Clinical trial results:
An open label, multi-center, extension study to evaluate long-term safety and tolerability of dovitinib in patients with solid tumors, who continue to receive treatment with dovitinib (TKI258) in Novartis-sponsored, single agent dovitinib studies, which have fulfilled the requirements for the primary objective, and are benefitting from continued dovitinib treatment as assessed by the investigator

Summary

EudraCT number	2014-000368-17
Trial protocol	IT ES DK NL AT BE
Global end of trial date	28 November 2016

Results information

Result version number	v1 (current)
This version publication date	02 November 2017
First version publication date	02 November 2017

Trial information

Trial identification

Sponsor protocol code	CTKI258A2X01B

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02116803
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	28 November 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 November 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate long-term safety and tolerability of dovitinib in patients with solid tumors, who are currently receiving treatment with single agent dovitinib within a Novartis sponsored study which has fulfilled the requirements for the primary objective

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.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 May 2014
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: 1
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Denmark: 3
Country: Number of subjects enrolled	Italy: 3
Country: Number of subjects enrolled	Japan: 1
Country: Number of subjects enrolled	United States: 2
Worldwide total number of subjects	12
EEA total number of subjects	9

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	7
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 12 patients were rolled over from parent studies and randomized by the time of study completion; 10 patients to dovitinib treatment group and 2 patients to dovitinib plus fulvestrant treatment arm.

Pre-assignment

Screening details:

There was no screening period for this study. Once consented, patients were evaluated for eligibility via the inclusion and exclusion criteria and immediately began study treatment.

Period 1

Period 1 title	Core Period (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Dovitinib

Arm description:

Participants were given single agent dovitinib starting with last assigned dose and regimen which patient received in parent study. Additional dose modifications were given at the discretion of the investigator based on guidance provided in the protocol and investigative brochure (IB).

Arm type	Experimental
Investigational medicinal product name	dovitinib
Investigational medicinal product code	TKI258
Other name	
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:

Capsules of 100 mg strength, and tablets of 100 mg strength and taken orally.

Arm title	dovitinib + fulvestrant

Arm description:

Participants were given dovitinib and fulvestrant coadministration starting with last assigned dose and regimen which patient received in parent study. Additional dose modifications were at the discretion of the investigator based on guidance provided in the protocol and IB.

Arm type	Experimental
Investigational medicinal product name	dovitinib
Investigational medicinal product code	TKI258
Other name	
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:

Capsules of 100 mg strength, and tablets of 100 mg strength and taken orally.

Investigational medicinal product name	fulvestrant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Intravenous use

Dosage and administration details:

Generally available as solution for injection in pre-filled syringes containing 250 mg of fulvestrant in 5

mL solution.

Number of subjects in period 1	Dovitinib	dovitinib + fulvestrant
Started	10	2
Completed	0	0
Not completed	10	2
Adverse event, serious fatal	1	-
Physician decision	1	-
Study terminated by Sponsor	2	1
Adverse event, non-fatal	2	1
Progressive disease	4	-

Baseline characteristics

Reporting groups	
Reporting group title	Dovitinib
Reporting group description:	
Participants were given single agent dovitinib starting with last assigned dose and regimen which patient received in parent study. Additional dose modifications were given at the discretion of the investigator based on guidance provided in the protocol and investigative brochure (IB).	
Reporting group title	dovitinib + fulvestrant
Reporting group description:	
Participants were given dovitinib and fulvestrant coadministration starting with last assigned dose and regimen which patient received in parent study. Additional dose modifications were at the discretion of the investigator based on guidance provided in the protocol and IB.	

Reporting group values	Dovitinib	dovitinib + fulvestrant	Total
Number of subjects	10	2	12
Age categorical 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)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	6	1	7
From 65-84 years	4	1	5
85 years and over	0	0	0
Age continuous Units: years			
median	60.3	72.0	
standard deviation	± 10.55	± 14.14	-
Gender categorical Units: Subjects			
Female	3	2	5
Male	7	0	7

End points

End points reporting groups

Reporting group title	Dovitinib

Reporting group description:

Participants were given single agent dovitinib starting with last assigned dose and regimen which patient received in parent study. Additional dose modifications were given at the discretion of the investigator based on guidance provided in the protocol and investigative brochure (IB).

Reporting group title	dovitinib + fulvestrant

Reporting group description:

Participants were given dovitinib and fulvestrant coadministration starting with last assigned dose and regimen which patient received in parent study. Additional dose modifications were at the discretion of the investigator based on guidance provided in the protocol and IB.

Primary: Severity of adverse events

End point title	Severity of adverse events[1]

End point description:

End point type	Primary

End point timeframe:

Until the last patient discontinued dovitinib up to 30 months

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: No statistical analysis was planned for this endpoint.

End point values	Dovitinib	dovitinib + fulvestrant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	2		
Units: number of subjects				
Any Primary system organ class	6	2		
Blood & lymphatic system disorders	1	0		
Cardiac disorders	2	1		
Ear and Labyrinth disorders	0	0		
Endocrine disorders	0	0		
Eye disorders	0	0		
Gastrointestinal disorders	1	0		
General disorders & administrative site conditions	1	0		
Infections and Infestations	1	0		
Injury, poisoning & procedural complications	0	0		
Investigations	2	0		
Metabolism and nutrition disorders	1	0		
Musculoskeletal & connective tissue disorders	1	0		
Neoplasms benign, malignant & unspecified	0	1		
Nervous system Disorders	0	0		
Psychiatric disorders	0	0		

Respiratory, thoracic & mediastinal disorders	1	0		
Skin and subcutaneous tissue disorders	0	0		
Vascular disorders	0	0		

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 reported in this record are from date of 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	19.1

Reporting groups

Reporting group title	Dovitinib+Fulvestrant

Reporting group description:

Dovitinib+Fulvestrant

Reporting group title	Dovitinib

Reporting group description:

Dovitinib

Serious adverse events	Dovitinib+Fulvestrant	Dovitinib	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 2 (100.00%)	4 / 10 (40.00%)	
number of deaths (all causes)	0	2	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
ADENOCARCINOMA OF COLON			
subjects affected / exposed	1 / 2 (50.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
ACUTE MYOCARDIAL INFARCTION			
subjects affected / exposed	1 / 2 (50.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRADYCARDIA			

subjects affected / exposed	0 / 2 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CORONARY ARTERY DISEASE			
subjects affected / exposed	0 / 2 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MYOCARDIAL ISCHAEMIA			
subjects affected / exposed	0 / 2 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
PLEURAL EFFUSION			
subjects affected / exposed	0 / 2 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
PNEUMOTHORAX			
subjects affected / exposed	0 / 2 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Infections and infestations			
PNEUMONIA			
subjects affected / exposed	0 / 2 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Dovitinib+Fulvestrant	Dovitinib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 2 (100.00%)	9 / 10 (90.00%)	
Vascular disorders			
ORTHOSTATIC HYPOTENSION			

subjects affected / exposed	1 / 2 (50.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	0 / 2 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
FACE OEDEMA			
subjects affected / exposed	0 / 2 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
FATIGUE			
subjects affected / exposed	1 / 2 (50.00%)	2 / 10 (20.00%)	
occurrences (all)	1	2	
OEDEMA PERIPHERAL			
subjects affected / exposed	0 / 2 (0.00%)	2 / 10 (20.00%)	
occurrences (all)	0	2	
PYREXIA			
subjects affected / exposed	0 / 2 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	0 / 2 (0.00%)	2 / 10 (20.00%)	
occurrences (all)	0	2	
DYSPNOEA			
subjects affected / exposed	0 / 2 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
DYSPNOEA EXERTIONAL			
subjects affected / exposed	0 / 2 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
PRODUCTIVE COUGH			
subjects affected / exposed	0 / 2 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Psychiatric disorders			
INSOMNIA			
subjects affected / exposed	0 / 2 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
RESTLESSNESS			

subjects affected / exposed	0 / 2 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Investigations			
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	0 / 2 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
BLOOD ALKALINE PHOSPHATASE INCREASED			
subjects affected / exposed	0 / 2 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
BLOOD CREATININE INCREASED			
subjects affected / exposed	0 / 2 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
GAMMA-GLUTAMYLTRANSFERASE INCREASED			
subjects affected / exposed	0 / 2 (0.00%)	2 / 10 (20.00%)	
occurrences (all)	0	2	
INTERNATIONAL NORMALISED RATIO INCREASED			
subjects affected / exposed	0 / 2 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
LYMPHOCYTE COUNT DECREASED			
subjects affected / exposed	0 / 2 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
PLATELET COUNT DECREASED			
subjects affected / exposed	0 / 2 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
CONTUSION			
subjects affected / exposed	0 / 2 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Cardiac disorders			
ANGINA PECTORIS			
subjects affected / exposed	1 / 2 (50.00%)	2 / 10 (20.00%)	
occurrences (all)	1	2	
Nervous system disorders			

HEADACHE			
subjects affected / exposed	0 / 2 (0.00%)	2 / 10 (20.00%)	
occurrences (all)	0	2	
NEURALGIA			
subjects affected / exposed	0 / 2 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	0 / 2 (0.00%)	2 / 10 (20.00%)	
occurrences (all)	0	2	
LEUKOPENIA			
subjects affected / exposed	0 / 2 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
INCREASED TENDENCY TO BRUISE			
subjects affected / exposed	0 / 2 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
NEUTROPENIA			
subjects affected / exposed	0 / 2 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
VERTIGO			
subjects affected / exposed	1 / 2 (50.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
EYE OEDEMA			
subjects affected / exposed	0 / 2 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	0 / 2 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
CONSTIPATION			
subjects affected / exposed	0 / 2 (0.00%)	3 / 10 (30.00%)	
occurrences (all)	0	3	
ABDOMINAL PAIN UPPER			
subjects affected / exposed	1 / 2 (50.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	

DIARRHOEA			
subjects affected / exposed	1 / 2 (50.00%)	3 / 10 (30.00%)	
occurrences (all)	1	3	
DRY MOUTH			
subjects affected / exposed	0 / 2 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
DYSPEPSIA			
subjects affected / exposed	0 / 2 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
GASTROOESOPHAGEAL REFLUX DISEASE			
subjects affected / exposed	0 / 2 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
NAUSEA			
subjects affected / exposed	1 / 2 (50.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Skin and subcutaneous tissue disorders			
PRURITUS			
subjects affected / exposed	0 / 2 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
SEBACEOUS GLAND DISORDER			
subjects affected / exposed	1 / 2 (50.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
RASH			
subjects affected / exposed	0 / 2 (0.00%)	3 / 10 (30.00%)	
occurrences (all)	0	3	
SKIN LESION			
subjects affected / exposed	0 / 2 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Endocrine disorders			
HYPOTHYROIDISM			
subjects affected / exposed	0 / 2 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	0 / 2 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	

ARTHRITIS			
subjects affected / exposed	0 / 2 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
MUSCLE SPASMS			
subjects affected / exposed	1 / 2 (50.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
MUSCULOSKELETAL PAIN			
subjects affected / exposed	0 / 2 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
PAIN IN EXTREMITY			
subjects affected / exposed	0 / 2 (0.00%)	3 / 10 (30.00%)	
occurrences (all)	0	3	
Infections and infestations			
BRONCHITIS			
subjects affected / exposed	1 / 2 (50.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
HERPES ZOSTER			
subjects affected / exposed	0 / 2 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
INFLUENZA			
subjects affected / exposed	0 / 2 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
NASOPHARYNGITIS			
subjects affected / exposed	0 / 2 (0.00%)	2 / 10 (20.00%)	
occurrences (all)	0	2	
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	0 / 2 (0.00%)	5 / 10 (50.00%)	
occurrences (all)	0	5	
HYPERKALAEMIA			
subjects affected / exposed	0 / 2 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
HYPERTRIGLYCERIDAEMIA			
subjects affected / exposed	0 / 2 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
HYPOCALCAEMIA			

subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	1 / 10 (10.00%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 October 2013	Amendment 1 allowed the enrollment of patients who were currently receiving dovitinib in combination with fulvestrant.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported