serious Adverse Events were collected throughout the duration of the study. Enrollment to the study began on 24-Jun-2013 and the study ended on 23-Mar-2015.

Adverse event reporting additional description:

An Adverse Event was 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 obtained.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Safety Set

Reporting group description:

The analysis group for Adverse Event, Serious Adverse Event, and Non-serious Adverse Event reporting is the Safety Set. The Safety Set consists of all patients from the Full Analysis Set who had at least one post-baseline safety assessment.

Serious adverse events	Safety Set		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 15 (20.00%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases To Central Nervous System			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metastatic Pain			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypotension			

subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial Fibrillation			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Coagulopathy			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Panic Attack			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal Failure Acute			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary Retention			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			

subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Safety Set		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 15 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanocytic Naevus			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Skin Papilloma			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Acrochordon			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Blepharal Papilloma			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Pyogenic Granuloma			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Seborrhoeic Keratosis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Vascular disorders			

Flushing			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	3		
Hypotension			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	9 / 15 (60.00%)		
occurrences (all)	9		
Asthenia			
subjects affected / exposed	4 / 15 (26.67%)		
occurrences (all)	4		
Oedema Peripheral			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	3		
Face Oedema			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Benign Prostatic Hyperplasia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Breast Pain			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Menstruation Irregular			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Vaginal Haemorrhage			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Dyspnoea			

subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Investigations			
Gamma-Glutamyltransferase Increased			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Alanine Aminotransferase Increased			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Amylase Increased			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Blood Alkaline Phosphatase Increased			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Blood Cholesterol Increased			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Blood Creatinine Increased			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Electrocardiogram Qt Prolonged			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Haemoglobin Increased			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Lipase Increased			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Weight Decreased			

subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Procedural Pain			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Toxicity To Various Agents			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Cardiac disorders			
Atrial Fibrillation			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Long Qt Syndrome			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 15 (26.67%)		
occurrences (all)	4		
Dysgeusia			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	3		
Aphasia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Convulsion			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Dizziness			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Hypogeusia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Neuralgia			

subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Paraesthesia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Peripheral Sensorimotor Neuropathy			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Tremor			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
VIIth Nerve Paralysis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	10 / 15 (66.67%)		
occurrences (all)	10		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 15 (33.33%)		
occurrences (all)	5		
Leukocytosis			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Eosinophilia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Thrombocytopenia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Ear Pain			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Eye disorders			

Cataract				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Conjunctival Hyperaemia				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Ophthalmoplegia				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Vision Blurred				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Gastrointestinal disorders				
Nausea				
subjects affected / exposed	3 / 15 (20.00%)			
occurrences (all)	3			
Vomiting				
subjects affected / exposed	3 / 15 (20.00%)			
occurrences (all)	3			
Constipation				
subjects affected / exposed	2 / 15 (13.33%)			
occurrences (all)	2			
Abdominal Pain Upper				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Dyspepsia				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Gingival Bleeding				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Haemorrhoidal Haemorrhage				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Haemorrhoids				

subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Inguinal Hernia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Rectal Haemorrhage			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Tongue Coated			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Hyperkeratosis			
subjects affected / exposed	12 / 15 (80.00%)		
occurrences (all)	12		
Alopecia			
subjects affected / exposed	10 / 15 (66.67%)		
occurrences (all)	10		
Palmar-Plantar Erythrodysaesthesia Syndrome			
subjects affected / exposed	9 / 15 (60.00%)		
occurrences (all)	9		
Dry Skin			
subjects affected / exposed	5 / 15 (33.33%)		
occurrences (all)	5		
Rash			
subjects affected / exposed	4 / 15 (26.67%)		
occurrences (all)	4		
Rash Maculo-Papular			
subjects affected / exposed	4 / 15 (26.67%)		
occurrences (all)	4		
Erythema			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	3		
Rash Papular			

subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Granuloma Skin			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Palmar Erythema			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Papule			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Rash Macular			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Skin Hypertrophy			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Haematuria			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Proteinuria			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	6 / 15 (40.00%)		
occurrences (all)	6		
Myalgia			

subjects affected / exposed	4 / 15 (26.67%)		
occurrences (all)	4		
Back Pain			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	3		
Muscular Weakness			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	3		
Musculoskeletal Pain			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Joint Swelling			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Musculoskeletal Chest Pain			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Pain In Extremity			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Infections and infestations			
Anal Abscess			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Folliculitis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Lower Respiratory Tract Infection			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Oral Candidiasis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Upper Respiratory Tract Infection			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		

Urinary Tract Infection subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Metabolism and nutrition disorders Decreased Appetite subjects affected / exposed occurrences (all) Hyperglycaemia subjects affected / exposed occurrences (all) Dehydration subjects affected / exposed occurrences (all) Hyperkalaemia subjects affected / exposed occurrences (all) Hypertriglyceridaemia subjects affected / exposed occurrences (all) Hypoalbuminaemia subjects affected / exposed occurrences (all) Hypokalaemia subjects affected / exposed occurrences (all) Hypophosphataemia subjects affected / exposed occurrences (all)	 4 / 15 (26.67%) 4 3 / 15 (20.00%) 3 2 / 15 (13.33%) 2 1 / 15 (6.67%) 1 1 / 15 (6.67%) 1 1 / 15 (6.67%) 1 1 / 15 (6.67%) 1 1 / 15 (6.67%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 June 2013	Amendment 1 consisted of the following revisions: • Safety results from a Phase 1 study of LGX818 as a single agent (Study CLGX818X2101) resulted in a RP2D for LGX818 single-agent of 300 mg/day. Updated safety data were added and the LGX818 starting dose was adjusted accordingly from 450 mg/day to 300 mg/day. • Safety results from a Phase 1 study of INC280 as a single agent (CINC280X2102) resulted in a revised starting dose for INC280. • Inclusion criteria for Part II were modified to define the refractory or resistant study population. • Criteria were added to define which patients were eligible to continue to receive LGX818 single agent after progression and during the analysis of their tumor biopsy and subsequent assignment to a combination arm in Part II.
15 July 2013	Amendment 2 consisted of the following revisions: • Hypomagnesaemia was added to exclusion criteria 25 and 28 and it was clarified that magnesium had to be within clinically relevant limits.
19 December 2013	Amendment 3 consisted of the following revisions: • Routine ophthalmic examinations were implemented at baseline, Day 85 (Cycle 4 Day 1 for 28-day cycles; Cycle 5 Day 1 for 21 day cycles), every 12 weeks thereafter, end of treatment and as clinically indicated in order to monitor the potential risk of retinal/ocular changes and included recommendations for LGX818 dose modifications for visual toxicity. • Definitions of ophthalmologic DLTs were provided.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
26 July 2014	Due to slow enrolment and after careful evaluation of the recent development in the treatment landscape of the patients with BRAF-mutant melanoma, recruitment was permanently halted on 26-Jul-2014 and a total of 15 patients were treated in the study. This recruitment halt was not a consequence of any safety concern and patients who were ongoing in the study continued to be treated as per protocol.	-

Notes:

Limitations and caveats

None reported