



Clinical trial results:

A Randomized, Phase 2 Study of Single-agent Erlotinib versus Oral Etoposide in Patients with Recurrent or Refractory Pediatric Ependymoma

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2009-016836-11 |
| Trial protocol | GB |
| Global end of trial date | 26 November 2012 |

Results information

| | |
|--------------------------------|---|
| Result version number | v2 (current) |
| This version publication date | 21 April 2016 |
| First version publication date | 22 April 2015 |
| Version creation reason | <ul style="list-style-type: none">• Correction of full data set Some administrative changes due to an additional Quality Control (QC) review. |

Trial information

Trial identification

| | |
|-----------------------|-------------|
| Sponsor protocol code | OSI-774-205 |
|-----------------------|-------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01032070 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | OSI Pharmaceuticals LLC |
| Sponsor organisation address | 1 Astellas Way, Northbrook, United States, |
| Public contact | Clinical Trial Disclosure, Astellas Pharma Global Development, Inc., Astellas.resultsdisclosure@astellas.com |
| Scientific contact | Clinical Trial Disclosure, Astellas Pharma Global Development, Inc., Astellas.resultsdisclosure@astellas.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? | Yes |

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 26 November 2012 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|------------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 26 November 2012 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to determine the objective response rate (ORR) of single-agent erlotinib versus oral etoposide in patients with recurrent paediatric ependymoma.

Protection of trial subjects:

This clinical study was written, conducted and reported in accordance with the protocol, ICH GCP Guidelines, and applicable local regulations, including the European Directive 2001/20/EC, on the protection of human rights, and with the ethical principles that have their origin in the Declaration of Helsinki. Astellas ensures that the use and disclosure of protected health information (PHI) obtained during a research study complies with the federal and/or regional legislation related to the privacy and protection of personal information.

The study was designed to consider stopping early at an interim analysis due to lack of efficacy, minimizing additional patient exposure to treatment that is unlikely to provide benefit.

Background therapy: -

Evidence for comparator: -

| | |
|---|-------------------|
| Actual start date of recruitment | 27 September 2010 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety |
| Long term follow-up duration | 12 Months |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | United Kingdom: 4 |
| Country: Number of subjects enrolled | Canada: 8 |
| Country: Number of subjects enrolled | United States: 13 |
| Worldwide total number of subjects | 25 |
| 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) | 12 |
| Adolescents (12-17 years) | 8 |
| Adults (18-64 years) | 5 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Patients who were candidates for participation in the study were screened for inclusion/exclusion criteria before enrollment in the study. If they have met the criteria, they were randomized into the study.

Period 1

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

Arms

| | |
|------------------------------|-----------|
| Are arms mutually exclusive? | Yes |
| Arm title | Erlotinib |

Arm description:

Participants who received erlotinib orally at a dose of 85 mg/m² per day continuously until either progression, death, patient request or investigator decision to discontinue study drug or intolerable toxicity.

The number of subjects that completed the study has been defined to be the subjects that has discontinued due to disease progression.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Erlotinib |
| Investigational medicinal product code | OSI-774 |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Erlotinib was to administered orally at a dose of 85 mg/m² per day continuously until either progression, death, patient request or investigator decision to discontinue study drug or intolerable toxicity. Erlotinib was provided as tablets containing erlotinib hydrochloride equivalent to 150, 100 and 25 mg of erlotinib.

| | |
|------------------|-----------|
| Arm title | Etoposide |
|------------------|-----------|

Arm description:

Participants who received etoposide orally at a dose of 50 mg/m² per day for 21 days followed by a 7-day rest period until either progression, death, patient request or investigator decision to discontinue study drug or intolerable toxicity.

The number of subjects that completed the study has been defined to be the subjects that has discontinued due to disease progression.

| | |
|--|-------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Etoposide |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, soft |
| Routes of administration | Oral use |

Dosage and administration details:

Etoposide 50 mg/m² per day was administered orally for 21 days followed by a 7-day rest period until either progression, death, patient request or investigator decision to discontinue study drug or intolerable toxicity.

| Number of subjects in period 1 | Erlotinib | Etoposide |
|---------------------------------------|-----------|-----------|
| Started | 13 | 12 |
| Completed | 13 | 8 |
| Not completed | 0 | 4 |
| Medical or ethical reasons | - | 2 |
| Withdrawal by Subject | - | 2 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|-----------|
| Reporting group title | Erlotinib |
|-----------------------|-----------|

Reporting group description:

Participants who received erlotinib orally at a dose of 85 mg/m² per day continuously until either progression, death, patient request or investigator decision to discontinue study drug or intolerable toxicity.

The number of subjects that completed the study has been defined to be the subjects that has discontinued due to disease progression.

| | |
|-----------------------|-----------|
| Reporting group title | Etoposide |
|-----------------------|-----------|

Reporting group description:

Participants who received etoposide orally at a dose of 50 mg/m² per day for 21 days followed by a 7-day rest period until either progression, death, patient request or investigator decision to discontinue study drug or intolerable toxicity.

The number of subjects that completed the study has been defined to be the subjects that has discontinued due to disease progression.

| Reporting group values | Erlotinib | Etoposide | Total |
|------------------------------------|-----------|-----------|-------|
| Number of subjects | 13 | 12 | 25 |
| Age categorical Units: Subjects | | | |

| | | | |
|---|----------------|---------------|----|
| Age continuous Units: years arithmetic mean standard deviation | 12.8 ± 5.87 | 9.2 ± 4.99 | - |
| Gender categorical Units: Subjects | | | |
| Female | 3 | 3 | 6 |
| Male | 10 | 9 | 19 |
| Race Units: Subjects | | | |
| Asian-Indian Subcontinent | 0 | 1 | 1 |
| Asian-Southeast Asia | 0 | 1 | 1 |
| Black | 1 | 1 | 2 |
| Other | 1 | 0 | 1 |
| White | 11 | 9 | 20 |
| Ethnicity Units: Subjects | | | |
| Hispanic/Latino | 1 | 2 | 3 |
| Not Hispanic/Latino | 12 | 10 | 22 |
| Tumor Type for Initial Disease Diagnosis Units: Subjects | | | |
| Anaplastic Ependymoma | 6 | 9 | 15 |
| Ependymoma | 6 | 3 | 9 |
| Myxopapillary Ependymoma | 1 | 0 | 1 |

| | | | |
|---|-----------------|-----------------|---|
| Body Surface Area Units: m ² arithmetic mean standard deviation | 1.51 ± 0.556 | 1.17 ± 0.439 | - |
| Total Number of Disease Recurrences Units: recurrences median full range (min-max) | 3 1 to 9 | 2 1 to 3 | - |

End points

End points reporting groups

| | |
|-----------------------|-----------|
| Reporting group title | Erlotinib |
|-----------------------|-----------|

Reporting group description:

Participants who received erlotinib orally at a dose of 85 mg/m² per day continuously until either progression, death, patient request or investigator decision to discontinue study drug or intolerable toxicity.

The number of subjects that completed the study has been defined to be the subjects that has discontinued due to disease progression.

| | |
|-----------------------|-----------|
| Reporting group title | Etoposide |
|-----------------------|-----------|

Reporting group description:

Participants who received etoposide orally at a dose of 50 mg/m² per day for 21 days followed by a 7-day rest period until either progression, death, patient request or investigator decision to discontinue study drug or intolerable toxicity.

The number of subjects that completed the study has been defined to be the subjects that has discontinued due to disease progression.

Primary: Percentage of participants with an Objective Response

| | |
|-----------------|---|
| End point title | Percentage of participants with an Objective Response |
|-----------------|---|

End point description:

Objective response is defined as a best overall response of CR (complete response) or PR (partial response), evaluated using modified International Society of Pediatric Oncology Brain, Tumor Subcommittee for the Reporting of Trials criteria. Response was confirmed at least 28 days after the first assessment where the response criteria were met. Response was assessed by magnetic resonance imaging (MRI) every 8 weeks. CR: Complete disappearance of all enhancing tumor and mass effect; On a stable or decreasing dose of corticosteroids (or receiving only adrenal replacement doses); Stable or improving neurologic examination sustained for ≥ 4 weeks; If cerebral spinal fluid (CSF) evaluation was positive, it must become negative (confirmed at least 2 times at consecutive samplings). PR: $\geq 50\%$ reduction in tumor size by bi-dimensional measurement; On a stable or decreasing dose of corticosteroids; Stable or improving neurologic examination sustained for ≥ 4 weeks.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From randomization until the end of treatment. The median time on treatment was 52 days for erlotinib and 58 days for etoposide.

| End point values | Erlotinib | Etoposide | | |
|-----------------------------------|-----------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 13 | 12 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 0 (0 to 24.7) | 16.7 (2.1 to 48.4) | | |

Statistical analyses

| | |
|---|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
| Comparison groups | Erlotinib v Etoposide |
| Number of subjects included in analysis | 25 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[1] |
| P-value | = 0.22 ^[2] |
| Method | Fisher exact |

Notes:

[1] - The study was not powered for this comparison due to small sample size.

[2] - P-value is not adjusted for multiple comparisons.

Secondary: Duration of Response

| | |
|-----------------|-------------------------------------|
| End point title | Duration of Response ^[3] |
|-----------------|-------------------------------------|

End point description:

Duration of response (complete or partial response [CR/PR]) was defined as the time from the date of the first documented response (CR/PR) to the first documented progression or death due to underlying cancer. If a participant had not progressed or died, the duration of overall response was censored at the date of last adequate disease assessment. Duration of response was only defined for participants whose best overall response was CR or PR. Progression was defined as a worsening of neurologic status that could not be explained by other causes, a > 25% increase in tumor size, the appearance of new lesions or CSF positivity, or increasing doses of corticosteroids required to maintain stable status. Due to the low number of participants, data cannot be calculated and is denoted as "99999" as applicable.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From randomization until the end of treatment. The median time on treatment was 52 days for erlotinib and 58 days for etoposide

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Data values are not provided for the erlotinib arm as there were no subjects analyzed (no participants achieved CR or PR), and no data can be calculated for the etoposide arm due to the low number of participants.

| | | | | |
|----------------------------------|------------------------|--|--|--|
| End point values | Etoposide | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 2 ^[4] | | | |
| Units: days | | | | |
| median (confidence interval 95%) | 99999 (99999 to 99999) | | | |

Notes:

[4] - These 2 participants experienced a PR and were censored at 174 and 463 days.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with a Minor Response

| | |
|-----------------|--|
| End point title | Percentage of participants with a Minor Response |
|-----------------|--|

End point description:

Best overall response of Minor response (MR), defined as: $\geq 25\%$ to $< 50\%$ reduction in tumor size by bi-dimensional measurement; On a stable or decreasing dose of corticosteroids; Stable or improving neurologic examination sustained for ≥ 4 weeks.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From randomization until the end of treatment. The median time on treatment was 52 days for erlotinib and 58 days for etoposide.

| End point values | Erlotinib | Etoposide | | |
|-----------------------------------|-----------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 13 | 12 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 0 (0 to 24.7) | 25 (5.5 to 57.2) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with Disease Control

| | |
|-----------------|---|
| End point title | Percentage of participants with Disease Control |
|-----------------|---|

End point description:

Disease control is a best overall response of CR or PR or MR or SD (stable disease): CR: Complete disappearance of all enhancing tumor and mass effect; On a stable or decreasing dose of corticosteroids (or receiving only adrenal replacement doses); Stable or improving neurologic examination sustained for ≥ 4 weeks; If CSF evaluation was positive, it must become negative (confirmed at least 2 times consecutively). PR: $\geq 50\%$ reduction in tumor size by bi-dimensional measurement; On a stable or decreasing dose of corticosteroids; Stable or improving neurologic examination sustained for ≥ 4 weeks. MR: $\geq 25\%$ to $< 50\%$ reduction in tumor size by bi-dimensional measurement; On a stable or decreasing dose of corticosteroids; Stable or improving neurologic examination sustained for ≥ 4 weeks. SD: Neurologic examination is at least stable; Maintenance corticosteroid dose is not increased; MRI meets neither the criteria for minor response nor for progressive disease; Sustained for ≥ 8 weeks.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From randomization until the end of treatment. The median time on treatment was 52 days for erlotinib and 58 days for etoposide.

| End point values | Erlotinib | Etoposide | | |
|-----------------------------------|--------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 13 | 12 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 15.4 (1.9 to 45.4) | 41.7 (15.2 to 72.3) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival

| | |
|-----------------|---------------------------|
| End point title | Progression Free Survival |
|-----------------|---------------------------|

End point description:

Defined as the time from randomization to disease progression based on central nervous system (CNS)-specific evaluation criteria as assessed by the investigator or death due to any cause, whichever occurs first. Participants did not progress or die before the data cutoff date for analysis were censored at the date of last disease assessment (including both radiologic assessment and neurologic assessment) where non-progression was documented. If a participant received any further anticancer therapy without prior documentation of disease progression, the participant was censored at the date of last disease assessment before starting new anti-cancer treatment. Participants were also censored at the date of last disease assessment with no documented progression if patients discontinued treatment for undocumented progression, toxicity or other reason before the data cutoff date for analysis. Due to low number of events, upper limit cannot be calculated and is denoted as "99999."

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From randomization until the end of treatment. The median time on treatment was 52 days for erlotinib and 58 days for etoposide.

| End point values | Erlotinib | Etoposide | | |
|----------------------------------|-----------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 13 | 12 | | |
| Units: days | | | | |
| median (confidence interval 95%) | 52 (29 to 62) | 65 (23 to 99999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with Prolonged Stable Disease

| | |
|-----------------|--|
| End point title | Percentage of participants with Prolonged Stable Disease |
|-----------------|--|

End point description:

Prolonged stable disease (SD) was defined as SD with a duration of at least 16 weeks. The percentage of participants with prolonged SD was defined as participants who achieved a best overall response of CR or PR or MR or SD, and did not progress within 16 weeks from randomization. Progression was defined as a worsening of neurologic status that could not be explained by other causes, a > 25% increase in tumor size, the appearance of new lesions or CSF positivity, or increasing doses of corticosteroids required to maintain stable status.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From randomization until the end of treatment. The median time on treatment was 52 days for erlotinib and 58 days for etoposide.

| End point values | Erlotinib | Etoposide | | |
|-----------------------------------|-----------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 13 | 12 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 0 (0 to 24.7) | 41.7 (15.2 to 72.3) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Stable Disease

| | |
|-----------------|----------------------------|
| End point title | Duration of Stable Disease |
|-----------------|----------------------------|

End point description:

Duration of stable disease (SD, defined as participants with an overall best response of complete, partial or minor response or stable disease) was defined as the time from the date of randomization to the first documented progression or death due to underlying cancer. If a participant had not progressed or died, the duration of SD was censored at the date of last adequate disease assessment. Duration of SD was only defined for participants whose best overall response was CR, PR, MR or SD. Progression was defined as a worsening of neurologic status that could not be explained by other causes, a > 25% increase in tumor size, the appearance of new lesions or CSF positivity, or increasing doses of corticosteroids required to maintain stable status.

Due to the low number of events, data cannot be calculated and is denoted as "99999" as applicable.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From randomization until the end of treatment. The median time on treatment was 52 days for erlotinib and 58 days for etoposide.

| End point values | Erlotinib | Etoposide | | |
|----------------------------------|-----------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 2 | 5 | | |
| Units: days | | | | |
| median (confidence interval 95%) | 79 (78 to 80) | 99999 (117 to 99999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

| | |
|-----------------|------------------|
| End point title | Overall Survival |
|-----------------|------------------|

End point description:

Overall survival was defined as the time from the date of randomization until the documented date of death. Participants who were still alive by the data cutoff date for analysis were censored on the last day the participant was known to be alive.

Due to the low number of events, overall survival cannot be reported in days, instead presented as the number of participants who died.

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| From the randomization up to 12 months after the last dose. Median duration of follow-up was 12.9 months for erlotinib and 14.4 months for etoposide | |

| End point values | Erlotinib | Etoposide | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 13 | 12 | | |
| Units: participants | 3 | 6 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Safety assessed through evaluation of physical exams, vital signs, clinical laboratory tests and adverse events (AEs)

| | |
|-----------------|---|
| End point title | Safety assessed through evaluation of physical exams, vital signs, clinical laboratory tests and adverse events (AEs) |
|-----------------|---|

End point description:

An AE was defined as any untoward medical occurrence in a study participant and did not necessarily have a causal relationship with the study treatment. Clinically significant vital sign assessments, findings associated with signs and/or symptoms requiring withdrawal, dose modification or medical intervention were recorded as AEs. An AE was considered serious if it resulted in death, a life-threatening situation, inpatient hospitalization or prolongation of an existing hospitalization, persistent or significant disability/incapacity, congenital anomaly/birth defect in the offspring of a patient who received study drug or other important medical events. The relationship of each AE to study drug was assessed as either related or not related.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From the date of first dose of study drug until 30 days after the last dose. The median time on treatment was 52 days for erlotinib and 58 days for etoposide.

| End point values | Erlotinib | Etoposide | | |
|---|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 13 | 12 | | |
| Units: participants | | | | |
| number (not applicable) | | | | |
| Any adverse event | 13 | 11 | | |
| Drug-related adverse event | 11 | 10 | | |
| Adverse event leading to death | 1 | 0 | | |
| Drug-related adverse event leading to death | 0 | 0 | | |
| Serious adverse event | 6 | 5 | | |
| Drug-related serious adverse event | 0 | 1 | | |
| AE leading to discontinuation | 0 | 0 | | |
| Drug-related AE leading to discontinuation | 0 | 0 | | |

| | | | | |
|---|---|---|--|--|
| AE leading to dose interruption | 2 | 5 | | |
| Drug-related AE leading to dose interruption | 1 | 3 | | |
| AE leading to dose interruption and reduction | 1 | 2 | | |
| Related AE leading to dose interruption/reduction | 1 | 2 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the curve from time 0 to 24 hours post-dose for erlotinib

| | |
|-----------------|---|
| End point title | Area under the curve from time 0 to 24 hours post-dose for erlotinib ^[5] |
|-----------------|---|

End point description:

Pharmacokinetic parameters were determined from the serial plasma concentration data obtained for erlotinib. Area under the plasma concentration-time curve from time zero to 24 hours (the dosing interval) measured at the steady state using sparse sampling.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Day 14 predose and 0.5 to 1.5 hours, 2 to 3 hours and 4 to 8 hours post-dose

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data values are not provided for the etoposide arm as the pharmacokinetic parameters were only measured for the investigative drug, and not for the comparator, as already pre-determined in the study plan/protocol.

| End point values | Erlotinib | | | |
|--|-------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 11 | | | |
| Units: h*ng/mL | | | | |
| geometric mean (confidence interval 95%) | 26716.7 (20269 to 35215.4) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum observed plasma concentration of erlotinib (Cmax)

| | |
|-----------------|--|
| End point title | Maximum observed plasma concentration of erlotinib (Cmax) ^[6] |
|-----------------|--|

End point description:

Pharmacokinetic parameters were determined from the serial plasma concentration data obtained for erlotinib. Maximum observed plasma concentration (Cmax) was measured at steady on Day 14 using sparse sampling.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Day 14 predose and 0.5 to 1.5 hours, 2 to 3 hours and 4 to 8 hours post-dose

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Data values are not provided for the etoposide arm as the pharmacokinetic parameters were only measured for the investigative drug, and not for the comparator, as already pre-determined in the study plan/protocol.

| End point values | Erlotinib | | | |
|--|---------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 11 | | | |
| Units: ng/mL | | | | |
| geometric mean (confidence interval 95%) | 1969.5 (1627.7 to 2382.9) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to maximum observed plasma concentration of erlotinib (Tmax)

| | |
|-----------------|--|
| End point title | Time to maximum observed plasma concentration of erlotinib (Tmax) ^[7] |
|-----------------|--|

End point description:

Pharmacokinetic parameters were determined from the serial plasma concentration data obtained for erlotinib. Time to the maximum observed plasma concentration of erlotinib (Tmax) was measured at steady state on Day 14 using sparse sampling.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Day 14 predose and 0.5 to 1.5 hours, 2 to 3 hours and 4 to 8 hours post-dose

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Data values are not provided for the etoposide arm as the pharmacokinetic parameters were only measured for the investigative drug, and not for the comparator, as already pre-determined in the study plan/protocol.

| End point values | Erlotinib | | | |
|--|------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 11 | | | |
| Units: hours | | | | |
| geometric mean (confidence interval 95%) | 2.1 (1.6 to 2.7) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent body clearance (CL/F) of erlotinib

| | |
|-----------------|--|
| End point title | Apparent body clearance (CL/F) of erlotinib ^[8] |
|-----------------|--|

End point description:

Pharmacokinetic parameters were determined from the serial plasma concentration data obtained for erlotinib. Apparent body clearance (CL/F) of erlotinib was measured at steady state on Day 14 using sparse sampling.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Day 14 predose and 0.5 to 1.5 hours, 2 to 3 hours and 4 to 8 hours post-dose

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Data values are not provided for the etoposide arm as the pharmacokinetic parameters were only measured for the investigative drug, and not for the comparator, as already pre-determined in the study plan/protocol.

| End point values | Erlotinib | | | |
|--|---------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 11 | | | |
| Units: mL/m ² | | | | |
| geometric mean (confidence interval 95%) | 2922.1 (2233.4 to 3823.3) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent volume of Distribution (V_z/F) of erlotinib

| | |
|-----------------|---|
| End point title | Apparent volume of Distribution (V _z /F) of erlotinib ^[9] |
|-----------------|---|

End point description:

Pharmacokinetic parameters were determined from the serial plasma concentration data obtained for erlotinib. The apparent volume of distribution (V_z/F) of erlotinib was measured at steady state on day 14 using sparse sampling.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Day 14 predose and 0.5 to 1.5 hours, 2 to 3 hours and 4 to 8 hours post-dose

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Data values are not provided for the etoposide arm as the pharmacokinetic parameters were only measured for the investigative drug, and not for the comparator, as already pre-determined in the study plan/protocol.

| End point values | Erlotinib | | | |
|--|----------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 11 | | | |
| Units: mL/m ² | | | | |
| geometric mean (confidence interval 95%) | 71628.5 (59572 to 86124.9) | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the date of first dose of study drug until 30 days after last dose. The median time on treatment was 52 days for erlotinib and 58 days for etoposide.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 13.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-----------|
| Reporting group title | Erlotinib |
|-----------------------|-----------|

Reporting group description: -

| | |
|-----------------------|-----------|
| Reporting group title | Etoposide |
|-----------------------|-----------|

Reporting group description: -

| Serious adverse events | Erlotinib | Etoposide | |
|---|-----------------|-----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 6 / 13 (46.15%) | 5 / 12 (41.67%) | |
| number of deaths (all causes) | 3 | 6 | |
| number of deaths resulting from adverse events | | | |
| Investigations | | | |
| Weight decreased | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 12 (8.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Malignant neoplasm progression | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Nervous system disorders | | | |
| Convulsion | | | |
| subjects affected / exposed | 2 / 13 (15.38%) | 1 / 12 (8.33%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Grand mal convulsion | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Headache | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 2 / 12 (16.67%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hemiparesis | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 12 (8.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hydrocephalus | | | |
| subjects affected / exposed | 2 / 13 (15.38%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Loss of consciousness | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 12 (8.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 12 (8.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastritis haemorrhagic | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|----------------|--|
| Lower gastrointestinal haemorrhage subjects affected / exposed | 1 / 13 (7.69%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Confusional state | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Pollakiuria | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 12 (8.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary hesitation | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 12 (8.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Lung infection | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 12 (8.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypokalaemia | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 12 (8.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypophosphataemia | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 12 (8.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Erlotinib | Etoposide | |
|---|-------------------|------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 13 / 13 (100.00%) | 11 / 12 (91.67%) | |
| Vascular disorders | | | |
| Epistaxis (vascular disorders) | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Hypotension | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 1 / 12 (8.33%) | |
| occurrences (all) | 1 | 1 | |
| Vena cava thrombosis | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 12 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| General disorders and administration site conditions | | | |
| Chills | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Fatigue | | | |
| subjects affected / exposed | 3 / 13 (23.08%) | 8 / 12 (66.67%) | |
| occurrences (all) | 3 | 16 | |
| Irritability | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Malaise | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 1 / 12 (8.33%) | |
| occurrences (all) | 1 | 1 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 2 / 13 (15.38%) | 1 / 12 (8.33%) | |
| occurrences (all) | 2 | 2 | |
| Pain | | | |
| subjects affected / exposed | 2 / 13 (15.38%) | 0 / 12 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 2 / 13 (15.38%) | 4 / 12 (33.33%) | |
| occurrences (all) | 3 | 5 | |
| Immune system disorders | | | |
| Multiple allergies | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 12 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Reproductive system and breast disorders | | | |
| Breast enlargement | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Bronchospasm | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Cough | | | |
| subjects affected / exposed | 2 / 13 (15.38%) | 4 / 12 (33.33%) | |
| occurrences (all) | 2 | 11 | |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 2 / 12 (16.67%) | |
| occurrences (all) | 1 | 2 | |
| Epistaxis | | | |

| | | | |
|-----------------------------|----------------|-----------------|--|
| subjects affected / exposed | 0 / 13 (0.00%) | 3 / 12 (25.00%) | |
| occurrences (all) | 0 | 3 | |
| Nasal congestion | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 3 / 12 (25.00%) | |
| occurrences (all) | 1 | 5 | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Postnasal drip | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 2 | |
| Productive cough | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Rhinitis allergic | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 12 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Rhinorrhoea | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 1 / 12 (8.33%) | |
| occurrences (all) | 1 | 1 | |
| Psychiatric disorders | | | |
| Agitation | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Confusional state | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 12 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Depressed mood | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Depression | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 2 / 12 (16.67%) | |
| occurrences (all) | 0 | 2 | |
| Insomnia | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 3 / 12 (25.00%) | |
| occurrences (all) | 0 | 5 | |

| | | | |
|--|-----------------|-----------------|--|
| Investigations | | | |
| Blood pressure increased | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 3 | |
| Blood urine present | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Heart rate increased | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 3 | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 1 / 12 (8.33%) | |
| occurrences (all) | 1 | 1 | |
| Platelet count decreased | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 12 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Urine output decreased | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Weight decreased | | | |
| subjects affected / exposed | 3 / 13 (23.08%) | 2 / 12 (16.67%) | |
| occurrences (all) | 3 | 3 | |
| Weight increased | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 3 | |
| Injury, poisoning and procedural complications | | | |
| Anthropod bite | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Catheter site pain | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Contusion | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 12 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Fall | | | |

| | | | |
|-----------------------------|-----------------|----------------|--|
| subjects affected / exposed | 1 / 13 (7.69%) | 1 / 12 (8.33%) | |
| occurrences (all) | 1 | 1 | |
| Head injury | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Procedural complication | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Procedural pain | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 12 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Nervous system disorders | | | |
| Upper motor neurone lesion | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Ageusia | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Amnesia | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Ataxia | | | |
| subjects affected / exposed | 2 / 13 (15.38%) | 0 / 12 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Cerebellar syndrome | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 1 / 12 (8.33%) | |
| occurrences (all) | 1 | 1 | |
| Coordination abnormal | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 4 | |
| Cranial nerve disorder | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Dizziness | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 1 / 12 (8.33%) | |
| occurrences (all) | 1 | 2 | |

| | | |
|-------------------------------|-----------------|-----------------|
| Facial palsy | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 1 / 12 (8.33%) |
| occurrences (all) | 1 | 1 |
| Headache | | |
| subjects affected / exposed | 5 / 13 (38.46%) | 7 / 12 (58.33%) |
| occurrences (all) | 10 | 16 |
| Hypersomnia | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 1 |
| Hypoaesthesia | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 1 / 12 (8.33%) |
| occurrences (all) | 1 | 1 |
| Loss of consciousness | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 |
| Meningism | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 |
| Muscle spasticity | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 1 |
| Nervous system disorder | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 |
| Nystagmus | | |
| subjects affected / exposed | 3 / 13 (23.08%) | 2 / 12 (16.67%) |
| occurrences (all) | 3 | 2 |
| Peripheral sensory neuropathy | | |
| subjects affected / exposed | 2 / 13 (15.38%) | 0 / 12 (0.00%) |
| occurrences (all) | 2 | 0 |
| Somnolence | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 12 (0.00%) |
| occurrences (all) | 2 | 0 |
| Tongue paralysis | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 3 |

| | | | |
|---|---------------------|----------------------|--|
| VIIth nerve paralysis subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 1 / 12 (8.33%) 1 | |
| VIth nerve paralysis subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 1 / 12 (8.33%) 3 | |
| Blood and lymphatic system disorders | | | |
| Anaemia subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 5 | 2 / 12 (16.67%) 4 | |
| Lymphopenia subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 1 / 12 (8.33%) 4 | |
| Ear and labyrinth disorders | | | |
| Ear pain subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | 1 / 12 (8.33%) 1 | |
| Tinnitus subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 1 / 12 (8.33%) 1 | |
| Tympanic membrane perforation subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | 0 / 12 (0.00%) 0 | |
| Eye disorders | | | |
| Diplopia subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 2 | 0 / 12 (0.00%) 0 | |
| Eye movement disorder subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | 0 / 12 (0.00%) 0 | |
| Optic nerve disorder subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 1 / 12 (8.33%) 1 | |
| Strabismus subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 2 / 12 (16.67%) 2 | |
| Vision blurred | | | |

| | | | |
|--|---------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | 1 / 12 (8.33%) 2 | |
| Gastrointestinal disorders | | | |
| Abdominal distension | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Abdominal pain | | | |
| subjects affected / exposed | 2 / 13 (15.38%) | 4 / 12 (33.33%) | |
| occurrences (all) | 2 | 6 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 12 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Constipation | | | |
| subjects affected / exposed | 3 / 13 (23.08%) | 6 / 12 (50.00%) | |
| occurrences (all) | 3 | 7 | |
| Diarrhoea | | | |
| subjects affected / exposed | 6 / 13 (46.15%) | 4 / 12 (33.33%) | |
| occurrences (all) | 6 | 13 | |
| Dry mouth | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 12 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Gastritis | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 2 / 12 (16.67%) | |
| occurrences (all) | 2 | 2 | |
| Gastroesophageal reflux disease | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 2 / 12 (16.67%) | |
| occurrences (all) | 0 | 3 | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 12 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Lip ulceration | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Mouth ulceration | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 1 / 12 (8.33%) | |
| occurrences (all) | 1 | 3 | |

| | | | |
|--|-----------------|-----------------|--|
| Nausea | | | |
| subjects affected / exposed | 3 / 13 (23.08%) | 5 / 12 (41.67%) | |
| occurrences (all) | 3 | 7 | |
| Retching | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Stomatitis | | | |
| subjects affected / exposed | 2 / 13 (15.38%) | 1 / 12 (8.33%) | |
| occurrences (all) | 2 | 3 | |
| Vomiting | | | |
| subjects affected / exposed | 6 / 13 (46.15%) | 8 / 12 (66.67%) | |
| occurrences (all) | 15 | 17 | |
| Skin and subcutaneous tissue disorders | | | |
| Acne | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 2 / 12 (16.67%) | |
| occurrences (all) | 0 | 2 | |
| Alopecia | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 4 / 12 (33.33%) | |
| occurrences (all) | 0 | 7 | |
| Dermatitis acneiform | | | |
| subjects affected / exposed | 3 / 13 (23.08%) | 0 / 12 (0.00%) | |
| occurrences (all) | 9 | 0 | |
| Dermatitis diaper | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Dry skin | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 2 / 12 (16.67%) | |
| occurrences (all) | 1 | 3 | |
| Erythema | | | |
| subjects affected / exposed | 2 / 13 (15.38%) | 0 / 12 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Hypoaesthesia facial | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Nail discolouration | | | |

| | | |
|-----------------------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 1 |
| Pain of skin | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 3 |
| Pruritus | | |
| subjects affected / exposed | 3 / 13 (23.08%) | 0 / 12 (0.00%) |
| occurrences (all) | 3 | 0 |
| Purpura | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 |
| Rash | | |
| subjects affected / exposed | 4 / 13 (30.77%) | 1 / 12 (8.33%) |
| occurrences (all) | 13 | 1 |
| Rash macular | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 2 / 12 (16.67%) |
| occurrences (all) | 1 | 2 |
| Rash maculo-papular | | |
| subjects affected / exposed | 2 / 13 (15.38%) | 0 / 12 (0.00%) |
| occurrences (all) | 2 | 0 |
| Rash papular | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 1 |
| Skin fissures | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 12 (0.00%) |
| occurrences (all) | 2 | 0 |
| Skin hyperpigmentation | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 1 |
| Skin striae | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 3 |
| Skin ulcer | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 |
| Swelling face | | |

| | | | |
|---|----------------------|----------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 1 / 12 (8.33%) 1 | |
| Renal and urinary disorders Bladder spasm subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 1 / 12 (8.33%) 1 | |
| Enuresis subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 1 / 12 (8.33%) 1 | |
| Urinary incontinence subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | 1 / 12 (8.33%) 1 | |
| Endocrine disorders Cushingoid subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 2 / 12 (16.67%) 3 | |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 2 / 12 (16.67%) 4 | |
| Back pain subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | 0 / 12 (0.00%) 0 | |
| Muscle spasms subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 1 / 12 (8.33%) 1 | |
| Muscular weakness subjects affected / exposed occurrences (all) | 3 / 13 (23.08%) 3 | 2 / 12 (16.67%) 5 | |
| Myalgia subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 1 / 12 (8.33%) 1 | |
| Neck pain subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | 1 / 12 (8.33%) 1 | |
| Pain in extremity | | | |

| | | | |
|--|---------------------|----------------------|--|
| subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | 4 / 12 (33.33%) 7 | |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Conjunctivitis infective | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Corneal infection | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Escherichia urinary tract infection | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 12 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Fungal skin infection | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Mucosal infection | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Otitis media | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 12 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Paronychia | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 12 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Sinusitis | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 2 / 12 (16.67%) | |
| occurrences (all) | 0 | 3 | |

| | | | |
|---|----------------------|----------------------|--|
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 3 / 12 (25.00%) 3 | |
| Urinary tract infection subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 1 / 12 (8.33%) 1 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite subjects affected / exposed occurrences (all) | 2 / 13 (15.38%) 2 | 2 / 12 (16.67%) 4 | |
| Dehydration subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | 0 / 12 (0.00%) 0 | |
| Hyokalaemia subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 2 / 12 (16.67%) 4 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

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| The protocol-specified lack of efficacy criteria were met at the second interim analysis dated 15 Aug 2012. Per the DMC recommendation and FDA's agreement, the enrollment of patients in this study and Study OSI-774-206 was permanently closed. |
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Notes: