



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 (\pm 999) | 999 (\pm 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

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 occurrences (all) | 3 / 15 (20.00%) 3 | | |
| Hypotension subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 1 | | |
| General disorders and administration site conditions | | | |
| Fatigue subjects affected / exposed occurrences (all) | 9 / 15 (60.00%) 9 | | |
| Asthenia subjects affected / exposed occurrences (all) | 4 / 15 (26.67%) 4 | | |
| Oedema Peripheral subjects affected / exposed occurrences (all) | 3 / 15 (20.00%) 3 | | |
| Face Oedema subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 1 | | |
| Pyrexia subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 1 | | |
| Reproductive system and breast disorders | | | |
| Benign Prostatic Hyperplasia subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 1 | | |
| Breast Pain subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 1 | | |
| Menstruation Irregular subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 1 | | |
| Vaginal Haemorrhage subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 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 occurrences (all) | 1 / 15 (6.67%) 1 | | |
| Injury, poisoning and procedural complications Procedural Pain subjects affected / exposed occurrences (all) Toxicity To Various Agents subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 1 1 / 15 (6.67%) 1 | | |
| Cardiac disorders Atrial Fibrillation subjects affected / exposed occurrences (all) Long Qt Syndrome subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 1 1 / 15 (6.67%) 1 | | |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) Dysgeusia subjects affected / exposed occurrences (all) Aphasia subjects affected / exposed occurrences (all) Convulsion subjects affected / exposed occurrences (all) Dizziness subjects affected / exposed occurrences (all) Hypogeusia subjects affected / exposed occurrences (all) Neuralgia | 4 / 15 (26.67%) 4 3 / 15 (20.00%) 3 1 / 15 (6.67%) 1 1 / 15 (6.67%) 1 1 / 15 (6.67%) 1 1 / 15 (6.67%) 1 | | |

| | | | |
|--------------------------------------|------------------|--|--|
| 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) | 4 / 15 (26.67%) 4 | | |
| Hyperglycaemia subjects affected / exposed occurrences (all) | 3 / 15 (20.00%) 3 | | |
| Dehydration subjects affected / exposed occurrences (all) | 2 / 15 (13.33%) 2 | | |
| Hyperkalaemia subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 1 | | |
| Hypertriglyceridaemia subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 1 | | |
| Hypoalbuminaemia subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 1 | | |
| Hypokalaemia subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 1 | | |
| Hypophosphataemia subjects affected / exposed occurrences (all) | 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 | <p>Amendment 1 consisted of the following revisions:</p> <ul style="list-style-type: none">• 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 | <p>Amendment 2 consisted of the following revisions:</p> <ul style="list-style-type: none">• 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 | <p>Amendment 3 consisted of the following revisions:</p> <ul style="list-style-type: none">• 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 | <p>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.</p> <p>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.</p> | - |

Notes:

Limitations and caveats

None reported