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	v1
This version publication date	22 February 2021
First version publication date	22 February 2021

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) 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			
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) This patient set included all patients enrolled in the trial who were documented to have taken at least one dose of study medication.			
Units: Age			
arithmetic mean	9.75	10.44	10.92
standard deviation	± 4.83	± 5.29	± 4.44
Sex: Female, Male			
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.			
Units: Participants			
Female	4	4	16
Male	4	5	23
Ethnicity (NIH/OMB)			
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.			
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) 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) 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			
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) This patient set included all patients enrolled in the trial who were documented to have taken at least one dose of study medication.			
Units: Age			
arithmetic mean			
standard deviation	-		
Sex: Female, Male			
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.			
Units: Participants			
Female	24		
Male	32		
Ethnicity (NIH/OMB)			
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.			
Units: Subjects			
Hispanic or Latino	0		
Not Hispanic or Latino	46		
Unknown or Not Reported	10		
Race (NIH/OMB)			
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.			
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 (AUCτ, ss) - Dose finding part

End point title	Area under the curve over dosing interval τ at steady state (AUCτ, ss) - Dose finding part[1][2]

End point description:

Area under the curve over dosing interval τ at steady state (AUCτ,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: This endpoint was evaluated only descriptively. Thus, no statistical hypothesis were tested.

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 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 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 cohort - 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	0	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 cohort - 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
Lethargy			
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
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
Hypophosphataemia			
subjects affected / exposed	1 / 8 (12.50%)	3 / 39 (7.69%)	1 / 9 (11.11%)
occurrences (all)	2	4	2
Hyponatraemia			
subjects affected / exposed	0 / 8 (0.00%)	4 / 39 (10.26%)	1 / 9 (11.11%)
occurrences (all)	0	6	3

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

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported