



Clinical trial results:

A randomized phase III study of imatinib dose optimization compared with nilotinib in patients with Chronic Myelogenous Leukemia and suboptimal response to standard-dose 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.nov> for complete trial results.

Summary

EudraCT number	2008-007054-35
Trial protocol	DE FI
Global end of trial date	25 July 2014

Results information

Result version number	v1 (current)
This version publication date	06 July 2018
First version publication date	06 July 2018

Trial information

Trial identification

Sponsor protocol code	CAMN107A2404
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00802841
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	25 July 2014
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	25 July 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the comparative efficacy between imatinib dose escalation and nilotinib, in terms of CCyR after 6 months, for patients with CML in chronic phase with suboptimal response to imatinib standard dose.

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	25 May 2009
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	Argentina: 10
Country: Number of subjects enrolled	Brazil: 34
Country: Number of subjects enrolled	China: 34
Country: Number of subjects enrolled	Colombia: 3
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Guatemala: 2
Country: Number of subjects enrolled	India: 41
Country: Number of subjects enrolled	Mexico: 10
Country: Number of subjects enrolled	Panama: 1
Country: Number of subjects enrolled	Poland: 4
Country: Number of subjects enrolled	Russian Federation: 47
Country: Number of subjects enrolled	Venezuela, Bolivarian Republic of: 3
Worldwide total number of subjects	191
EEA total number of subjects	6

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)	174
From 65 to 84 years	17
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were randomized in 1:1 ratio to imatinib 600 mg QD or nilotinib 400 mg BID for a 2 year study period.

Pre-assignment

Screening details:

Cross-over from one arm to the other was allowed for intolerant patients anytime during treatment, patients who failed to achieve CCyR after 6 months of treatment, loss of response, loss of CHR, loss of best achieved cytogenetic response any time during treatment, or other reason approved by the Study Management Committee.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Nilotinib

Arm description:

Participants received 400 mg nilotinib twice daily (BID).

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

Dosage and administration details:

400 mg b.i.d.

Arm title	Imatinib
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Arm description:

Participants received 600 mg imatinib once daily (QD).

Arm type	Active comparator
Investigational medicinal product name	Imatinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

600 mg qd

Number of subjects in period 1	Nilotinib	Imatinib
Started	96	95
Full Analysis Set	96	95
Cross-over set	13	56
Safety Set	96	93
Completed	0	0
Not completed	96	95
Adverse event, serious fatal	1	2
Treatment duration completed	66	76
Consent withdrawn by subject	9	5
Disease progression	7	3
Adverse event, non-fatal	8	2
Protocol deviation	2	6
Administrative problems	1	-
Lost to follow-up	2	1

Baseline characteristics

Reporting groups

Reporting group title	Nilotinib
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Reporting group description:

Participants received 400 mg nilotinib twice daily (BID).

Reporting group title	Imatinib
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Reporting group description:

Participants received 600 mg imatinib once daily (QD).

Reporting group values	Nilotinib	Imatinib	Total
Number of subjects	96	95	191
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)	89	85	174
From 65-84 years	7	10	17
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	44.6	44.2	
standard deviation	± 14.47	± 15.02	-
Gender, Male/Female Units: Participants			
Female	42	37	79
Male	54	58	112

End points

End points reporting groups

Reporting group title	Nilotinib
Reporting group description: Participants received 400 mg nilotinib twice daily (BID).	
Reporting group title	Imatinib
Reporting group description: Participants received 600 mg imatinib once daily (QD).	

Primary: Percentage of participants with Complete Cytogenetic Response (CCyR)

End point title	Percentage of participants with Complete Cytogenetic Response (CCyR)
End point description: CCyR was assessed from bone marrow samples. CCyR was defined as having 0% Philadelphia positive (Ph+) chromosome metaphases in bone marrow.	
End point type	Primary
End point timeframe: 6 months	

End point values	Nilotinib	Imatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	95		
Units: Percentage of participants				
number (not applicable)	50	42.1		

Statistical analyses

Statistical analysis title	Complete cytogenetic response
Comparison groups	Imatinib v Nilotinib
Number of subjects included in analysis	191
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3106
Method	Fisher exact

Secondary: Percentage of participants with Major Molecular Response (MMR)

End point title	Percentage of participants with Major Molecular Response (MMR)
End point description: MMR was defined as having a fusion gene of the Bcr and Abl genes of (BCR-ABL) less than or equal to	

0.1% on the International Scale (IS).

End point type	Secondary
End point timeframe:	
12 and 24 months	

End point values	Nilotinib	Imatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	95		
Units: Percentage of participants				
number (not applicable)				
12 months	36.5	25.3		
24 months	37.5	35.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with CCyR

End point title	Percentage of participants with CCyR
End point description:	
CCyR was assessed from bone marrow samples. CCyR was defined as having 0% Philadelphia positive (Ph+) chromosome metaphases in bone marrow.	
End point type	Secondary
End point timeframe:	
12 and 24 months	

End point values	Nilotinib	Imatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	95		
Units: Percentage of participants				
number (not applicable)				
12 months	53.1	55.8		
24 months	51	61.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to CCyR

End point title	Time to CCyR
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End point description:	
Time to CCyR was defined as time from date of randomization to date of first documented CCyR.	
End point type	Secondary
End point timeframe:	
24 months	

End point values	Nilotinib	Imatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	95		
Units: Months				
median (confidence interval)	5.55 (5.52 to 5.98)	5.85 (5.59 to 11.04)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of CCyR

End point title	Duration of CCyR
End point description:	
Duration of CCyR was defined as time from the date of randomization to the date of first loss of CCyR or death, whichever came first.	
End point type	Secondary
End point timeframe:	
24 months	

End point values	Nilotinib	Imatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	95		
Units: Months				
median (confidence interval)	9999 (999 to 99999)	17.2 (17.2 to 99999)		

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 randomization to the date of documented disease	

progression to accelerated phase or blast crisis (AP/BC), or death due to any cause.

End point type	Secondary
End point timeframe:	
24 months	

End point values	Nilotinib	Imatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	95		
Units: Months				
median (confidence interval)	9999 (999 to 99999)	9999 (999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Event-Free Survival (EFS)

End point title	Event-Free Survival (EFS)
End point description:	
EFS was defined as the time from the date of randomization to the date of the first occurrence of any of the following: loss of Complete Hematological Response (CHR), loss of Partial Cytogenetic Response (PCyR), loss of CCyR, death on treatment or progression to AP/BC.	
End point type	Secondary
End point timeframe:	
24 months	

End point values	Nilotinib	Imatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	95		
Units: Months				
median (confidence interval)	9999 (999 to 99999)	24.3 (23.8 to 99999)		

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 time from date of randomization to the date of the death.	

End point type	Secondary
End point timeframe:	
24 months	

End point values	Nilotinib	Imatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	95		
Units: Months				
median (confidence interval)	9999 (999 to 99999)	25.7 (9 to 99999)		

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
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Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Nilotinib 400 mg BID
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Reporting group description:

Nilotinib 400 mg BID

Reporting group title	Cross-over to nilotinib 400 mg BID
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Reporting group description:

Cross-over to nilotinib 400 mg BID

Reporting group title	Cross-over to imatinib 600 mg QD
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Reporting group description:

Cross-over to imatinib 600 mg QD

Reporting group title	Imatinib 600 mg QD
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Reporting group description:

Imatinib 600 mg QD

Serious adverse events	Nilotinib 400 mg BID	Cross-over to nilotinib 400 mg BID	Cross-over to imatinib 600 mg QD
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 96 (11.46%)	4 / 56 (7.14%)	1 / 13 (7.69%)
number of deaths (all causes)	1	1	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Blast cell crisis			
subjects affected / exposed	1 / 96 (1.04%)	1 / 56 (1.79%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial cancer			

subjects affected / exposed	0 / 96 (0.00%)	0 / 56 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Arterial occlusive disease			
subjects affected / exposed	1 / 96 (1.04%)	0 / 56 (0.00%)	0 / 13 (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
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	0 / 96 (0.00%)	1 / 56 (1.79%)	0 / 13 (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
Investigations			
Haemoglobin decreased			
subjects affected / exposed	0 / 96 (0.00%)	0 / 56 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaria antibody test positive			
subjects affected / exposed	0 / 96 (0.00%)	0 / 56 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 96 (1.04%)	0 / 56 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	2 / 96 (2.08%)	0 / 56 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			

subjects affected / exposed	1 / 96 (1.04%)	0 / 56 (0.00%)	0 / 13 (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
Tachyarrhythmia			
subjects affected / exposed	0 / 96 (0.00%)	0 / 56 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 96 (1.04%)	0 / 56 (0.00%)	0 / 13 (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
Leukocytosis			
subjects affected / exposed	1 / 96 (1.04%)	0 / 56 (0.00%)	0 / 13 (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
Lymphadenopathy			
subjects affected / exposed	0 / 96 (0.00%)	1 / 56 (1.79%)	0 / 13 (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
Thrombocytopenia			
subjects affected / exposed	2 / 96 (2.08%)	1 / 56 (1.79%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Retinal detachment			
subjects affected / exposed	0 / 96 (0.00%)	0 / 56 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Pancreatitis acute			
subjects affected / exposed	1 / 96 (1.04%)	0 / 56 (0.00%)	0 / 13 (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

Hepatobiliary disorders			
Cholecystitis chronic			
subjects affected / exposed	0 / 96 (0.00%)	0 / 56 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	0 / 96 (0.00%)	1 / 56 (1.79%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	0 / 96 (0.00%)	0 / 56 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Autoimmune thyroiditis			
subjects affected / exposed	1 / 96 (1.04%)	0 / 56 (0.00%)	0 / 13 (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
Hyperthyroidism			
subjects affected / exposed	1 / 96 (1.04%)	0 / 56 (0.00%)	0 / 13 (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
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	1 / 96 (1.04%)	0 / 56 (0.00%)	0 / 13 (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
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 96 (0.00%)	0 / 56 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis B			

subjects affected / exposed	0 / 96 (0.00%)	0 / 56 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 96 (0.00%)	1 / 56 (1.79%)	0 / 13 (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

Serious adverse events	Imatinib 600 mg QD		
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 93 (9.68%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Blast cell crisis			
subjects affected / exposed	1 / 93 (1.08%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Endometrial cancer			
subjects affected / exposed	1 / 93 (1.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Arterial occlusive disease			
subjects affected / exposed	0 / 93 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	0 / 93 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations			
Haemoglobin decreased			

subjects affected / exposed	1 / 93 (1.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Malaria antibody test positive			
subjects affected / exposed	1 / 93 (1.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 93 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Angina pectoris			
subjects affected / exposed	0 / 93 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Angina unstable			
subjects affected / exposed	0 / 93 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tachyarrhythmia			
subjects affected / exposed	0 / 93 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 93 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Leukocytosis			
subjects affected / exposed	0 / 93 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lymphadenopathy			

subjects affected / exposed	0 / 93 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	1 / 93 (1.08%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Retinal detachment			
subjects affected / exposed	1 / 93 (1.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Pancreatitis acute			
subjects affected / exposed	0 / 93 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis chronic			
subjects affected / exposed	1 / 93 (1.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	1 / 93 (1.08%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	1 / 93 (1.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Endocrine disorders			
Autoimmune thyroiditis			

subjects affected / exposed	1 / 93 (1.08%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperthyroidism			
subjects affected / exposed	0 / 93 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	0 / 93 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 93 (1.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatitis B			
subjects affected / exposed	1 / 93 (1.08%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	0 / 93 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Nilotinib 400 mg BID	Cross-over to nilotinib 400 mg BID	Cross-over to imatinib 600 mg QD
Total subjects affected by non-serious adverse events			
subjects affected / exposed	80 / 96 (83.33%)	44 / 56 (78.57%)	11 / 13 (84.62%)
Vascular disorders			
Hypertension			

subjects affected / exposed occurrences (all)	5 / 96 (5.21%) 5	2 / 56 (3.57%) 2	1 / 13 (7.69%) 1
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	6 / 96 (6.25%)	0 / 56 (0.00%)	0 / 13 (0.00%)
occurrences (all)	6	0	0
Influenza like illness			
subjects affected / exposed	1 / 96 (1.04%)	0 / 56 (0.00%)	2 / 13 (15.38%)
occurrences (all)	4	0	3
Generalised oedema			
subjects affected / exposed	0 / 96 (0.00%)	0 / 56 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Oedema peripheral			
subjects affected / exposed	5 / 96 (5.21%)	1 / 56 (1.79%)	0 / 13 (0.00%)
occurrences (all)	7	1	0
Pyrexia			
subjects affected / exposed	12 / 96 (12.50%)	6 / 56 (10.71%)	2 / 13 (15.38%)
occurrences (all)	14	6	2
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 96 (5.21%)	0 / 56 (0.00%)	1 / 13 (7.69%)
occurrences (all)	5	0	1
Oropharyngeal pain			
subjects affected / exposed	3 / 96 (3.13%)	1 / 56 (1.79%)	1 / 13 (7.69%)
occurrences (all)	4	1	1
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 96 (0.00%)	0 / 56 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	20 / 96 (20.83%)	9 / 56 (16.07%)	0 / 13 (0.00%)
occurrences (all)	30	15	0
Aspartate aminotransferase increased			

subjects affected / exposed	7 / 96 (7.29%)	4 / 56 (7.14%)	0 / 13 (0.00%)
occurrences (all)	12	5	0
Bilirubin conjugated increased			
subjects affected / exposed	8 / 96 (8.33%)	5 / 56 (8.93%)	0 / 13 (0.00%)
occurrences (all)	17	8	0
Blood bilirubin increased			
subjects affected / exposed	13 / 96 (13.54%)	11 / 56 (19.64%)	0 / 13 (0.00%)
occurrences (all)	35	20	0
Blood phosphorus decreased			
subjects affected / exposed	1 / 96 (1.04%)	0 / 56 (0.00%)	1 / 13 (7.69%)
occurrences (all)	2	0	1
Gamma-glutamyltransferase increased			
subjects affected / exposed	8 / 96 (8.33%)	3 / 56 (5.36%)	0 / 13 (0.00%)
occurrences (all)	12	3	0
Haemoglobin decreased			
subjects affected / exposed	3 / 96 (3.13%)	3 / 56 (5.36%)	0 / 13 (0.00%)
occurrences (all)	5	3	0
Platelet count decreased			
subjects affected / exposed	2 / 96 (2.08%)	4 / 56 (7.14%)	1 / 13 (7.69%)
occurrences (all)	4	7	1
Weight increased			
subjects affected / exposed	3 / 96 (3.13%)	4 / 56 (7.14%)	1 / 13 (7.69%)
occurrences (all)	3	4	1
White blood cell count increased			
subjects affected / exposed	1 / 96 (1.04%)	0 / 56 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	1
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	0 / 96 (0.00%)	1 / 56 (1.79%)	1 / 13 (7.69%)
occurrences (all)	0	1	1
Cardiac disorders			
Tachycardia			
subjects affected / exposed	2 / 96 (2.08%)	0 / 56 (0.00%)	1 / 13 (7.69%)
occurrences (all)	2	0	1
Nervous system disorders			

Dizziness subjects affected / exposed occurrences (all)	3 / 96 (3.13%) 3	3 / 56 (5.36%) 3	1 / 13 (7.69%) 1
Headache subjects affected / exposed occurrences (all)	14 / 96 (14.58%) 18	8 / 56 (14.29%) 9	4 / 13 (30.77%) 4
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	11 / 96 (11.46%) 15	10 / 56 (17.86%) 14	4 / 13 (30.77%) 4
Leukocytosis subjects affected / exposed occurrences (all)	1 / 96 (1.04%) 1	1 / 56 (1.79%) 1	1 / 13 (7.69%) 1
Leukopenia subjects affected / exposed occurrences (all)	10 / 96 (10.42%) 17	9 / 56 (16.07%) 15	0 / 13 (0.00%) 0
Lymphopenia subjects affected / exposed occurrences (all)	3 / 96 (3.13%) 6	3 / 56 (5.36%) 6	1 / 13 (7.69%) 1
Neutropenia subjects affected / exposed occurrences (all)	11 / 96 (11.46%) 28	13 / 56 (23.21%) 18	1 / 13 (7.69%) 1
Thrombocytopenia subjects affected / exposed occurrences (all)	19 / 96 (19.79%) 33	13 / 56 (23.21%) 30	3 / 13 (23.08%) 4
Eye disorders			
Eyelid oedema subjects affected / exposed occurrences (all)	1 / 96 (1.04%) 1	0 / 56 (0.00%) 0	0 / 13 (0.00%) 0
Papilloedema subjects affected / exposed occurrences (all)	0 / 96 (0.00%) 0	0 / 56 (0.00%) 0	1 / 13 (7.69%) 1
Periorbital oedema subjects affected / exposed occurrences (all)	2 / 96 (2.08%) 2	1 / 56 (1.79%) 1	2 / 13 (15.38%) 2
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	1 / 96 (1.04%)	0 / 56 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	1
Abdominal pain upper			
subjects affected / exposed	6 / 96 (6.25%)	0 / 56 (0.00%)	0 / 13 (0.00%)
occurrences (all)	6	0	0
Anal fissure			
subjects affected / exposed	0 / 96 (0.00%)	0 / 56 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Diarrhoea			
subjects affected / exposed	6 / 96 (6.25%)	1 / 56 (1.79%)	1 / 13 (7.69%)
occurrences (all)	7	1	1
Dyspepsia			
subjects affected / exposed	2 / 96 (2.08%)	0 / 56 (0.00%)	2 / 13 (15.38%)
occurrences (all)	2	0	2
Nausea			
subjects affected / exposed	5 / 96 (5.21%)	4 / 56 (7.14%)	2 / 13 (15.38%)
occurrences (all)	5	5	3
Proctalgia			
subjects affected / exposed	0 / 96 (0.00%)	0 / 56 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Stomatitis			
subjects affected / exposed	0 / 96 (0.00%)	0 / 56 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Tongue haematoma			
subjects affected / exposed	0 / 96 (0.00%)	0 / 56 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Vomiting			
subjects affected / exposed	4 / 96 (4.17%)	5 / 56 (8.93%)	3 / 13 (23.08%)
occurrences (all)	5	6	7
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	14 / 96 (14.58%)	9 / 56 (16.07%)	0 / 13 (0.00%)
occurrences (all)	30	10	0
Skin and subcutaneous tissue disorders			

Hyperhidrosis subjects affected / exposed occurrences (all)	0 / 96 (0.00%) 0	1 / 56 (1.79%) 1	1 / 13 (7.69%) 1
Rash subjects affected / exposed occurrences (all)	22 / 96 (22.92%) 24	9 / 56 (16.07%) 11	1 / 13 (7.69%) 1
Pruritus subjects affected / exposed occurrences (all)	8 / 96 (8.33%) 11	3 / 56 (5.36%) 5	0 / 13 (0.00%) 0
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	9 / 96 (9.38%) 11	2 / 56 (3.57%) 4	1 / 13 (7.69%) 1
Myalgia subjects affected / exposed occurrences (all)	8 / 96 (8.33%) 8	2 / 56 (3.57%) 2	0 / 13 (0.00%) 0
Pain in extremity subjects affected / exposed occurrences (all)	3 / 96 (3.13%) 3	3 / 56 (5.36%) 3	0 / 13 (0.00%) 0
Infections and infestations			
Influenza subjects affected / exposed occurrences (all)	0 / 96 (0.00%) 0	0 / 56 (0.00%) 0	1 / 13 (7.69%) 1
Upper respiratory tract infection subjects affected / exposed occurrences (all)	5 / 96 (5.21%) 7	1 / 56 (1.79%) 1	0 / 13 (0.00%) 0
Metabolism and nutrition disorders			
Hypercholesterolaemia subjects affected / exposed occurrences (all)	4 / 96 (4.17%) 4	3 / 56 (5.36%) 3	0 / 13 (0.00%) 0
Hyperglycaemia subjects affected / exposed occurrences (all)	11 / 96 (11.46%) 18	2 / 56 (3.57%) 4	0 / 13 (0.00%) 0
Hypocalcaemia subjects affected / exposed occurrences (all)	5 / 96 (5.21%) 6	1 / 56 (1.79%) 1	0 / 13 (0.00%) 0

Hypokalaemia			
subjects affected / exposed	1 / 96 (1.04%)	1 / 56 (1.79%)	1 / 13 (7.69%)
occurrences (all)	1	1	1
Hypophosphataemia			
subjects affected / exposed	10 / 96 (10.42%)	1 / 56 (1.79%)	1 / 13 (7.69%)
occurrences (all)	22	1	4

Non-serious adverse events	Imatinib 600 mg QD		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	61 / 93 (65.59%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 93 (2.15%)		
occurrences (all)	2		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 93 (3.23%)		
occurrences (all)	3		
Influenza like illness			
subjects affected / exposed	0 / 93 (0.00%)		
occurrences (all)	0		
Generalised oedema			
subjects affected / exposed	0 / 93 (0.00%)		
occurrences (all)	0		
Oedema peripheral			
subjects affected / exposed	1 / 93 (1.08%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	8 / 93 (8.60%)		
occurrences (all)	8		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 93 (2.15%)		
occurrences (all)	2		
Oropharyngeal pain			

subjects affected / exposed	2 / 93 (2.15%)		
occurrences (all)	2		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 93 (0.00%)		
occurrences (all)	0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	5 / 93 (5.38%)		
occurrences (all)	7		
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 93 (3.23%)		
occurrences (all)	4		
Bilirubin conjugated increased			
subjects affected / exposed	1 / 93 (1.08%)		
occurrences (all)	1		
Blood bilirubin increased			
subjects affected / exposed	1 / 93 (1.08%)		
occurrences (all)	3		
Blood phosphorus decreased			
subjects affected / exposed	2 / 93 (2.15%)		
occurrences (all)	2		
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 93 (0.00%)		
occurrences (all)	0		
Haemoglobin decreased			
subjects affected / exposed	8 / 93 (8.60%)		
occurrences (all)	10		
Platelet count decreased			
subjects affected / exposed	3 / 93 (3.23%)		
occurrences (all)	3		
Weight increased			
subjects affected / exposed	3 / 93 (3.23%)		
occurrences (all)	3		
White blood cell count increased			

subjects affected / exposed occurrences (all)	0 / 93 (0.00%) 0		
Injury, poisoning and procedural complications Animal bite subjects affected / exposed occurrences (all)	0 / 93 (0.00%) 0		
Cardiac disorders Tachycardia subjects affected / exposed occurrences (all)	0 / 93 (0.00%) 0		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all)	4 / 93 (4.30%) 5 6 / 93 (6.45%) 7		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Leukocytosis subjects affected / exposed occurrences (all) Leukopenia subjects affected / exposed occurrences (all) Lymphopenia subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all)	18 / 93 (19.35%) 22 0 / 93 (0.00%) 0 22 / 93 (23.66%) 39 6 / 93 (6.45%) 8 23 / 93 (24.73%) 49 24 / 93 (25.81%) 47		

Eye disorders			
Eyelid oedema			
subjects affected / exposed	10 / 93 (10.75%)		
occurrences (all)	13		
Papilloedema			
subjects affected / exposed	0 / 93 (0.00%)		
occurrences (all)	0		
Periorbital oedema			
subjects affected / exposed	2 / 93 (2.15%)		
occurrences (all)	2		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 93 (2.15%)		
occurrences (all)	2		
Abdominal pain upper			
subjects affected / exposed	4 / 93 (4.30%)		
occurrences (all)	4		
Anal fissure			
subjects affected / exposed	0 / 93 (0.00%)		
occurrences (all)	0		
Diarrhoea			
subjects affected / exposed	15 / 93 (16.13%)		
occurrences (all)	17		
Dyspepsia			
subjects affected / exposed	2 / 93 (2.15%)		
occurrences (all)	2		
Nausea			
subjects affected / exposed	14 / 93 (15.05%)		
occurrences (all)	27		
Proctalgia			
subjects affected / exposed	0 / 93 (0.00%)		
occurrences (all)	0		
Stomatitis			
subjects affected / exposed	0 / 93 (0.00%)		
occurrences (all)	0		
Tongue haematoma			

subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	0 / 93 (0.00%) 0 10 / 93 (10.75%) 20		
Hepatobiliary disorders Hyperbilirubinaemia subjects affected / exposed occurrences (all)	1 / 93 (1.08%) 1		
Skin and subcutaneous tissue disorders Hyperhidrosis subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all)	0 / 93 (0.00%) 0 4 / 93 (4.30%) 6 0 / 93 (0.00%) 0		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all)	3 / 93 (3.23%) 3 1 / 93 (1.08%) 1 1 / 93 (1.08%) 1		
Infections and infestations Influenza subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 93 (0.00%) 0 5 / 93 (5.38%) 8		

Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	0 / 93 (0.00%)		
occurrences (all)	0		
Hyperglycaemia			
subjects affected / exposed	2 / 93 (2.15%)		
occurrences (all)	3		
Hypocalcaemia			
subjects affected / exposed	3 / 93 (3.23%)		
occurrences (all)	4		
Hypokalaemia			
subjects affected / exposed	0 / 93 (0.00%)		
occurrences (all)	0		
Hypophosphataemia			
subjects affected / exposed	3 / 93 (3.23%)		
occurrences (all)	6		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 February 2009	The primary reason for Amendment 1 was to include European sites as participants. The secondary reason was to clarify the timing of the interim analysis and to incorporate the Independent Data Monitoring Committee that would monitor safety throughout the study and review safety and efficacy data during the interim analysis. The number of interim analyses was updated from two to one.
17 June 2009	Amendment 2 was implemented to add the EU-DRACT number for European sites. This amendment only applied to Europe and was not applicable to Latin America.
03 May 2010	Amendment 3: The protocol has been revised to modify certain inclusion and exclusion criteria such as primarily INF-a usage and Bone Marrow testing for confirmation of study inclusion. The changes were implemented following thorough analysis of reasons for screening failure of patients considered for the protocol under previous amendment. These changes will not affect the study endpoints or objectives but merely allow for patient that would otherwise be eligible for this study to be included. Also addressed in this amendment is the change in ELN 2009 recommendations to allow for patients at 3 months of treatment with imatinib to be evaluated for suboptimal response.
20 December 2010	Amendment 4 was issued to revise the Case Report Forms (CRFs) and Data Management section as well as to update the language in the IVRS/IWRS section in accordance with Novartis SOPs. In addition, this amendment clarified the Visit Assessment Schedule and OS follow up.
15 March 2012	Amendment 5 was issued to update safety information and to clarify patient eligibility criteria. The safety update included pregnancy language, cardiac, death and sudden cardiac death and CYP34a inhibitors/inducers. The pregnancy language was updated since the reproductive-developmental toxicity profiles of nilotinib and imatinib do not indicate genotoxicity, pregnancy outcomes from female partners of male patients participating in this study were collected. The main eligibility criteria clarifications were to prior therapy, definition of intolerance and definition of chronic phase CML. An additional change was made to the secondary endpoints. The rate of CHR was removed as a secondary endpoint. Patients with no CHR at baseline are considered treatment failures and were thus not eligible for the study. All patients were expected to be in CHR at baseline. However, it was possible for patients to have loss of CHR on study. Loss of CHR, which needed to be confirmed, was retained as a study endpoint CHR as it was one of the events included in the definition of EFS.
16 January 2014	The major reason for amendment 6 was to ensure alignment and consistency of pregnancy prevention language with the nilotinib program language, nilotinib label, and Novartis internal pregnancy guidelines. These changes have also been incorporated into the consent form. In addition, the risks associated with nilotinib in the consent form have been updated to reflect the current investigators brochure.

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.nov> for complete trial results.

Notes: