# Clinical trial results:
# Phase I/II open label, dose escalation trial to determine the MTD, safety, PK and efficacy of afatinib monotherapy in children aged 1 year to <18 years with recurrent/refractory neuroectodermal tumours, rhabdomyosarcoma and/or other solid tumours with known ErbB pathway deregulation regardless of tumour histology

## Summary

| | |
|---|---|
| EudraCT number | 2014-002123-10 |
| Trial protocol | ES DE GB AT FR DK IT NL IE |
| Global end of trial date | 05 August 2020 |

**Results information**

| | |
|---|---|
| Result version number | v2 (current) |
| This version publication date | 14 November 2021 |
| First version publication date | 22 February 2021 |
| Version creation reason | |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | 1200.120 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02372006 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Boehringer Ingelheim |
| Sponsor organisation address | Binger Str. 173, Ingelheim am Rhein, Germany, 55216 |
| Public contact | Boehringer Ingelheim, Call Center, Boehringer Ingelheim, 001 8002430127, clintriage.rdg@boehringer-ingelheim.com |
| Scientific contact | Boehringer Ingelheim, Call Center, Boehringer Ingelheim, 001 8002430127, clintriage.rdg@boehringer-ingelheim.com |

Notes:

**Paediatric regulatory details**

| | |
|---|---|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMEA-001596-PIP02-17 |
| 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 | 14 October 2020 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 05 August 2020 |
| Global end of trial reached? | Yes |
| Global end of trial date | 05 August 2020 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The objective of the Phase I dose finding part was to determine the maximum tolerated dose (MTD), safety, and pharmacokinetics of afatinib in paediatric patients across all applicable tumour entities. The objective of the MTD expansion cohorts/Phase II part was to assess anti-tumour activity, safety, and pharmacokinetics of afatinib in a larger number of patients.

Protection of trial subjects:

Prior to the initiation of any trial-related procedure, all patients´ parents/legally accepted representatives were informed about the trial verbally and in writing by the investigator. The parents/legally accepted representatives were allowed sufficient time to consider participation in the trial and to ask questions concerning the details of the trial. Because a high rate of screening failures was expected for the MTD expansion cohorts/Phase II part, a pre-screening informed consent was allowed to be used to enable collection and testing of tumour tissue for ErbB deregulations. Upon confirmation of positivity for selection biomarkers and before proceeding with trial procedures, the informed consent/assent for trial entry had to be signed. The patient’s parents/legally accepted representatives and (where applicable) the patient were informed that they were free to withdraw their consent at any time during the trial without penalty or prejudice. They were informed that the patient’s personal trial-related data would be considered confidential and used by BI in accordance with the local data protection laws. The level of disclosure was explained to the parents/legally accepted representatives. The 397 enrolled participants in age category of "In Utero" was actually with age missing.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 22 May 2015 |
| 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: 6 |
| Country: Number of subjects enrolled | Austria: 12 |
| Country: Number of subjects enrolled | Canada: 33 |
| Country: Number of subjects enrolled | Denmark: 39 |
| Country: Number of subjects enrolled | France: 102 |
| Country: Number of subjects enrolled | Germany: 8 |
| Country: Number of subjects enrolled | Italy: 71 |

| | |
|---|---|
| Country: Number of subjects enrolled | Netherlands: 4 |
| Country: Number of subjects enrolled | Spain: 44 |
| Country: Number of subjects enrolled | United States: 51 |
| Country: Number of subjects enrolled | United Kingdom: 193 |
| Worldwide total number of subjects | 563 |
| EEA total number of subjects | 280 |

Notes:

| **Subjects enrolled per age group** | |
|---|---|
| In utero | 397 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 96 |
| Adolescents (12-17 years) | 68 |
| Adults (18-64 years) | 2 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

Phase I/II open label, dose escalation trial to determine the MTD, safety, PK and efficacy of afatinib monotherapy in children aged ≥1 year to <18 years with recurrent/refractory neuroectodermal tumours, rhabdomyosarcoma and/or other solid tumours with known ErbB pathway deregulation regardless of tumour histology.

### Pre-assignment

Screening details:

Only subjects that met all the study inclusion and none of the exclusion criteria were to be entered in the study. All subjects were free to withdraw from the clinical trial at any time for any reason given. Close monitoring of all subjects was adhered to throughout the trial conduct. Rescue medication was allowed for all patients as required.

### Period 1

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

Blinding implementation details:

This study is open label

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Dose finding - level 0 |

Arm description:

Afatinib, dose level 0. (Once daily at 80% of the recommended adult dose per m2 body surface area using allometric scaling): Oral solid single-unit film-coated tablets for pediatric patients who are able to swallow them. Oral liquid formulation for patients who cannot swallow the film-coated tablets, or for doses which cannot be achieved by the film-coated tablets, or for pediatric patients who did not accept the film-coated tablets. Therapy with afatinib continued as long as the individual patient benefited from the therapy, did not develop secondary malignancy, and did not meet one of the criteria requiring withdrawal from treatment. Afatinib in film-coated tablet form can be given in tablets of 20, 30, 40 and 50 milligram (mg). The tablet dose is related to the free base equivalent to afatinib. The dose of afatinib as capsule and solvent for oral solution is given as a 200 mg capsule to be dissolved in aqueous solvent (2 capsules per 100 milliliter (ml) solvent) i.e. 4 mg per ml.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Afatinib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet, Capsule, Powder and solvent for oral solution |
| Routes of administration | Oral use |

Dosage and administration details:

Once daily at 80% of the recommended adult dose per m2 body surface area [BSA] using allometric scaling: Oral solid single-unit film-coated tablets for pediatric patients who are able to swallow them. Oral liquid formulation for patients who cannot swallow the film-coated tablets, or for doses which cannot be achieved by the film-coated tablets, or for pediatric patients who did not accept the film-coated tablets. Therapy continued as long as the individual patient benefited from the therapy, did not develop secondary malignancy, and did not meet one of the criteria requiring withdrawal from treatment. Afatinib in film-coated tablet from can be given in tablets of 20, 30, 40 and 50 mg. The dose in film-coated tablets is related to the free base equivalent to afatinib. The dose of afatinib as capsule and solvent for oral solution is given as a 200 mg capsule to be dissolved in aqueous solvent (2 capsules per 100 milliliter solvent) i.e. 4 milligram per milliliter.

| | |
|---|---|
| **Arm title** | Dose finding - level 1 |

Arm description:

Afatinib, dose level 1. (Once daily at 100% of the recommended adult dose per m2 body surface area using allometric scaling):
Oral solid single-unit film-coated tablets for pediatric patients who are able to swallow them. Oral liquid formulation for
patients who cannot swallow the film-coated tablets, or for doses which cannot be achieved by the film-coated tablets,
or for pediatric patients who did not accept the film-coated tablets.
Therapy with afatinib continued as long as the individual patient benefited from the therapy, did not develop secondary
malignancy, and did not meet one of the criteria requiring withdrawal from treatment.
Afatinib in film-coated tablet form can be given in tablets of 20, 30, 40 and 50 milligram (mg). The tablet dose is
related to the free base equivalent to afatinib. The dose of afatinib as capsule and solvent for oral solution is given as a
200 mg capsule to be dissolved in aqueous solvent (2 capsules per 100 milliliter (ml) solvent) i.e. 4 mg per ml.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Afatinib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet, Capsule, Powder and solvent for oral solution |
| Routes of administration | Oral use |

Dosage and administration details:

Once daily at 100% of the recommended adult dose per m2 body surface area [BSA] using allometric scaling: Oral solid single-unit film-coated tablets for pediatric patients who are able to swallow them. Oral liquid formulation for patients who cannot swallow the film-coated tablets, or for doses which cannot be achieved by the film-coated tablets, or for pediatric patients who did not accept the film-coated tablets. Therapy continued as long as the individual patient benefited from the therapy, did not develop secondary malignancy, and did not meet one of the criteria requiring withdrawal from treatment. Afatinib in film-coated tablet from can be given in tablets of 20, 30, 40 and 50 mg. The dose in film-coated tablets is related to the free base equivalent to afatinib. The dose of afatinib as capsule and solvent for oral solution is given as a 200 mg capsule to be dissolved in aqueous solvent (2 capsules per 100 milliliter solvent) i.e. 4 milligram per milliliter.

| | |
|---|---|
| **Arm title** | Maximum tolerated dose (MTD) expansion cohort - level 0 |

Arm description:

Afatinib, dose level 0. (Once daily at 80% of the recommended adult dose per m2 body surface area using allometric scaling): Oral solid single-unit film-coated tablets for pediatric patients who are able to swallow them. Oral liquid formulation for patients who cannot swallow the film-coated tablets, or for doses which cannot be achieved by the film-coated tablets, or for pediatric patients who did not accept the film-coated tablets. Therapy with afatinib continued as long as the individual patient benefited from the therapy, did not develop secondary malignancy, and did not meet one of the criteria requiring withdrawal from treatment. Afatinib in film-coated tablet form can be given in tablets of 20, 30, 40 and 50 milligram (mg). The tablet dose is related to the free base equivalent to afatinib. The dose of afatinib as capsule and solvent for oral solution is given as a 200 mg capsule to be dissolved in aqueous solvent (2 capsules per 100 milliliter (ml) solvent) i.e. 4 mg per ml.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Afatinib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet, Capsule, Powder and solvent for oral solution |
| Routes of administration | Oral use |

Dosage and administration details:

Once daily at 80% of the recommended adult dose per m2 body surface area [BSA] using allometric scaling: Oral solid single-unit film-coated tablets for pediatric patients who are able to swallow them. Oral liquid formulation for patients who cannot swallow the film-coated tablets, or for doses which cannot be achieved by the film-coated tablets, or for pediatric patients who did not accept the film-coated tablets. Therapy continued as long as the individual patient benefited from the therapy, did not develop secondary malignancy, and did not meet one of the criteria requiring withdrawal from treatment. Afatinib in film-coated tablet from can be given in tablets of 20, 30, 40 and 50 mg. The dose in film-coated tablets is related to the free base equivalent to afatinib. The dose of afatinib as capsule

and solvent for oral solution is given as a 200 mg capsule to be dissolved in aqueous solvent (2 capsules per 100 milliliter solvent) i.e. 4 milligram per milliliter.

| **Number of subjects in period 1**[1] | Dose finding - level 0 | Dose finding - level 1 | Maximum tolerated dose (MTD) expansion cohort - level 0 |
|---|---|---|---|
| Started | 8 | 9 | 39 |
| Completed | 0 | 0 | 0 |
| Not completed | 8 | 9 | 39 |
| Consent withdrawn by subject | - | 1 | 1 |
| Drug limiting toxicity | - | 1 | - |
| Adverse event, non-fatal | - | - | 3 |
| Progressive disease | 8 | 7 | 34 |
| Other reason for not completing | - | - | 1 |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Baseline characteristics are based on patients who were randomised after successfully completing the screening period and received at least one dose of the trial medication.

## Baseline characteristics

### Reporting groups

| Reporting group title | Dose finding - level 0 |
|---|---|

Reporting group description:

Afatinib, dose level 0. (Once daily at 80% of the recommended adult dose per m2 body surface area using allometric scaling): Oral solid single-unit film-coated tablets for pediatric patients who are able to swallow them. Oral liquid formulation for patients who cannot swallow the film-coated tablets, or for doses which cannot be achieved by the film-coated tablets, or for pediatric patients who did not accept the film-coated tablets. Therapy with afatinib continued as long as the individual patient benefited from the therapy, did not develop secondary malignancy, and did not meet one of the criteria requiring withdrawal from treatment. Afatinib in film-coated tablet form can be given in tablets of 20, 30, 40 and 50 milligram (mg). The tablet dose is related to the free base equivalent to afatinib. The dose of afatinib as capsule and solvent for oral solution is given as a 200 mg capsule to be dissolved in aqueous solvent (2 capsules per 100 milliliter (ml) solvent) i.e. 4 mg per ml.

| Reporting group title | Dose finding - level 1 |
|---|---|

Reporting group description:

Afatinib, dose level 1. (Once daily at 100% of the recommended adult dose per m2 body surface area using allometric scaling):
Oral solid single-unit film-coated tablets for pediatric patients who are able to swallow them. Oral liquid formulation for
patients who cannot swallow the film-coated tablets, or for doses which cannot be achieved by the film-coated tablets,
or for pediatric patients who did not accept the film-coated tablets.
Therapy with afatinib continued as long as the individual patient benefited from the therapy, did not develop secondary
malignancy, and did not meet one of the criteria requiring withdrawal from treatment.
Afatinib in film-coated tablet form can be given in tablets of 20, 30, 40 and 50 milligram (mg). The tablet dose is
related to the free base equivalent to afatinib. The dose of afatinib as capsule and solvent for oral solution is given as a
200 mg capsule to be dissolved in aqueous solvent (2 capsules per 100 milliliter (ml) solvent) i.e. 4 mg per ml.

| Reporting group title | Maximum tolerated dose (MTD) expansion cohort - level 0 |
|---|---|

Reporting group description:

Afatinib, dose level 0. (Once daily at 80% of the recommended adult dose per m2 body surface area using allometric scaling): Oral solid single-unit film-coated tablets for pediatric patients who are able to swallow them. Oral liquid formulation for patients who cannot swallow the film-coated tablets, or for doses which cannot be achieved by the film-coated tablets, or for pediatric patients who did not accept the film-coated tablets. Therapy with afatinib continued as long as the individual patient benefited from the therapy, did not develop secondary malignancy, and did not meet one of the criteria requiring withdrawal from treatment. Afatinib in film-coated tablet form can be given in tablets of 20, 30, 40 and 50 milligram (mg). The tablet dose is related to the free base equivalent to afatinib. The dose of afatinib as capsule and solvent for oral solution is given as a 200 mg capsule to be dissolved in aqueous solvent (2 capsules per 100 milliliter (ml) solvent) i.e. 4 mg per ml.

| **Reporting group values** | Dose finding - level 0 | Dose finding - level 1 | Maximum tolerated dose (MTD) expansion cohort - level 0 |
|---|---|---|---|
| Number of subjects | 8 | 9 | 39 |
| Age categorical | | | |
| Treated set (TS)<br>This patient set included all patients enrolled in the trial who were documented to have taken at least one dose of study medication. | | | |
| Units: Years | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |

| | | | |
|---|---|---|---|
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 4 | 4 | 20 |
| Adolescents (12-17 years) | 4 | 5 | 18 |
| Adults (18-64 years) | 0 | 0 | 1 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous | | | |
| Treated set (TS)<br>This patient set included all patients enrolled in the trial who were documented to have taken at least one dose of study medication. | | | |
| Units: years | | | |
| arithmetic mean | 9.75 | 10.44 | 10.92 |
| standard deviation | ± 4.83 | ± 5.29 | ± 4.44 |
| Sex: Female, Male | | | |
| Treated set (TS)<br>This patient set included all patients enrolled in the trial who were documented to have taken at least one dose of study medication. | | | |
| Units: Participants | | | |
| Female | 4 | 4 | 16 |
| Male | 4 | 5 | 23 |
| Ethnicity (NIH/OMB) | | | |
| Treated set (TS)<br>This patient set included all patients enrolled in the trial who were documented to have taken at least one dose of study medication. | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 0 | 0 | 0 |
| Not Hispanic or Latino | 4 | 5 | 37 |
| Unknown or Not Reported | 4 | 4 | 2 |
| Race (NIH/OMB) | | | |
| Treated set (TS)<br>This patient set included all patients enrolled in the trial who were documented to have taken at least one dose of study medication. | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 0 | 0 | 1 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 0 | 0 | 2 |
| White | 3 | 4 | 29 |
| More than one race | 1 | 0 | 0 |
| Unknown or Not Reported | 4 | 5 | 7 |

| **Reporting group values** | Total | | |
|---|---|---|---|
| Number of subjects | 56 | | |
| Age categorical | | | |
| Treated set (TS)<br>This patient set included all patients enrolled in the trial who were documented to have taken at least one dose of study medication. | | | |
| Units: Years | | | |
| In utero | 0 | | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | | |
| Newborns (0-27 days) | 0 | | |
| Infants and toddlers (28 days-23 months) | 0 | | |

| | | | |
|---|---|---|---|
| Children (2-11 years) | 28 | | |
| Adolescents (12-17 years) | 27 | | |
| Adults (18-64 years) | 1 | | |
| From 65-84 years | 0 | | |
| 85 years and over | 0 | | |
| Age Continuous | | | |
| Treated set (TS)<br>This patient set included all patients enrolled in the trial who were documented to have taken at least one dose of study medication. | | | |
| Units: years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Sex: Female, Male | | | |
| Treated set (TS)<br>This patient set included all patients enrolled in the trial who were documented to have taken at least one dose of study medication. | | | |
| Units: Participants | | | |
| Female | 24 | | |
| Male | 32 | | |
| Ethnicity (NIH/OMB) | | | |
| Treated set (TS)<br>This patient set included all patients enrolled in the trial who were documented to have taken at least one dose of study medication. | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 0 | | |
| Not Hispanic or Latino | 46 | | |
| Unknown or Not Reported | 10 | | |
| Race (NIH/OMB) | | | |
| Treated set (TS)<br>This patient set included all patients enrolled in the trial who were documented to have taken at least one dose of study medication. | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 0 | | |
| Asian | 1 | | |
| Native Hawaiian or Other Pacific Islander | 0 | | |
| Black or African American | 2 | | |
| White | 36 | | |
| More than one race | 1 | | |
| Unknown or Not Reported | 16 | | |

## End points

### End points reporting groups

| Reporting group title | Dose finding - level 0 |
|---|---|

Reporting group description:

Afatinib, dose level 0. (Once daily at 80% of the recommended adult dose per m2 body surface area using allometric scaling): Oral solid single-unit film-coated tablets for pediatric patients who are able to swallow them. Oral liquid formulation for patients who cannot swallow the film-coated tablets, or for doses which cannot be achieved by the film-coated tablets, or for pediatric patients who did not accept the film-coated tablets. Therapy with afatinib continued as long as the individual patient benefited from the therapy, did not develop secondary malignancy, and did not meet one of the criteria requiring withdrawal from treatment. Afatinib in film-coated tablet form can be given in tablets of 20, 30, 40 and 50 milligram (mg). The tablet dose is related to the free base equivalent to afatinib. The dose of afatinib as capsule and solvent for oral solution is given as a 200 mg capsule to be dissolved in aqueous solvent (2 capsules per 100 milliliter (ml) solvent) i.e. 4 mg per ml.

| Reporting group title | Dose finding - level 1 |
|---|---|

Reporting group description:

Afatinib, dose level 1. (Once daily at 100% of the recommended adult dose per m2 body surface area using allometric scaling):
Oral solid single-unit film-coated tablets for pediatric patients who are able to swallow them. Oral liquid formulation for
patients who cannot swallow the film-coated tablets, or for doses which cannot be achieved by the film-coated tablets,
or for pediatric patients who did not accept the film-coated tablets.
Therapy with afatinib continued as long as the individual patient benefited from the therapy, did not develop secondary
malignancy, and did not meet one of the criteria requiring withdrawal from treatment.
Afatinib in film-coated tablet form can be given in tablets of 20, 30, 40 and 50 milligram (mg). The tablet dose is
related to the free base equivalent to afatinib. The dose of afatinib as capsule and solvent for oral solution is given as a
200 mg capsule to be dissolved in aqueous solvent (2 capsules per 100 milliliter (ml) solvent) i.e. 4 mg per ml.

| Reporting group title | Maximum tolerated dose (MTD) expansion cohort - level 0 |
|---|---|

Reporting group description:

Afatinib, dose level 0. (Once daily at 80% of the recommended adult dose per m2 body surface area using allometric scaling): Oral solid single-unit film-coated tablets for pediatric patients who are able to swallow them. Oral liquid formulation for patients who cannot swallow the film-coated tablets, or for doses which cannot be achieved by the film-coated tablets, or for pediatric patients who did not accept the film-coated tablets. Therapy with afatinib continued as long as the individual patient benefited from the therapy, did not develop secondary malignancy, and did not meet one of the criteria requiring withdrawal from treatment. Afatinib in film-coated tablet form can be given in tablets of 20, 30, 40 and 50 milligram (mg). The tablet dose is related to the free base equivalent to afatinib. The dose of afatinib as capsule and solvent for oral solution is given as a 200 mg capsule to be dissolved in aqueous solvent (2 capsules per 100 milliliter (ml) solvent) i.e. 4 mg per ml.

### Primary: Area under the curve over dosing interval τ at steady state ($AUC_{\tau, ss}$) - Dose finding part

| End point title | Area under the curve over dosing interval τ at steady state ($AUC_{\tau, ss}$) - Dose finding part[1][2] |
|---|---|

End point description:

Area under the curve over dosing interval τ at steady state ($AUC_{\tau,ss}$) was reported. Pharmacokinetics (PK) analysis set (PKS): This patient set included all patients in the TS who provided at least one PK endpoint that was not excluded due to a protocol
deviation relevant to the evaluation of PK or due to PK non-evaluability.

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

End point timeframe:

Pre-dose before afatinib administration then 1 hour (h), 2 h, 3 h, 4 h, 5 h, 6 h, 8 h and 24 h after administration at steady state on Day 8.

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: This endpoint was evaluated only descriptively. Thus, no statistical hypothesis were tested.

[2] - 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: Only those arms for which the comparisons are presented in the clinical trial report thus, those that would yield meaningful results were reported.

| **End point values** | Dose finding - level 0 | Dose finding - level 1 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 7 | 6 | | |
| Units: hours times nanogram per milliliter | | | | |
| geometric mean (geometric coefficient of variation) | 681 (± 43.8) | 1380 (± 29.0) | | |

## Statistical analyses

No statistical analyses for this end point

## Primary: Maximum measured concentration of the analyte in plasma at steady state (Cmax,ss) - Dose finding part

| End point title | Maximum measured concentration of the analyte in plasma at steady state (Cmax,ss) - Dose finding part[3][4] |
|---|---|

End point description:

Maximum measured concentration of the analyte in plasma at steady state (Cmax,ss) - Dose finding part was reported. Pharmacokinetics (PK) analysis set (PKS): This patient set included all patients in the TS who provided at least one PK endpoint that was not excluded due to a protocol deviation relevant to the evaluation of PK or due to PK non-evaluability. Only participants with non-missing results were included in the analysis.

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

End point timeframe:

Pre-dose before afatinib administration then 1 hour (h), 2 h, 3 h, 4 h, 5 h, 6 h, 8 h and 24 h after administration at steady state on Day 8.

Notes:

[3] - 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: This endpoint was evaluated only descriptively. Thus, no statistical hypothesis were tested.

[4] - 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: Only those arms for which the comparisons are presented in the clinical trial report thus, those that would yield meaningful results were reported.

| **End point values** | Dose finding - level 0 | Dose finding - level 1 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 7 | 6 | | |
| Units: nanogram per mililiter | | | | |
| geometric mean (geometric coefficient of variation) | 53.0 (± 48.8) | 115 (± 39.3) | | |

## Statistical analyses

No statistical analyses for this end point

## Primary: Number of participants with objective response - maximum tolerated dose (MTD) expansion cohort

| End point title | Number of participants with objective response - maximum tolerated dose (MTD) expansion cohort[5][6] |
|---|---|

End point description:

Number of participants with objective response in maximum tolerated dose (MTD) expansion cohort was reported. The objective response was defined as a best overall response of complete response or partial response based on investigator's assessment according to the institutional response evaluation criteria for the given tumour type, assessed every 8 weeks until progression. Treated set (TS): This patient set included all patients enrolled in the trial who were documented to have taken at least one dose of study medication.

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

End point timeframe:

Assessed every 8 weeks until progression of disease, up to 336 days.

Notes:

[5] - 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: This endpoint was evaluated only descriptively. Thus, no statistical hypothesis were tested.

[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: Only those arms for which the comparisons are presented in the clinical trial report thus, those that would yield meaningful results were reported.

| **End point values** | Maximum tolerated dose (MTD) expansion cohort - level 0 | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 39 | | | |
| Units: Participants | 3 | | | |

## Statistical analyses

No statistical analyses for this end point

## Primary: Number of participants with Dose Limiting Toxicity adverse events - Dose finding part

| End point title | Number of participants with Dose Limiting Toxicity adverse events - Dose finding part[7][8] |
|---|---|

End point description:

Number of participants with Dose Limiting Toxicity adverse events in Dose finding part was reported. Treated set (TS) This patient set included all patients enrolled in the trial who were documented to have taken at least one dose of study medication.

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

End point timeframe:

During the first course (28 days) of treatment.

Notes:

[7] - 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: This endpoint was evaluated only descriptively. Thus, no statistical hypothesis were tested.

[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: Only those arms for which the comparisons are presented in the clinical trial report thus, those that would yield meaningful results were reported.

| End point values | Dose finding - level 0 | Dose finding - level 1 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 | 9 | | |
| Units: Participants | 1 | 2 | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of participants with objective response - Dose finding part

| End point title | Number of participants with objective response - Dose finding part[9] |
|---|---|

End point description:

Number of participants with objective response in Dose finding part was reported. The objective response was defined as a best overall response of complete response or partial response based on investigator's assessment according to the institutional response evaluation criteria for the given tumour type, assessed every 8 weeks until progression. Treated set (TS): This patient set included all patients enrolled in the trial who were documented to have taken at least one dose of study medication.

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

End point timeframe:

Assessed every 8 weeks until progression of disease, up to 336 days.

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: Only those arms for which the comparisons are presented in the clinical trial report thus, those that would yield meaningful results were reported.

| End point values | Dose finding - level 0 | Dose finding - level 1 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 | 9 | | |
| Units: Participants | 0 | 0 | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to 24 hours (AUC0-24) - Dose finding part

| End point title | Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to 24 hours (AUC0-24) - Dose finding part[10] |
|---|---|

End point description:

Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to 24 hours (AUC0-24) for Dose finding part was reported. Pharmacokinetics (PK) analysis set (PKS): This patient set included all patients in the TS who provided at least one PK endpoint that was not excluded

due to a protocol deviation relevant to the evaluation of PK or due to PK non-evaluability. Only participants with non-missing results were included in the analysis.

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

End point timeframe:

Pre-dose before afatinib administration then 1 hour (h), 2 h, 3 h, 4 h, 5 h, 6 h, 8 h and 24 h after administration on Day 1.

Notes:

[10] - 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: Only those arms for which the comparisons are presented in the clinical trial report thus, those that would yield meaningful results were reported.

| **End point values** | Dose finding - level 0 | Dose finding - level 1 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 | 8 | | |
| Units: hours times nanogram per mililiter | | | | |
| geometric mean (geometric coefficient of variation) | 383 (± 46.4) | 512 (± 40.6) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Maximum measured concentration (Cmax) - Dose finding part/maximum tolerated dose (MTD) expansion cohort

| End point title | Maximum measured concentration (Cmax) - Dose finding part/maximum tolerated dose (MTD) expansion cohort |
|---|---|

End point description:

Maximum measured concentration (Cmax) for Dose finding part/maximum tolerated dose expansion cohort was reported. Pharmacokinetics (PK) analysis set (PKS): This patient set included all patients in the TS who provided at least one PK endpoint that was not excluded due to a protocol deviation relevant to the evaluation of PK or due to PK non-evaluability. Only participants with non-missing results were included in the analysis.

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

End point timeframe:

Pre-dose before afatinib administration then 1 hour (h), 2 h, 3 h, 4 h, 5 h, 6 h, 8 h and 24 h after administration on Day 1.

| **End point values** | Dose finding - level 0 | Dose finding - level 1 | Maximum tolerated dose (MTD) expansion cohort - level 0 | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 8 | 8 | 36 | |
| Units: nanogram per mililiter | | | | |
| geometric mean (geometric coefficient of variation) | 36.4 (± 55.9) | 43.8 (± 61.2) | 30.5 (± 90.3) | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time from (last) dosing to the maximum measured concentration (tmax) - Dose finding part/maximum tolerated dose (MTD) expansion cohort

| End point title | Time from (last) dosing to the maximum measured concentration (tmax) - Dose finding part/maximum tolerated dose (MTD) expansion cohort |
|---|---|

End point description:

Times from (last) dosing to the maximum measured concentration (tmax) for Dose finding oart/maximum tolerated dose (MTD) expansion cohort was reported. Pharmacokinetics (PK) analysis set (PKS): This patient set included all patients in the TS who provided at least one PK endpoint that was not excluded due to a protocol deviation relevant to the evaluation of PK or due to PK non-evaluability. Only participants with non-missing results were included in the analysis.

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

End point timeframe:

Pre-dose before afatinib administration then 1 hour (h), 2 h, 3 h, 4 h, 5 h, 6 h, 8 h and 24 h after administration on Day 1.

| **End point values** | Dose finding - level 0 | Dose finding - level 1 | Maximum tolerated dose (MTD) expansion cohort - level 0 | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 8 | 8 | 36 | |
| Units: Hours | | | | |
| median (full range (min-max)) | 3.02 (2.00 to 6.00) | 3.43 (2.00 to 6.02) | 3.98 (1.00 to 8.00) | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time from (last) dosing to the maximum measured concentration at steady state (tmax,ss) - Dose finding part/maximum tolerated dose (MTD) expansion cohort

| End point title | Time from (last) dosing to the maximum measured concentration at steady state (tmax,ss) - Dose finding part/maximum tolerated dose (MTD) expansion cohort |
|---|---|

End point description:

Time from (last) dosing to the maximum measured concentration at steady state (tmax,ss) for Dose finding part/maximum tolerated dose (MTD) expansion cohort was reported. Pharmacokinetics (PK) analysis set (PKS): This patient set included all patients in the TS who provided at least one PK endpoint

that was not excluded due to a protocol deviation relevant to the evaluation of PK or due to PK non-evaluability. Only participants with non-missing results were included in the analysis.

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

End point timeframe:

Pre-dose before afatinib administration then 1 hour (h), 2 h, 3 h, 4 h, 5 h, 6 h, 8 h and 24 h after administration at steady state on Day 8.

| **End point values** | Dose finding - level 0 | Dose finding - level 1 | Maximum tolerated dose (MTD) expansion cohort - level 0 | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 7 | 6 | 25 | |
| Units: Hours | | | | |
| median (full range (min-max)) | 3.00 (2.00 to 6.00) | 2.75 (2.00 to 5.05) | 4.17 (2.00 to 8.00) | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Progression free survival - maximum tolerated dose (MTD) expansion cohort

| End point title | Progression free survival - maximum tolerated dose (MTD) expansion cohort[11] |
|---|---|

End point description:

Progression free survival for maximum tolerated dose (MTD) expansion cohort was reported. Progression free survival (PFS) was defined as the duration from the date of first treatment until the date of the first documented progression or death due to any cause. If a patient did not have an event, PFS was censored at the date of last adequate tumour assessment. Median PFS was estimated by Kaplan-Meier. Treated set (TS) This patient set included all patients enrolled in the trial who were documented to have taken at least one dose of study medication.

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

End point timeframe:

From the first treatment until date of first progression or death, up to 336 days.

Notes:

[11] - 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: Only those arms for which the comparisons are presented in the clinical trial report thus, those that would yield meaningful results were reported.

| **End point values** | Maximum tolerated dose (MTD) expansion cohort - level 0 | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 39 | | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 8.0 (6.4 to 8.29) | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Accumulation (or effective) half-life - Dose finding part/maximum tolerated dose (MTD) expansion cohort

| End point title | Accumulation (or effective) half-life - Dose finding part/maximum tolerated dose (MTD) expansion cohort |
|---|---|

End point description:

Accumulation (or effective) half-life for Dose finding part/maximum tolerated dose (MTD) expansion cohort was reported. Pharmacokinetics (PK) analysis set (PKS): This patient set included all patients in the TS who provided at least one PK endpoint that was not excluded due to a protocol deviation relevant to the evaluation of PK or due to PK non-evaluability. Only participants with non-missing results were included in the analysis.

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

End point timeframe:

Pre-dose before afatinib administration then 1 hour (h), 2 h, 3 h, 4 h, 5 h, 6 h, 8 h and 24 h after administration at steady state on Day 8.

| **End point values** | Dose finding - level 0 | Dose finding - level 1 | Maximum tolerated dose (MTD) expansion cohort - level 0 | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 7 | 6 | 24 | |
| Units: hours | | | | |
| geometric mean (geometric coefficient of variation) | 18.7 (± 44.3) | 31.0 (± 56.7) | 30.3 (± 83.6) | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Duration of objective response - maximum tolerated dose (MTD) expansion cohort

| End point title | Duration of objective response - maximum tolerated dose (MTD) expansion cohort[12] |
|---|---|

End point description:

Duration of objective response for maximum tolerated dose (MTD) expansion cohort was reported. Treated set (TS) This patient set included all patients enrolled in the trial who were documented to have taken at least one dose of study medication.

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

End point timeframe:

From first documented response until the earliest of disease progression or death, up to 336 days.

Notes:

[12] - 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: Only those arms for which the comparisons are presented in the clinical trial report thus, those that would yield meaningful results were reported.

| **End point values** | Maximum tolerated dose (MTD) expansion cohort - level 0 | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 39 | | | |
| Units: Days | | | | |
| median (full range (min-max)) | 62 (57 to 170) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Area under the curve over dosing interval τ at steady state ($AUC_{\tau, ss}$) - maximum tolerated dose (MTD) expansion cohort

| End point title | Area under the curve over dosing interval τ at steady state ($AUC_{\tau, ss}$) - maximum tolerated dose (MTD) expansion cohort[13] |
|---|---|

End point description:

Area under the curve over dosing interval τ at steady state ($AUC_{\tau, ss}$) for maximum tolerated dose (MTD) expansion cohort was reported. Pharmacokinetics (PK) analysis set (PKS): This patient set included all patients in the TS who provided at least one PK endpoint that was not excluded due to a protocol deviation relevant to the evaluation of PK or due to PK non-evaluability. Only participants with non-missing results were included in the analysis.

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

End point timeframe:

Pre-dose before afatinib administration then 1 hour (h), 2 h, 3 h, 4 h, 5 h, 6 h, 8 h and 24 h after administration at steady state on Day 8.

Notes:

[13] - 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: Only those arms for which the comparisons are presented in the clinical trial report thus, those that would yield meaningful results were reported.

| **End point values** | Maximum tolerated dose (MTD) expansion cohort - level 0 | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 25 | | | |
| Units: hours times nanogram per milliliter | | | | |
| geometric mean (geometric coefficient of variation) | 780 (± 60.7) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Maximum measured concentration of the analyte in plasma at steady state (Cmax,ss) - maximum tolerated dose (MTD) expansion cohort

| End point title | Maximum measured concentration of the analyte in plasma at steady state (Cmax,ss) - maximum tolerated dose (MTD) expansion cohort[14] |
|---|---|

End point description:

Maximum measured concentration of the analyte in plasma at steady state (Cmax,ss) for maximum tolerated dose (MTD) expansion cohort was reported. Pharmacokinetics (PK) analysis set (PKS): This patient set included all patients in the TS who provided at least one PK endpoint that was not excluded due to a protocol deviation relevant to the evaluation of PK or due to PK non-evaluability. Only participants with non-missing results were included in the analysis.

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

End point timeframe:

Pre-dose before afatinib administration then 1 hour (h), 2 h, 3 h, 4 h, 5 h, 6 h, 8 h and 24 h after administration at steady state on Day 8.

Notes:

[14] - 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: Only those arms for which the comparisons are presented in the clinical trial report thus, those that would yield meaningful results were reported.

| **End point values** | Maximum tolerated dose (MTD) expansion cohort - level 0 | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 25 | | | |
| Units: nanogram per mililiter | | | | |
| geometric mean (geometric coefficient of variation) | 52.5 (± 61.0) | | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From the first drug administration until end of study period, up to 336 days.

Adverse event reporting additional description:

Treated set (TS) This patient set included all patients enrolled in the trial who were documented to have taken at least one dose of study medication.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 23.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Dose finding Level 0 |

Reporting group description:

Afatinib, dose level 0. (Once daily at 80% of the recommended adult dose per m2 body surface area using allometric scaling): Oral solid single-unit film-coated tablets for pediatric patients who are able to swallow them. Oral liquid formulation for patients who cannot swallow the film-coated tablets, or for doses which cannot be achieved by the film-coated tablets, or for pediatric patients who did not accept the film-coated tablets. Therapy with afatinib continued as long as the individual patient benefited from the therapy, did not develop secondary malignancy, and did not meet one of the criteria requiring withdrawal from treatment. Afatinib in film-coated tablet form can be given in tablets of 20, 30, 40 and 50 milligram (mg). The tablet dose is related to the free base equivalent to afatinib. The dose of afatinib as capsule and solvent for oral solution is given as a 200 mg capsule to be dissolved in aqueous solvent (2 capsules per 100 milliliter (ml) solvent) i.e. 4 mg per ml.

| | |
|---|---|
| Reporting group title | Maximum tolerated dose (MTD) expansion - Level 0 |

Reporting group description:

Afatinib, dose level 0. (Once daily at 80% of the recommended adult dose per m2 body surface area using allometric scaling): Oral solid single-unit film-coated tablets for pediatric patients who are able to swallow them. Oral liquid formulation for patients who cannot swallow the film-coated tablets, or for doses which cannot be achieved by the film-coated tablets, or for pediatric patients who did not accept the film-coated tablets. Therapy with afatinib continued as long as the individual patient benefited from the therapy, did not develop secondary malignancy, and did not meet one of the criteria requiring withdrawal from treatment. Afatinib in film-coated tablet form can be given in tablets of 20, 30, 40 and 50 milligram (mg). The tablet dose is related to the free base equivalent to afatinib. The dose of afatinib as capsule and solvent for oral solution is given as a 200 mg capsule to be dissolved in aqueous solvent (2 capsules per 100 milliliter (ml) solvent) i.e. 4 mg per ml.

| | |
|---|---|
| Reporting group title | Dose finding Level 1 |

Reporting group description:

Afatinib, dose level 1. (Once daily at 100% of the recommended adult dose per m2 body surface area using allometric scaling): Oral solid single-unit film-coated tablets for pediatric patients who are able to swallow them. Oral liquid formulation for patients who cannot swallow the film-coated tablets, or for doses which cannot be achieved by the film-coated tablets, or for pediatric patients who did not accept the film-coated tablets. Therapy with afatinib continued as long as the individual patient benefited from the therapy, did not develop secondary malignancy, and did not meet one of the criteria requiring withdrawal from treatment. Afatinib in film-coated tablet form can be given in tablets of 20, 30, 40 and 50 milligram (mg). The tablet dose is related to the free base equivalent to afatinib. The dose of afatinib as capsule and solvent for oral solution is given as a 200 mg capsule to be dissolved in aqueous solvent (2 capsules per 100 milliliter (ml) solvent) i.e. 4 mg per ml.

| **Serious adverse events** | Dose finding Level 0 | Maximum tolerated dose (MTD) expansion - Level 0 | Dose finding Level 1 |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 7 / 8 (87.50%) | 20 / 39 (51.28%) | 6 / 9 (66.67%) |

| | | | |
|---|---|---|---|
| number of deaths (all causes) | 8 | 29 | 9 |
| number of deaths resulting from adverse events | 0 | 3 | 0 |
| Nervous system disorders | | | |
| Altered state of consciousness | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 39 (2.56%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aphasia | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 39 (2.56%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Encephalopathy | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 39 (2.56%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Generalised tonic-clonic seizure | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 39 (2.56%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhage intracranial | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 39 (2.56%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Headache | | | |
| subjects affected / exposed | 3 / 8 (37.50%) | 0 / 39 (0.00%) | 1 / 9 (11.11%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hemiparesis | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 39 (2.56%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hydrocephalus | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 8 (0.00%) | 2 / 39 (5.13%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Intracranial pressure increased | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 39 (2.56%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Somnolence | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 39 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Status epilepticus | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 39 (0.00%) | 1 / 9 (11.11%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Blood and lymphatic system disorders** | | | |
| Lymphopenia | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 39 (2.56%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **General disorders and administration site conditions** | | | |
| General physical health deterioration | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 39 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 2 / 39 (5.13%) | 1 / 9 (11.11%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Eye disorders** | | | |
| Blindness | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 39 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 39 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ascites | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 39 (2.56%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 39 (0.00%) | 3 / 9 (33.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 3 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Stomatitis | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 2 / 39 (5.13%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 3 / 8 (37.50%) | 2 / 39 (5.13%) | 2 / 9 (22.22%) |
| occurrences causally related to treatment / all | 1 / 4 | 1 / 2 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 39 (2.56%) | 1 / 9 (11.11%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoxia | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 2 / 39 (5.13%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 39 (0.00%) | 1 / 9 (11.11%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 39 (2.56%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory arrest | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 39 (2.56%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Respiratory distress | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 39 (2.56%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis acneiform | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 39 (2.56%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin ulcer | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 39 (2.56%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 39 (2.56%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Urinary tract disorder | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 39 (2.56%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Gastroenteritis viral | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 39 (2.56%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Paronychia | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 39 (2.56%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 39 (2.56%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Viral infection | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 39 (2.56%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 39 (0.00%) | 2 / 9 (22.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dehydration | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 39 (0.00%) | 1 / 9 (11.11%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypernatraemia | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 39 (0.00%) | 1 / 9 (11.11%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 39 (2.56%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypokalaemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 39 (0.00%) | 1 / 9 (11.11%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 39 (2.56%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| **Non-serious adverse events** | Dose finding Level 0 | Maximum tolerated dose (MTD) expansion - Level 0 | Dose finding Level 1 |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 8 / 8 (100.00%) | 38 / 39 (97.44%) | 9 / 9 (100.00%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Tumour pain | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 39 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 3 / 39 (7.69%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 2 / 39 (5.13%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Disease progression | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 39 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Fatigue | | | |
| subjects affected / exposed | 4 / 8 (50.00%) | 10 / 39 (25.64%) | 1 / 9 (11.11%) |
| occurrences (all) | 4 | 11 | 1 |
| Mucosal inflammation | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 7 / 39 (17.95%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 7 | 1 |

| | | | |
|---|---|---|---|
| Pain | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 39 (2.56%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 5 / 39 (12.82%) | 2 / 9 (22.22%) |
| occurrences (all) | 1 | 5 | 2 |
| Xerosis | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 2 / 39 (5.13%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 2 | 1 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 39 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 0 | 1 |
| Cough | | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 5 / 39 (12.82%) | 0 / 9 (0.00%) |
| occurrences (all) | 2 | 5 | 0 |
| Epistaxis | | | |
| subjects affected / exposed | 4 / 8 (50.00%) | 7 / 39 (17.95%) | 1 / 9 (11.11%) |
| occurrences (all) | 6 | 9 | 1 |
| Hypoxia | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 39 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Nasal congestion | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 39 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Nasal oedema | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 39 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 0 | 1 |
| Nasal pruritus | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 39 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 0 | 1 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 2 / 39 (5.13%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Pharyngeal inflammation | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 39 (2.56%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Tachypnoea | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 39 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 39 (2.56%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 1 | 1 |
| Insomnia | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 39 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 5 / 39 (12.82%) | 1 / 9 (11.11%) |
| occurrences (all) | 2 | 5 | 2 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 3 / 39 (7.69%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 5 | 2 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 39 (2.56%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 2 | 2 |
| Blood lactate dehydrogenase increased | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 2 / 39 (5.13%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 3 | 0 |
| Blood thyroid stimulating hormone increased | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 39 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Blood uric acid increased | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 2 / 39 (5.13%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| C-reactive protein increased | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 2 / 39 (5.13%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Gamma-glutamyltransferase | | | |

| | | | |
|---|---|---|---|
| increased | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 2 / 39 (5.13%) | 1 / 9 (11.11%) |
| occurrences (all) | 2 | 2 | 1 |
| Lymphocyte count decreased | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 4 / 39 (10.26%) | 3 / 9 (33.33%) |
| occurrences (all) | 0 | 5 | 5 |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 2 / 39 (5.13%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Platelet count decreased | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 39 (2.56%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Weight decreased | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 10 / 39 (25.64%) | 3 / 9 (33.33%) |
| occurrences (all) | 1 | 14 | 3 |
| White blood cell count decreased | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 3 / 39 (7.69%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 4 | 2 |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 39 (2.56%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 1 | 1 |
| Upper limb fracture | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 39 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 0 | 1 |
| Cardiac disorders | | | |
| Sinus bradycardia | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 2 / 39 (5.13%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Sinus tachycardia | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 2 / 39 (5.13%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Nervous system disorders | | | |
| Aphasia | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 39 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |

| | | | |
|---|---|---|---|
| Ataxia | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 2 / 39 (5.13%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Dizziness | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 2 / 39 (5.13%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Dysarthria | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 2 / 39 (5.13%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Headache | | | |
| subjects affected / exposed | 3 / 8 (37.50%) | 9 / 39 (23.08%) | 3 / 9 (33.33%) |
| occurrences (all) | 3 | 9 | 3 |
| Lethargy | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 2 / 39 (5.13%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Neurological decompensation | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 39 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Peripheral motor neuropathy | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 39 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Somnolence | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 39 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| VIth nerve disorder | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 39 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 3 / 8 (37.50%) | 7 / 39 (17.95%) | 1 / 9 (11.11%) |
| occurrences (all) | 3 | 9 | 1 |
| Leukopenia | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 39 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Lymphopenia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 8 (0.00%) | 2 / 39 (5.13%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 3 | 1 |
| Neutropenia | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 39 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Eye disorders | | | |
| Dry eye | | | |
| subjects affected / exposed | 3 / 8 (37.50%) | 3 / 39 (7.69%) | 0 / 9 (0.00%) |
| occurrences (all) | 3 | 4 | 0 |
| Eye discharge | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 39 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 0 | 1 |
| Eye pruritus | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 39 (2.56%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Keratitis | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 39 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 0 | 1 |
| Punctate keratitis | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 39 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Vision blurred | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 39 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Visual acuity reduced | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 39 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 4 / 8 (50.00%) | 8 / 39 (20.51%) | 2 / 9 (22.22%) |
| occurrences (all) | 12 | 14 | 2 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 39 (2.56%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Anal haemorrhage | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 39 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Angular cheilitis | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 39 (2.56%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Cheilitis | | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 6 / 39 (15.38%) | 2 / 9 (22.22%) |
| occurrences (all) | 2 | 6 | 2 |
| Constipation | | | |
| subjects affected / exposed | 6 / 8 (75.00%) | 4 / 39 (10.26%) | 1 / 9 (11.11%) |
| occurrences (all) | 7 | 4 | 1 |
| Diarrhoea | | | |
| subjects affected / exposed | 6 / 8 (75.00%) | 30 / 39 (76.92%) | 6 / 9 (66.67%) |
| occurrences (all) | 21 | 52 | 10 |
| Dyschezia | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 39 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Dysphagia | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 39 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 1 | 0 | 1 |
| Glossitis | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 39 (2.56%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Lip dry | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 5 / 39 (12.82%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 5 | 0 |
| Mouth ulceration | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 39 (2.56%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Nausea | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 15 / 39 (38.46%) | 2 / 9 (22.22%) |
| occurrences (all) | 1 | 17 | 2 |
| Oral pain | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 3 / 39 (7.69%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Stomatitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 8 (37.50%) | 9 / 39 (23.08%) | 1 / 9 (11.11%) |
| occurrences (all) | 3 | 9 | 1 |
| Tongue eruption | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 39 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Vomiting | | | |
| subjects affected / exposed | 3 / 8 (37.50%) | 16 / 39 (41.03%) | 6 / 9 (66.67%) |
| occurrences (all) | 7 | 25 | 10 |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 39 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Dermatitis | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 39 (2.56%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 1 | 1 |
| Dermatitis acneiform | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 9 / 39 (23.08%) | 1 / 9 (11.11%) |
| occurrences (all) | 1 | 9 | 1 |
| Dermatitis diaper | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 39 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 0 | 1 |
| Dry skin | | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 10 / 39 (25.64%) | 4 / 9 (44.44%) |
| occurrences (all) | 3 | 10 | 4 |
| Eczema | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 39 (2.56%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Erythema | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 2 / 39 (5.13%) | 2 / 9 (22.22%) |
| occurrences (all) | 0 | 2 | 2 |
| Hair colour changes | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 39 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hand dermatitis | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 39 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 0 | 1 |

| | | | |
|---|---|---|---|
| Hyperhidrosis | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 39 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pruritus | | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 3 / 39 (7.69%) | 0 / 9 (0.00%) |
| occurrences (all) | 2 | 3 | 0 |
| Rash | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 4 / 39 (10.26%) | 1 / 9 (11.11%) |
| occurrences (all) | 1 | 8 | 1 |
| Rash maculo-papular | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 4 / 39 (10.26%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 4 | 1 |
| Rash papular | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 2 / 39 (5.13%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Skin fissures | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 39 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 1 | 0 | 1 |
| Skin irritation | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 39 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 0 | 1 |
| Renal and urinary disorders | | | |
| Proteinuria | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 39 (2.56%) | 0 / 9 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Urinary retention | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 39 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Groin pain | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 2 / 39 (5.13%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Muscle spasms | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 2 / 39 (5.13%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Infections and infestations | | | |

| | | | |
|---|---|---|---|
| Conjunctivitis | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 3 / 39 (7.69%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 3 | 0 |
| Cystitis | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 39 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Ear infection | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 39 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 0 | 1 |
| Escherichia infection | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 39 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Herpes zoster | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 39 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 0 | 1 |
| Impetigo | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 39 (2.56%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Infection | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 39 (2.56%) | 0 / 9 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 2 / 39 (5.13%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 2 | 1 |
| Paronychia | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 9 / 39 (23.08%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 11 | 0 |
| Pharyngitis | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 39 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 0 | 1 |
| Rhinitis | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 2 / 39 (5.13%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Tinea capitis | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 39 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |

| | | | |
|---|---|---|---|
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 39 (2.56%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 39 (2.56%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Viral infection | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 39 (2.56%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 1 | 1 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 3 / 8 (37.50%) | 7 / 39 (17.95%) | 1 / 9 (11.11%) |
| occurrences (all) | 3 | 7 | 1 |
| Dehydration | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 39 (2.56%) | 2 / 9 (22.22%) |
| occurrences (all) | 0 | 1 | 2 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 2 / 39 (5.13%) | 1 / 9 (11.11%) |
| occurrences (all) | 1 | 2 | 1 |
| Hyperkalaemia | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 39 (2.56%) | 0 / 9 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Hypermagnesaemia | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 39 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hypernatraemia | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 39 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 1 | 0 | 2 |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 39 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 1 | 0 | 1 |
| Hypocalcaemia | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 39 (2.56%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 1 | 2 |
| Hypoglycaemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 8 (25.00%) | 0 / 39 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 3 / 39 (7.69%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 5 | 4 |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 39 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 0 | 3 |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 4 / 39 (10.26%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 6 | 3 |
| Hypophosphataemia | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 3 / 39 (7.69%) | 1 / 9 (11.11%) |
| occurrences (all) | 2 | 4 | 2 |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 04 May 2015 | Addition of optional cerebrospinal fluid PK sampling: Assess afatinib penetration into the cerebrospinal fluid /<br>Implemented only after approval of the IRB/IEC/<br>Competent Authorities.<br>Addition of details on handling of<br>strong P-gp inhibitors/ inducers: Assure that MTD determination was not affected by the<br>use of strong P-gp inhibitors or inducers /<br>Implemented without IRB/IEC/Competent Authority<br>approval as changes involved logistical or<br>administrative aspects only. |
| 18 August 2016 | Clarifications, e.g. regarding the<br>possible use of a pre-screening<br>informed consent for the<br>collection and testing of tumour<br>tissue sample and collection of<br>tumour images during the<br>screening period. |
| 02 June 2017 | Change from Phase I trial to<br>adaptive Phase I/II design,<br>clarification of pre-screening<br>informed consent use and<br>alternative PK samplings. To comply with the Written Request received from FDA and to follow the contraception guidance per ICH<br>M3 (R2)2 and HMA CTFG /<br>Implemented only after approval of the IRB/IEC/<br>Competent Authorities |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported