



Clinical trial results:

A phase II, open-label, single-arm, non-randomized, multi-center study to evaluate the efficacy of oral TKI258 as second-line therapy in patients with either FGFR2 mutated or wild-type advanced and/or metastatic endometrial cancer

Summary

EudraCT number	2011-000266-35
Trial protocol	IT ES GB
Global end of trial date	26 March 2014

Results information

Result version number	v1 (current)
This version publication date	13 July 2016
First version publication date	30 July 2015

Trial information

Trial identification

Sponsor protocol code	CTKI258A2211
-----------------------	--------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01379534
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111 ,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111 ,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	26 March 2014
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	26 March 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess the antitumor activity of TKI258, as measured by an 18-week progression free survival (PFS) rate, in patients with pre-treated endometrial cancer, with or without FGFR2 mutation.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial

In addition to receiving the study treatment, all patients were to receive best supportive care (BSC, define as; drug or non-drug therapies, nutritional support, physical therapy, or any other treatment alternative that the Investigator believes to be in the patient's best interest, but excluding other antineoplastic treatments) as per standard local practice for the treatment of pre-existing medical conditions or AEs that could arise during the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 November 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Italy: 8
Country: Number of subjects enrolled	United States: 33
Country: Number of subjects enrolled	New Zealand: 3
Country: Number of subjects enrolled	Brazil: 1
Worldwide total number of subjects	53
EEA total number of subjects	16

Notes:

Subjects enrolled per age group

In utero	0
----------	---

Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	24
From 65 to 84 years	29
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were treated with TKI258 until disease progression, unacceptable toxicity, death or discontinuation due to any other reason. All participants were followed for at least 30 days after their last dose of study drug for safety assessment. The treatment and followup periods were combined for patient disposition (listing 16.2.1-1.1).

Pre-assignment

Screening details:

Either archival tumor tissue or a fresh fixed biopsy was required for the FGFR2 mutation analysis. Only the FGFR2 mutation analysis results during a molecular pre-screening period were used to classify patients into Group 1 (FGFR2 mutated - MUT) or Group 2 (FGFR2 wild type - WT) and if could not be determined, patient was a screen failure.

Period 1

Period 1 title	Treatment/Tumor Followup Phases (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	FGFR2 (MUT)

Arm description:

Participants were diagnosed with mutational status of FGFR2 as mutated and treated with 500 mg of TKI258 on a 5 day on / 2 days off dosing regimen for 13 weeks.

Arm type	Mutational status of FGFR2
Investigational medicinal product name	Dovitinib
Investigational medicinal product code	TKI258
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Dovitinib was dosed on a flat scale of 500 mg (i.e., five 100 mg tablets), administered orally on a 5 days on / 2 days off schedule which was repeated every week (i.e., every 7 days). Patients were instructed to swallow the required number of tablets at approximately the same time each day, except on the days of PK sampling.

- Dovitinib could be ingested with or without food, including days on which blood samples were drawn for PK analyses.
- On the days of PK sampling, patients were instructed to bring their dose of dovitinib to the Investigative site whereby the administration of dovitinib was supervised by the site's study personnel. For patients who were unable to tolerate the protocol-specified dosing scheme, dose reductions or delays were permitted to manage dovitinib-related toxicities.

Arm title	FGFR2 (WT)
------------------	------------

Arm description:

Participants were diagnosed with mutational status of FGFR2 as wild type and treated with 500 mg of TKI258 on a 5 day on / 2 days off dosing regimen for 13 weeks.

Arm type	tumor type
Investigational medicinal product name	Dovitinib
Investigational medicinal product code	TKI258
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Dovitinib was dosed on a flat scale of 500 mg (i.e., five 100 mg tablets), administered orally on a 5 days on / 2 days off schedule which was repeated every week (i.e., every 7 days). Patients were instructed to swallow the required number of tablets at approximately the same time each day, except on the days of PK sampling.

- Dovitinib could be ingested with or without food, including days on which blood samples were drawn for PK analyses.
- On the days of PK sampling, patients were instructed to bring their dose of dovitinib to the Investigative site whereby the administration of dovitinib was supervised by the site's study personnel. For patients who were unable to tolerate the protocol-specified dosing scheme, dose reductions or delays were permitted to manage dovitinib-related toxicities.

Number of subjects in period 1	FGFR2 (MUT)	FGFR2 (WT)
Started	22	31
Completed	0	0
Not completed	22	31
Adverse event, serious fatal	-	1
Consent withdrawn by subject	2	2
Adverse event, non-fatal	4	5
Lost to follow-up	-	1
Lack of efficacy	16	22

Baseline characteristics

Reporting groups

Reporting group title	FGFR2 (MUT)
-----------------------	-------------

Reporting group description:

Participants were diagnosed with mutational status of FGFR2 as mutated and treated with 500 mg of TKI258on a 5 day on / 2 days off dosing regimen for 13 weeks.

Reporting group title	FGFR2 (WT)
-----------------------	------------

Reporting group description:

Participants were diagnosed with mutational status of FGFR2 as wild type and treated with 500 mg of TKI258on a 5 day on / 2 days off dosing regimen for 13 weeks.

Reporting group values	FGFR2 (MUT)	FGFR2 (WT)	Total
Number of subjects	22	31	53
Age categorical			
Units: Subjects			
Adults (18-64 years)	11	13	24
From 65-84 years	11	18	29
Gender categorical			
Units: Subjects			
Female	22	31	53

End points

End points reporting groups

Reporting group title	FGFR2 (MUT)
Reporting group description: Participants were diagnosed with mutational status of FGFR2 as mutated and treated with 500 mg of TKI258on a 5 day on / 2 days off dosing regimen for 13 weeks.	
Reporting group title	FGFR2 (WT)
Reporting group description: Participants were diagnosed with mutational status of FGFR2 as wild type and treated with 500 mg of TKI258on a 5 day on / 2 days off dosing regimen for 13 weeks.	

Primary: Progression Free Survival (PFS) Rate

End point title	Progression Free Survival (PFS) Rate ^[1]
End point description: The 18-week PFS was defined as the percentage of participants who did not have a progression event at week 18. Participants who progressed, died, had response assessment of unknown (UNK) or discontinued before 18 weeks of observation without progression were counted as "failure". Progressive disease was assessed as per investigator assessment using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.	
End point type	Primary
End point timeframe: Up to 18 weeks	

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: The study met the futility boundary for both study groups. The 18-week PFS rate was calculated from the investigator's assessment according to RECIST v1.1 and its posterior distribution using the PAS. Treatment effect was to be concluded if the observed 18-week PFS rate was $\geq 50\%$ and there was ≥ 0.95 probability that the 18-week PFS rate was $> 20\%$, i.e. the chance that the 18-week PFS rate was $\leq 20\%$ was less than 0.05. Kaplan-Meier method was used with its 95% confidence interval.

End point values	FGFR2 (MUT)	FGFR2 (WT)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	31		
Units: Percentage of Participants				
number (confidence interval 95%)				
Percentage of Participants(Progression Free Rate)	31.8 (13.9 to 54.9)	29 (14.2 to 48)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate (ORR)

End point title	Overall Response Rate (ORR)
End point description: ORR is defined as the percentage of participants with a best overall response of complete response (CR)	

or partial response (PR).

End point type	Secondary
End point timeframe:	
Baseline and every 6 weeks until disease progression, up to 18 weeks	

End point values	FGFR2 (MUT)	FGFR2 (WT)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	31		
Units: Percentage of Participants				
number (confidence interval 95%)	4.5 (0.1 to 22.8)	16.1 (5.5 to 33.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR)

End point title	Disease Control Rate (DCR)
End point description:	
DCR was defined as the percentage of participants with a best overall response of CR or PR or stable disease (SD).	
End point type	Secondary
End point timeframe:	
Baseline and every 6 weeks until disease progression, up to 18 weeks	

End point values	FGFR2 (MUT)	FGFR2 (WT)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	31		
Units: Percentage of Participants				
number (confidence interval 95%)	63.6 (40.7 to 82.8)	51.6 (33.1 to 69.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DR)

End point title	Duration of Response (DR)
End point description:	
This outcome measure was not analyzed. The analysis was not required because there were too few responders.	

End point type	Secondary
End point timeframe:	
up to 18 weeks	

End point values	FGFR2 (MUT)	FGFR2 (WT)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[2]	0 ^[3]		
Units: Time to Event				
arithmetic mean (confidence interval 95%)	(to)	(to)		

Notes:

[2] - The analysis was not required because there were too few responders.

[3] - The analysis was not required because there were too few responders.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)
End point description:	
OS was defined as the time from date of treatment to the date of death from any cause. If a participant was not known to have died at the date of analysis cut-off, the OS was censored at the last date of contact. Full Analysis Set (FAS): The FAS included all participants who received at least one dose of study medication.	
End point type	Secondary
End point timeframe:	
Up to 18 weeks	

End point values	FGFR2 (MUT)	FGFR2 (WT)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	31		
Units: Months				
median (confidence interval 95%)	20.2 (8.2 to 20.2)	9.3 (6 to 15.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)
End point description:	
PFS was defined as the time from the date of start of treatment to the date of the first documented progression or death due to any cause. If a participant did not have an event, PFS was censored at the	

date of last adequate response assessment before the data analysis cut-off date or the start date of new antineoplastic therapy after study drug discontinuation.

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

End point timeframe:

Up to 18 weeks

End point values	FGFR2 (MUT)	FGFR2 (WT)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	31		
Units: Months				
median (confidence interval 95%)	4.1 (2.6 to 5.5)	2.7 (1.4 to 6.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Adverse Events, Serious Adverse Events and Deaths

End point title	Number of Participants With Adverse Events, Serious Adverse Events and Deaths
-----------------	---

End point description:

Adverse event monitoring was conducted throughout the study.

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

End point timeframe:

up to 30 days after the last dose of study drug, up to 18 weeks

End point values	FGFR2 (MUT)	FGFR2 (WT)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	31		
Units: Participants				
Adverse Events (serious and non-serious)	22	31		
Serious adverse events	10	20		
Deaths	1	4		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse events are reported in this record from First Patient First Treatment until Last Patient Last Visit.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

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

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	FGFR2 WT
-----------------------	----------

Reporting group description:

Participants diagnosed with FGFR2 as wild type were dosed with TKI258 on a flat scale of 500mg administered orally on a 5 days on /2 days off schedule which was repeated every week (i.e., every 7 days)

Reporting group title	FGFR2 MUT
-----------------------	-----------

Reporting group description:

Participants with FGFR2 as mutated were treated with 500 mg of TKI258 orally on a 5 day on/2 days off dosing regimen which was repeated every week (i.e., every 7 days)

Serious adverse events	FGFR2 WT	FGFR2 MUT	
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 31 (64.52%)	10 / 22 (45.45%)	
number of deaths (all causes)	4	1	
number of deaths resulting from adverse events	1	0	
Vascular disorders			
DEEP VEIN THROMBOSIS			
subjects affected / exposed	0 / 31 (0.00%)	2 / 22 (9.09%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
EMBOLISM			
subjects affected / exposed	2 / 31 (6.45%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOTENSION			

subjects affected / exposed	2 / 31 (6.45%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERTENSION			
subjects affected / exposed	2 / 31 (6.45%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ORTHOSTATIC HYPOTENSION			
subjects affected / exposed	1 / 31 (3.23%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PELVIC VENOUS THROMBOSIS			
subjects affected / exposed	0 / 31 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERIPHERAL ISCHAEMIA			
subjects affected / exposed	0 / 31 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
FATIGUE			
subjects affected / exposed	1 / 31 (3.23%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LOCALISED OEDEMA			
subjects affected / exposed	1 / 31 (3.23%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PYREXIA			
subjects affected / exposed	2 / 31 (6.45%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
OEDEMA PERIPHERAL			

subjects affected / exposed	2 / 31 (6.45%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MALAISE			
subjects affected / exposed	1 / 31 (3.23%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
FEMALE GENITAL TRACT FISTULA			
subjects affected / exposed	2 / 31 (6.45%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VAGINAL HAEMORRHAGE			
subjects affected / exposed	1 / 31 (3.23%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
PLEURAL EFFUSION			
subjects affected / exposed	2 / 31 (6.45%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LUNG INFILTRATION			
subjects affected / exposed	1 / 31 (3.23%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA ASPIRATION			
subjects affected / exposed	1 / 31 (3.23%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY EMBOLISM			
subjects affected / exposed	2 / 31 (6.45%)	3 / 22 (13.64%)	
occurrences causally related to treatment / all	2 / 2	2 / 3	
deaths causally related to treatment / all	1 / 1	0 / 0	

RESPIRATORY FAILURE			
subjects affected / exposed	1 / 31 (3.23%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Investigations			
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	1 / 31 (3.23%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	1 / 31 (3.23%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TRANSAMINASES INCREASED			
subjects affected / exposed	1 / 31 (3.23%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BLOOD BILIRUBIN INCREASED			
subjects affected / exposed	1 / 31 (3.23%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PLATELET COUNT DECREASED			
subjects affected / exposed	1 / 31 (3.23%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
GASTROENTERITIS RADIATION			
subjects affected / exposed	1 / 31 (3.23%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
GASTROINTESTINAL ARTERIOVENOUS MALFORMATION			

subjects affected / exposed	1 / 31 (3.23%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
CARDIAC ARREST			
subjects affected / exposed	1 / 31 (3.23%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Nervous system disorders			
CEREBROVASCULAR ACCIDENT			
subjects affected / exposed	0 / 31 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEADACHE			
subjects affected / exposed	1 / 31 (3.23%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERIPHERAL SENSORY NEUROPATHY			
subjects affected / exposed	1 / 31 (3.23%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SPINAL CORD COMPRESSION			
subjects affected / exposed	1 / 31 (3.23%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SYNCOPE			
subjects affected / exposed	1 / 31 (3.23%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TRANSIENT ISCHAEMIC ATTACK			
subjects affected / exposed	0 / 31 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			

ANAEMIA			
subjects affected / exposed	1 / 31 (3.23%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PANCYTOPENIA			
subjects affected / exposed	1 / 31 (3.23%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	2 / 31 (6.45%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
ABDOMINAL PAIN UPPER			
subjects affected / exposed	0 / 31 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COLITIS ISCHAEMIC			
subjects affected / exposed	1 / 31 (3.23%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIARRHOEA			
subjects affected / exposed	3 / 31 (9.68%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	2 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LOWER GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	1 / 31 (3.23%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DYSPHAGIA			
subjects affected / exposed	1 / 31 (3.23%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

NAUSEA			
subjects affected / exposed	2 / 31 (6.45%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PANCREATIC DUCT DILATATION			
subjects affected / exposed	1 / 31 (3.23%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SMALL INTESTINAL OBSTRUCTION			
subjects affected / exposed	3 / 31 (9.68%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VOMITING			
subjects affected / exposed	5 / 31 (16.13%)	2 / 22 (9.09%)	
occurrences causally related to treatment / all	2 / 6	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
HEPATITIS TOXIC			
subjects affected / exposed	0 / 31 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
JAUNDICE			
subjects affected / exposed	0 / 31 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
ERYTHEMA MULTIFORME			
subjects affected / exposed	1 / 31 (3.23%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
HYDRONEPHROSIS			

subjects affected / exposed	0 / 31 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RENAL FAILURE			
subjects affected / exposed	1 / 31 (3.23%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY TRACT OBSTRUCTION			
subjects affected / exposed	1 / 31 (3.23%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RENAL FAILURE ACUTE			
subjects affected / exposed	2 / 31 (6.45%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
UROGENITAL FISTULA			
subjects affected / exposed	1 / 31 (3.23%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
GROIN PAIN			
subjects affected / exposed	0 / 31 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PAIN IN EXTREMITY			
subjects affected / exposed	0 / 31 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
SEPSIS			
subjects affected / exposed	1 / 31 (3.23%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

URINARY TRACT INFECTION			
subjects affected / exposed	2 / 31 (6.45%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
UROSEPSIS			
subjects affected / exposed	0 / 31 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	1 / 31 (3.23%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEHYDRATION			
subjects affected / exposed	3 / 31 (9.68%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	2 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOVOLAEMIA			
subjects affected / exposed	0 / 31 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPONATRAEMIA			
subjects affected / exposed	1 / 31 (3.23%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOKALAEMIA			
subjects affected / exposed	1 / 31 (3.23%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	FGFR2 WT	FGFR2 MUT	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	31 / 31 (100.00%)	21 / 22 (95.45%)	
Vascular disorders			
DEEP VEIN THROMBOSIS			
subjects affected / exposed	2 / 31 (6.45%)	1 / 22 (4.55%)	
occurrences (all)	2	1	
EMBOLISM			
subjects affected / exposed	1 / 31 (3.23%)	2 / 22 (9.09%)	
occurrences (all)	1	2	
HYPERTENSION			
subjects affected / exposed	8 / 31 (25.81%)	4 / 22 (18.18%)	
occurrences (all)	17	8	
HYPOTENSION			
subjects affected / exposed	2 / 31 (6.45%)	2 / 22 (9.09%)	
occurrences (all)	3	2	
General disorders and administration site conditions			
FATIGUE			
subjects affected / exposed	16 / 31 (51.61%)	9 / 22 (40.91%)	
occurrences (all)	19	10	
ASTHENIA			
subjects affected / exposed	5 / 31 (16.13%)	4 / 22 (18.18%)	
occurrences (all)	5	5	
LOCAL SWELLING			
subjects affected / exposed	0 / 31 (0.00%)	2 / 22 (9.09%)	
occurrences (all)	0	2	
OEDEMA PERIPHERAL			
subjects affected / exposed	4 / 31 (12.90%)	2 / 22 (9.09%)	
occurrences (all)	6	3	
PAIN			
subjects affected / exposed	6 / 31 (19.35%)	0 / 22 (0.00%)	
occurrences (all)	7	0	
Reproductive system and breast disorders			
VAGINAL HAEMORRHAGE			
subjects affected / exposed	1 / 31 (3.23%)	3 / 22 (13.64%)	
occurrences (all)	1	3	

VAGINAL DISCHARGE subjects affected / exposed occurrences (all)	2 / 31 (6.45%) 2	1 / 22 (4.55%) 1	
Respiratory, thoracic and mediastinal disorders			
COUGH subjects affected / exposed occurrences (all)	6 / 31 (19.35%) 6	2 / 22 (9.09%) 3	
EPISTAXIS subjects affected / exposed occurrences (all)	3 / 31 (9.68%) 3	0 / 22 (0.00%) 0	
DYSPNOEA subjects affected / exposed occurrences (all)	7 / 31 (22.58%) 8	2 / 22 (9.09%) 2	
PLEURITIC PAIN subjects affected / exposed occurrences (all)	2 / 31 (6.45%) 2	0 / 22 (0.00%) 0	
OROPHARYNGEAL PAIN subjects affected / exposed occurrences (all)	2 / 31 (6.45%) 2	0 / 22 (0.00%) 0	
Psychiatric disorders			
ANXIETY subjects affected / exposed occurrences (all)	2 / 31 (6.45%) 2	0 / 22 (0.00%) 0	
INSOMNIA subjects affected / exposed occurrences (all)	2 / 31 (6.45%) 2	2 / 22 (9.09%) 2	
Investigations			
AMYLASE INCREASED subjects affected / exposed occurrences (all)	2 / 31 (6.45%) 2	0 / 22 (0.00%) 0	
ALANINE AMINOTRANSFERASE INCREASED subjects affected / exposed occurrences (all)	3 / 31 (9.68%) 4	4 / 22 (18.18%) 5	
ASPARTATE AMINOTRANSFERASE INCREASED			

subjects affected / exposed	2 / 31 (6.45%)	3 / 22 (13.64%)	
occurrences (all)	3	4	
BLOOD ALKALINE PHOSPHATASE INCREASED			
subjects affected / exposed	8 / 31 (25.81%)	3 / 22 (13.64%)	
occurrences (all)	10	4	
BLOOD BILIRUBIN INCREASED			
subjects affected / exposed	0 / 31 (0.00%)	2 / 22 (9.09%)	
occurrences (all)	0	2	
BLOOD CHOLESTEROL INCREASED			
subjects affected / exposed	3 / 31 (9.68%)	1 / 22 (4.55%)	
occurrences (all)	3	1	
BLOOD CREATININE INCREASED			
subjects affected / exposed	4 / 31 (12.90%)	3 / 22 (13.64%)	
occurrences (all)	5	3	
GAMMA-GLUTAMYLTRANSFERASE INCREASED			
subjects affected / exposed	2 / 31 (6.45%)	2 / 22 (9.09%)	
occurrences (all)	2	2	
LIPASE INCREASED			
subjects affected / exposed	2 / 31 (6.45%)	2 / 22 (9.09%)	
occurrences (all)	2	5	
LYMPHOCYTE COUNT DECREASED			
subjects affected / exposed	2 / 31 (6.45%)	1 / 22 (4.55%)	
occurrences (all)	3	3	
PLATELET COUNT DECREASED			
subjects affected / exposed	2 / 31 (6.45%)	1 / 22 (4.55%)	
occurrences (all)	2	1	
WEIGHT DECREASED			
subjects affected / exposed	5 / 31 (16.13%)	7 / 22 (31.82%)	
occurrences (all)	7	8	
Injury, poisoning and procedural complications			
CONTUSION			
subjects affected / exposed	2 / 31 (6.45%)	0 / 22 (0.00%)	
occurrences (all)	2	0	
FALL			

subjects affected / exposed occurrences (all)	2 / 31 (6.45%) 2	0 / 22 (0.00%) 0	
Nervous system disorders			
DIZZINESS			
subjects affected / exposed occurrences (all)	7 / 31 (22.58%) 9	3 / 22 (13.64%) 4	
PARAESTHESIA			
subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0	2 / 22 (9.09%) 3	
HEADACHE			
subjects affected / exposed occurrences (all)	6 / 31 (19.35%) 7	5 / 22 (22.73%) 5	
DYSGEUSIA			
subjects affected / exposed occurrences (all)	2 / 31 (6.45%) 2	2 / 22 (9.09%) 2	
SOMNOLENCE			
subjects affected / exposed occurrences (all)	2 / 31 (6.45%) 2	0 / 22 (0.00%) 0	
Blood and lymphatic system disorders			
LYMPHOPENIA			
subjects affected / exposed occurrences (all)	3 / 31 (9.68%) 4	1 / 22 (4.55%) 1	
ANAEMIA			
subjects affected / exposed occurrences (all)	10 / 31 (32.26%) 16	3 / 22 (13.64%) 5	
LEUKOPENIA			
subjects affected / exposed occurrences (all)	2 / 31 (6.45%) 3	0 / 22 (0.00%) 0	
NEUTROPENIA			
subjects affected / exposed occurrences (all)	2 / 31 (6.45%) 2	1 / 22 (4.55%) 3	
THROMBOCYTOPENIA			
subjects affected / exposed occurrences (all)	4 / 31 (12.90%) 5	0 / 22 (0.00%) 0	
Ear and labyrinth disorders			

TINNITUS			
subjects affected / exposed	2 / 31 (6.45%)	0 / 22 (0.00%)	
occurrences (all)	2	0	
Eye disorders			
EYE DISCHARGE			
subjects affected / exposed	2 / 31 (6.45%)	0 / 22 (0.00%)	
occurrences (all)	2	0	
DRY EYE			
subjects affected / exposed	4 / 31 (12.90%)	2 / 22 (9.09%)	
occurrences (all)	4	2	
OCULAR HYPERAEMIA			
subjects affected / exposed	3 / 31 (9.68%)	0 / 22 (0.00%)	
occurrences (all)	3	0	
VISION BLURRED			
subjects affected / exposed	2 / 31 (6.45%)	0 / 22 (0.00%)	
occurrences (all)	2	0	
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	6 / 31 (19.35%)	5 / 22 (22.73%)	
occurrences (all)	7	5	
ABDOMINAL PAIN LOWER			
subjects affected / exposed	2 / 31 (6.45%)	1 / 22 (4.55%)	
occurrences (all)	2	1	
ABDOMINAL PAIN UPPER			
subjects affected / exposed	2 / 31 (6.45%)	0 / 22 (0.00%)	
occurrences (all)	3	0	
CONSTIPATION			
subjects affected / exposed	6 / 31 (19.35%)	4 / 22 (18.18%)	
occurrences (all)	9	5	
DRY MOUTH			
subjects affected / exposed	3 / 31 (9.68%)	3 / 22 (13.64%)	
occurrences (all)	3	4	
DIARRHOEA			
subjects affected / exposed	24 / 31 (77.42%)	14 / 22 (63.64%)	
occurrences (all)	48	24	
DYSPEPSIA			

subjects affected / exposed	5 / 31 (16.13%)	4 / 22 (18.18%)	
occurrences (all)	7	4	
GASTROESOPHAGEAL REFLUX DISEASE			
subjects affected / exposed	2 / 31 (6.45%)	1 / 22 (4.55%)	
occurrences (all)	2	1	
FLATULENCE			
subjects affected / exposed	4 / 31 (12.90%)	2 / 22 (9.09%)	
occurrences (all)	4	2	
NAUSEA			
subjects affected / exposed	21 / 31 (67.74%)	16 / 22 (72.73%)	
occurrences (all)	28	19	
VOMITING			
subjects affected / exposed	21 / 31 (67.74%)	14 / 22 (63.64%)	
occurrences (all)	32	31	
STOMATITIS			
subjects affected / exposed	2 / 31 (6.45%)	1 / 22 (4.55%)	
occurrences (all)	2	1	
Skin and subcutaneous tissue disorders			
DERMATITIS ACNEIFORM			
subjects affected / exposed	2 / 31 (6.45%)	1 / 22 (4.55%)	
occurrences (all)	2	1	
RASH MACULO-PAPULAR			
subjects affected / exposed	0 / 31 (0.00%)	2 / 22 (9.09%)	
occurrences (all)	0	3	
RASH			
subjects affected / exposed	11 / 31 (35.48%)	9 / 22 (40.91%)	
occurrences (all)	12	9	
PRURITUS			
subjects affected / exposed	3 / 31 (9.68%)	4 / 22 (18.18%)	
occurrences (all)	3	4	
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME			
subjects affected / exposed	1 / 31 (3.23%)	2 / 22 (9.09%)	
occurrences (all)	1	2	
Renal and urinary disorders			

DYSURIA			
subjects affected / exposed	4 / 31 (12.90%)	0 / 22 (0.00%)	
occurrences (all)	4	0	
PROTEINURIA			
subjects affected / exposed	3 / 31 (9.68%)	1 / 22 (4.55%)	
occurrences (all)	5	3	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	2 / 31 (6.45%)	1 / 22 (4.55%)	
occurrences (all)	2	1	
BACK PAIN			
subjects affected / exposed	2 / 31 (6.45%)	6 / 22 (27.27%)	
occurrences (all)	2	6	
BONE PAIN			
subjects affected / exposed	2 / 31 (6.45%)	0 / 22 (0.00%)	
occurrences (all)	2	0	
MUSCLE SPASMS			
subjects affected / exposed	3 / 31 (9.68%)	1 / 22 (4.55%)	
occurrences (all)	4	3	
PAIN IN EXTREMITY			
subjects affected / exposed	9 / 31 (29.03%)	6 / 22 (27.27%)	
occurrences (all)	9	8	
MYALGIA			
subjects affected / exposed	2 / 31 (6.45%)	2 / 22 (9.09%)	
occurrences (all)	2	3	
MUSCULOSKELETAL PAIN			
subjects affected / exposed	3 / 31 (9.68%)	0 / 22 (0.00%)	
occurrences (all)	3	0	
MUSCULAR WEAKNESS			
subjects affected / exposed	2 / 31 (6.45%)	0 / 22 (0.00%)	
occurrences (all)	2	0	
Infections and infestations			
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	2 / 31 (6.45%)	0 / 22 (0.00%)	
occurrences (all)	4	0	
URINARY TRACT INFECTION			

subjects affected / exposed occurrences (all)	3 / 31 (9.68%) 5	3 / 22 (13.64%) 3	
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	9 / 31 (29.03%)	9 / 22 (40.91%)	
occurrences (all)	10	10	
DEHYDRATION			
subjects affected / exposed	5 / 31 (16.13%)	1 / 22 (4.55%)	
occurrences (all)	8	1	
HYPERCHOLESTEROLAEMIA			
subjects affected / exposed	4 / 31 (12.90%)	1 / 22 (4.55%)	
occurrences (all)	4	1	
HYPERGLYCAEMIA			
subjects affected / exposed	5 / 31 (16.13%)	2 / 22 (9.09%)	
occurrences (all)	8	2	
HYPOALBUMINAEMIA			
subjects affected / exposed	5 / 31 (16.13%)	1 / 22 (4.55%)	
occurrences (all)	8	1	
HYPERTRIGLYCERIDAEMIA			
subjects affected / exposed	9 / 31 (29.03%)	2 / 22 (9.09%)	
occurrences (all)	10	8	
HYPOCALCAEMIA			
subjects affected / exposed	4 / 31 (12.90%)	0 / 22 (0.00%)	
occurrences (all)	5	0	
HYPOMAGNESAEMIA			
subjects affected / exposed	6 / 31 (19.35%)	4 / 22 (18.18%)	
occurrences (all)	7	5	
HYPONATRAEMIA			
subjects affected / exposed	5 / 31 (16.13%)	1 / 22 (4.55%)	
occurrences (all)	6	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 October 2011	The protocol was amended to remove the exploratory analysis of plasma biomarkers FGF23 and FGF19 from this study. The scientific rationale for removing these plasma biomarkers was that sufficient samples were collected in the phase I and phase II studies, and indirect proof of FGFR1 inhibition by dovitinib (increase in plasma FGF23) was obtained in clinical trials.
01 July 2012	The primary purpose of this protocol amendment was to allow dovitinib to be administered with or without food. New clinical data had shown no clinically relevant food-effect on the exposure of dovitinib.
08 November 2013	The primary purpose of this protocol amendment was to update the clinical PK and concomitant medications sections of the protocol based on preliminary PK findings from CTXI258A2119, a drug-drug interaction study which assessed the effect of dovitinib on the PK of caffeine, diclofenac, omeprazole, and midazolam.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

The study met the protocol defined futility boundary for both the FGFR2 mutated and FGFR2 wild-type groups at the interim analysis as defined by the protocol and did not continue to Stage 2.
--

Notes: