Clinical trial results:
DOVIGIST: Phase II trial to evaluate the efficacy and safety of Dovitinib (TKI258) in patients with gastrointestinal stromal tumors refractory and/or intolerant to imatinib.

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.novfor complete trial results.

Summary

EudraCT number	2011-001725-24
Trial protocol	BE ES FI IT DE
Global end of trial date	31 July 2014

Results information

Result version number	v1 (current)
This version publication date	07 July 2018
First version publication date	07 July 2018

Trial information

Trial identification

Sponsor protocol code	CTKI258AIC02

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01478373
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	31 July 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 July 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the antitumor activity of dovitinib in terms of disease control rate (DCR): Complete Response (CR) + Partial Response (PR) + Stable Disease (SD), at 12 weeks in patients with documented disease progression while on therapy with imatinib for unresectable and/or metastatic gastrointestinal stromal tumors (GIST), recurrent GIST on adjuvant imatinib or within the first 3 months after discontinuation of adjuvant imatinib and/ or, unresectable and/or metastatic GIST intolerant to imatinib.

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	31 January 2012
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: 11
Country: Number of subjects enrolled	France: 16
Country: Number of subjects enrolled	Italy: 11
Country: Number of subjects enrolled	Germany: 1
Worldwide total number of subjects	39
EEA total number of subjects	39

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)	26
From 65 to 84 years	13
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

39 Patients enrolled. One patient was a protocol deviation which excluded the patient from the Full Analysis Set.

Period 1

Period 1 title	Treatment Phase
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Dovitinib

Arm description:

Patients received Dovitinib (TKI258) on an outpatient basis at the dose of 500 mg qd for 5 days followed by 2 days off, every week for cycle of 4 weeks (28d) until disease progression, unacceptable toxicity, or consent withdrawal.

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

Dosage and administration details:

Patients received Dovitinib (TKI258) on an outpatient basis at the dose of 500 mg qd for 5 days followed by 2 days off, every week for cycle of 4 weeks (28d) until disease progression, unacceptable toxicity, or consent withdrawal.

Number of subjects in period 1	Dovitinib
Started	39
Completed	38
Not completed	1
Protocol deviation	1

Period 2

Period 2 title	Survival Phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Dovitinib

Arm description:

Patients received Dovitinib (TKI258) on an outpatient basis at the dose of 500 mg qd for 5 days followed by 2 days off, every week for cycle of 4 weeks (28d) until disease progression, unacceptable toxicity, or consent withdrawal.

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

Dosage and administration details:

Patients received Dovitinib (TKI258) on an outpatient basis at the dose of 500 mg qd for 5 days followed by 2 days off, every week for cycle of 4 weeks (28d) until disease progression, unacceptable toxicity, or consent withdrawal.

Number of subjects in period 2	Dovitinib
Started	38
Completed	0
Not completed	38
Adverse event, non-fatal	8
Progressive Disease	27
crossover to another study	2
Protocol deviation	1

Baseline characteristics

Reporting groups	
Reporting group title	Dovitinib
Reporting group description:	
Patients received Dovitinib (TKI258) on an outpatient basis at the dose of 500 mg qd for 5 days followed by 2 days off, every week for cycle of 4 weeks (28d) until disease progression, unacceptable toxicity, or consent withdrawal.	

Reporting group values	Dovitinib	Total	
Number of subjects	39	39	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	26	26	
From 65-84 years	13	13	
85 years and over	0	0	
Age Continuous | Units: Years			
arithmetic mean	59.2		
standard deviation	± 10.14	-	
Gender, Male/Female Units: Participants			
Female	17	17	
Male	22	22	

End points

End points reporting groups

Reporting group title	Dovitinib

Reporting group description:

Patients received Dovitinib (TKI258) on an outpatient basis at the dose of 500 mg qd for 5 days followed by 2 days off, every week for cycle of 4 weeks (28d) until disease progression, unacceptable toxicity, or consent withdrawal.

Reporting group title	Dovitinib

Reporting group description:

Patients received Dovitinib (TKI258) on an outpatient basis at the dose of 500 mg qd for 5 days followed by 2 days off, every week for cycle of 4 weeks (28d) until disease progression, unacceptable toxicity, or consent withdrawal.

Primary: Antitumor activity of Dovitinib in terms of disease control rate (DCR): Complete Response+Partial Response +Stable Disease

End point title	Antitumor activity of Dovitinib in terms of disease control rate (DCR): Complete Response+Partial Response +Stable Disease[1]

End point description:

DCR is defined as the proportion of patients with a best overall response of Complete Responses (CR), Partial Response (PR) and Stable Disease (SD) at 12 weeks according to RECIST (version 1.1).

End point type	Primary

End point timeframe:

12 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: Statistical analysis between treatment groups does not apply as this is a single arm exact binomial single-stage Phase II study.

End point values	Dovitinib			
Subject group type	Reporting group			
Number of subjects analysed	38			
Units: Percentage of Participants				
number (confidence interval)	52.6 (38.2 to 66.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival (PFS) of patients treated with Dovitinib

End point title	Progression-free survival (PFS) of patients treated with Dovitinib

End point description:

The PFS duration: time from entry into the study to the date of the first documented progression (assessed using conventional RECIST (version 1.1) or death due to any cause.

End point type	Secondary

End point timeframe:

9 months

End point values	Dovitinib			
Subject group type	Reporting group			
Number of subjects analysed	38			
Units: Days				
median (confidence interval)	141 (86 to 225)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to treatment failure (TTF)of patients treated with Dovitinib

End point title	Time to treatment failure (TTF)of patients treated with Dovitinib

End point description:

TTF: the date of entry into the study to the earliest date of the first objective tumor progression, date of death due to any cause, or date of discontinuation due to reasons other than 'Protocol deviation' or 'Administrative problems'.

End point type	Secondary

End point timeframe:

9 months

End point values	Dovitinib			
Subject group type	Reporting group			
Number of subjects analysed	38			
Units: Days				
median (confidence interval)	122 (81 to 223)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response or stable disease (SD)

End point title	Duration of response or stable disease (SD)

End point description:

Duration of response or stable disease: time from the date of entry into the study to the earliest date of the first objective tumor progression or death.

End point type	Secondary

End point timeframe:

9 months

End point values	Dovitinib			
Subject group type	Reporting group			
Number of subjects analysed	38			
Units: Days				
arithmetic mean (standard deviation)	193.2 (± 117.78)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to tumor progression (TTP)of patients treated with Dovitinib

End point title	Time to tumor progression (TTP)of patients treated with Dovitinib

End point description:

TTP: time from the date of entry into the study to first documentation of tumor progression or death due to the underlying cancer.

End point type	Secondary

End point timeframe:

9 months

End point values	Dovitinib			
Subject group type	Reporting group			
Number of subjects analysed	38			
Units: Days				
median (confidence interval)	141 (85 to 229)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall response rate (ORR) of patients treated with Dovitinib

End point title	Overall response rate (ORR) of patients treated with Dovitinib

End point description:

Outcome Measure Description: ORR: proportion of patients whose best overall response is either complete response (CR) or partial response (PR) according to RECIST (version 1.1).

End point type	Secondary

End point timeframe:

Baseline, 12 weeks

End point values	Dovitinib			
Subject group type	Reporting group			
Number of subjects analysed	38			
Units: Percentage of Participants				
number (confidence interval)	2.6 (0.1 to 11.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS) of patients treated with Dovitinib

End point title	Overall survival (OS) of patients treated with Dovitinib

End point description:

Outcome Measure Description: OS: time from the date of entry into the study to the date of death due to any cause. A patient who has not died by the date of the analysis cut-off would have the OS censored at the time of the last contact before the cut-off date.

End point type	Secondary

End point timeframe:

21 months (9 months of estimated treatment plus 12 months of survival follow up)

End point values	Dovitinib			
Subject group type	Reporting group			
Number of subjects analysed	38			
Units: Months				
median (confidence interval)	9999.9 (-99999.99 to 99999.99)			

Statistical analyses

No statistical analyses for this end point

Secondary: DCR (CR+PR+SD) at the end of treatment

End point title	DCR (CR+PR+SD) at the end of treatment

End point description:

DCR is defined as the proportion of patients with a best overall response of CR, PR and SD at the end of dovitinib treatment according to RECIST (version 1.1).

End point type	Secondary

End point timeframe:
End of Treatment

End point values	Dovitinib			
Subject group type	Reporting group			
Number of subjects analysed	38			
Units: Percentate of Participants				
number (confidence interval)	52.6 (38.2 to 66.7)			

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	14.1

Reporting groups

Reporting group title	Dovitinib

Reporting group description:

Dovitinib

Serious adverse events	Dovitinib		
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 39 (41.03%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant melanoma			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Prostate cancer			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Aortic thrombosis			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Phlebitis			

subjects affected / exposed	1 / 39 (2.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Asthenia				
subjects affected / exposed	1 / 39 (2.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fatigue				
subjects affected / exposed	4 / 39 (10.26%)			
occurrences causally related to treatment / all	2 / 5			
deaths causally related to treatment / all	0 / 0			
General physical health deterioration				
subjects affected / exposed	1 / 39 (2.56%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Inflammation				
subjects affected / exposed	1 / 39 (2.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Localised oedema				
subjects affected / exposed	1 / 39 (2.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Mucosal dryness				
subjects affected / exposed	1 / 39 (2.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Oedema peripheral				
subjects affected / exposed	1 / 39 (2.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Systemic inflammatory response syndrome				

subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hiccups			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Lung disorder			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Mania			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Red blood cell count decreased			

subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Weight decreased			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Tachycardia			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Neuropathy peripheral			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Paraesthesia			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Leukopenia			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Pancytopenia				
subjects affected / exposed	1 / 39 (2.56%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal pain				
subjects affected / exposed	1 / 39 (2.56%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Abdominal pain upper				
subjects affected / exposed	1 / 39 (2.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ascites				
subjects affected / exposed	1 / 39 (2.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	2 / 39 (5.13%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	1 / 39 (2.56%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Peritoneal haemorrhage				
subjects affected / exposed	1 / 39 (2.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	3 / 39 (7.69%)			
occurrences causally related to treatment / all	2 / 7			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				

Cholestasis			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Toxic skin eruption			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
H1N1 influenza			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tracheobronchitis			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Dehydration			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Dovitinib		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	36 / 39 (92.31%)		
Vascular disorders			

Deep vein thrombosis subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2		
Hypertension subjects affected / exposed occurrences (all)	13 / 39 (33.33%) 16		
Hypotension subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2		
General disorders and administration site conditions Chest pain subjects affected / exposed occurrences (all)	4 / 39 (10.26%) 4		
Asthenia subjects affected / exposed occurrences (all)	15 / 39 (38.46%) 22		
Fatigue subjects affected / exposed occurrences (all)	14 / 39 (35.90%) 22		
Malaise subjects affected / exposed occurrences (all)	3 / 39 (7.69%) 3		
Mucosal inflammation subjects affected / exposed occurrences (all)	4 / 39 (10.26%) 6		
Pyrexia subjects affected / exposed occurrences (all)	7 / 39 (17.95%) 7		
Oedema peripheral subjects affected / exposed occurrences (all)	3 / 39 (7.69%) 3		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2		
Dysphonia			

subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	3		
Dyspnoea			
subjects affected / exposed	6 / 39 (15.38%)		
occurrences (all)	9		
Epistaxis			
subjects affected / exposed	4 / 39 (10.26%)		
occurrences (all)	4		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	4		
Insomnia			
subjects affected / exposed	4 / 39 (10.26%)		
occurrences (all)	4		
Sleep disorder			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	11 / 39 (28.21%)		
occurrences (all)	15		
Alanine aminotransferase increased			
subjects affected / exposed	10 / 39 (25.64%)		
occurrences (all)	19		
Blood bilirubin increased			
subjects affected / exposed	4 / 39 (10.26%)		
occurrences (all)	6		
Blood alkaline phosphatase increased			
subjects affected / exposed	13 / 39 (33.33%)		
occurrences (all)	15		
Blood calcium decreased			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Blood lactate dehydrogenase increased			

subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	3		
Blood triglycerides increased			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
C-reactive protein increased			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Gamma-glutamyltransferase increased			
subjects affected / exposed	14 / 39 (35.90%)		
occurrences (all)	18		
Lipase increased			
subjects affected / exposed	4 / 39 (10.26%)		
occurrences (all)	8		
Protein total decreased			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	5		
Weight decreased			
subjects affected / exposed	12 / 39 (30.77%)		
occurrences (all)	13		
Nervous system disorders			
Dysaesthesia			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	3		
Dysgeusia			
subjects affected / exposed	6 / 39 (15.38%)		
occurrences (all)	8		
Headache			
subjects affected / exposed	8 / 39 (20.51%)		
occurrences (all)	12		
Neuropathy peripheral			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Paraesthesia			

subjects affected / exposed	6 / 39 (15.38%)		
occurrences (all)	7		
Sciatica			
subjects affected / exposed	4 / 39 (10.26%)		
occurrences (all)	4		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 39 (15.38%)		
occurrences (all)	9		
Neutropenia			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	7		
Thrombocytopenia			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	3		
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Vertigo			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	3		
Eye disorders			
Dry eye			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Keratitis			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	3		
Lacrimation increased			
subjects affected / exposed	6 / 39 (15.38%)		
occurrences (all)	7		
Ocular hyperaemia			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Periorbital oedema			

subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	10 / 39 (25.64%)		
occurrences (all)	12		
Abdominal pain upper			
subjects affected / exposed	7 / 39 (17.95%)		
occurrences (all)	12		
Constipation			
subjects affected / exposed	7 / 39 (17.95%)		
occurrences (all)	8		
Diarrhoea			
subjects affected / exposed	28 / 39 (71.79%)		
occurrences (all)	48		
Dry mouth			
subjects affected / exposed	6 / 39 (15.38%)		
occurrences (all)	8		
Dyspepsia			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	3		
Gastric disorder			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	4		
Haemorrhoids			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	3		
Stomatitis			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Nausea			
subjects affected / exposed	17 / 39 (43.59%)		
occurrences (all)	26		
Toothache			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		

Vomiting subjects affected / exposed occurrences (all)	21 / 39 (53.85%) 33		
Hepatobiliary disorders Hepatocellular injury subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2		
Skin and subcutaneous tissue disorders Dermatitis acneiform subjects affected / exposed occurrences (all) Dermatitis allergic subjects affected / exposed occurrences (all) Dry skin subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all)	 2 / 39 (5.13%) 2 2 / 39 (5.13%) 2 8 / 39 (20.51%) 8 2 / 39 (5.13%) 2 6 / 39 (15.38%) 6		
Renal and urinary disorders Pollakiuria subjects affected / exposed occurrences (all) Proteinuria subjects affected / exposed occurrences (all)	 4 / 39 (10.26%) 4 4 / 39 (10.26%) 7		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) Muscle spasms	 5 / 39 (12.82%) 6		

subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	4		
Musculoskeletal pain			
subjects affected / exposed	4 / 39 (10.26%)		
occurrences (all)	5		
Musculoskeletal stiffness			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	3		
Myalgia			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	4		
Pain in extremity			
subjects affected / exposed	7 / 39 (17.95%)		
occurrences (all)	13		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Urinary tract infection			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	4		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	14 / 39 (35.90%)		
occurrences (all)	17		
Dyslipidaemia			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	3		
Hypercholesterolaemia			
subjects affected / exposed	4 / 39 (10.26%)		
occurrences (all)	5		
Hyperkalaemia			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	4		
Hypertriglyceridaemia			

subjects affected / exposed	13 / 39 (33.33%)		
occurrences (all)	25		
Hypoalbuminaemia			
subjects affected / exposed	7 / 39 (17.95%)		
occurrences (all)	7		
Hypocalcaemia			
subjects affected / exposed	4 / 39 (10.26%)		
occurrences (all)	4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 October 2011	This amendment included modifications to the original protocol in order to modify the exclusion criteria and also modifications to parts of the protocol in order to correct some wording mistakes and update some clinical parts.
11 January 2012	This amendment included modifications to the protocol to revise the exclusion criterion pertaining to left ventricular ejection fraction based on the recommendation of ESMO regarding monitoring of cardio toxicity of chemotherapeutic and radiotherapy-related agents.
19 July 2012	This amendment included modifications to the protocol with the main aim to comply with request from German Health Authorities (BfArM) raised on 27-Feb-2012. Inclusion and exclusion criteria were modified and other minor changes were implemented. The inclusion criterion was modified to specify that patients with documented disease progression on prior therapy with imatinib at a dose of at least 400 mg/day or patients with unresectable and/or metastatic GIST intolerant to imatinib were eligible for the study. The exclusion criteria were amended to include QT-related medical conditions, usage of effective contraception and two highly effective birth-control methods for women of child-bearing age and to specify that the treatment with acetylsalicylic at the dialy dose of 100 mg or lower was allowed.
09 July 2013	This amendment included updates to the safety information (based on Investigator's Brochure v10.0, safety cut-off 10-Sep-2012) and to revise the concomitant medication section in order to align it with the preliminary drug-drug interaction data from the CTKI258A2119 study.

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.

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.novfor complete trial results.

Notes: