Clinical trial results:
An Open Label, Randomized Study of Nilotinib vs. Standard Imatinib (400/600 mg QD) Comparing the Kinetics of Complete Molecular Response for CML-CP Patients With Evidence of Persistent Leukemia by RQ-PCR.

Due to EudraCT system limitations, which EMA is aware of, results of crossover studies and data using 999 as data points are not accurately represented in this record. Please go to https://www.novctrd.com/CtrdWeb/home.nov for complete trial results

Summary

EudraCT number	2009-012616-40
Trial protocol	FR GB ES
Global end of trial date	03 July 2015
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	CAMN107A2405
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00760877
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	03 July 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 July 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to compare the rate of confirmed best cumulative response (CMR) within the first year of study therapy with nilotinib or imatinib (for a definition of confirmed CMR.

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	12 June 2009
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	Argentina: 1
Country: Number of subjects enrolled	Australia: 48
Country: Number of subjects enrolled	Brazil: 82
Country: Number of subjects enrolled	Canada: 36
Country: Number of subjects enrolled	France: 31
Country: Number of subjects enrolled	Spain: 9
Worldwide total number of subjects	207
EEA total number of subjects	40

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)	179
From 65 to 84 years	28
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants were randomized 1:1 to either nilotinib or imatinib. Participants in the imatinib arm were permitted to cross-over to nilotinib after 2 years on study if CMR was not achieved, or at any time during the study if participants experienced treatment failure, had confirmed loss of major molecular response (MMR) or had confirmed loss of CMR.

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 Nilotinib 400 mg orally twice daily (bid) for 48 months.

Arm type	Experimental
Investigational medicinal product name	Nilotinib
Investigational medicinal product code	AMN107
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Nilotinib 400 mg orally twice daily (bid) for 48 months.

Arm title	Imatinib

Arm description:

Participants received Imatinib 400 mg or 600 mg once daily (qd) (based on the participant\'s dose prior to randomization) for 48 months.

Arm type	Active comparator
Investigational medicinal product name	Imatinib
Investigational medicinal product code	
Other name	Glivec/Gleevec
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Imatinib 400 mg or 600 mg once daily (qd) (based on the participant's dose prior to randomization) for 48 months. Participants were permitted to cross over to Nilotinib at 2 years if participants had not achieved CMR or at any time during the study if participants experienced treatment failure, had confirmed loss of MMR or confirmed loss of CMR.

Number of subjects in period 1	Nilotinib	Imatinib
Started	104	103
Cross-over to Nilotinib	0 [1]	46 [2]
Safety set	101	103
Completed	59	77
Not completed	45	26
Adverse event, serious fatal	2	1
Non-compliance with protocol treatment	2	1
Consent withdrawn by subject	7	3
Physician decision	1	2
Treatment failure	1	-
Adverse event, non-fatal	19	12
Participants transferred to AMN107A2408	11	1
Participant diagnosed with AML	-	1
Pregnancy	1	4
Participant not eligible to cross-over	-	1
Protocol deviation	1	-

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: As this was a crossover study, only 46 patients crossed over to the Nilotinib Arm. This is why the numbers are different in Period 2.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: As this was a crossover study, only 46 patients crossed over to the Nilotinib Arm. This is why the numbers are different in Period 2.

Baseline characteristics

Reporting groups	
Reporting group title	Nilotinib
Reporting group description:	
Participants received Nilotinib 400 mg orally twice daily (bid) for 48 months.	
Reporting group title	Imatinib
Reporting group description:	
Participants received Imatinib 400 mg or 600 mg once daily (qd) (based on the participant\'s dose prior to randomization) for 48 months.	

Reporting group values	Nilotinib	Imatinib	Total
Number of subjects	104	103	207
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)	90	89	179
From 65-84 years	14	14	28
85 years and over	0	0	0
Age Continuous			
Units: Years			
arithmetic mean	48.3	49.9	
standard deviation	± 13.26	± 13.07	-
Gender, Male/Female			
Units: Participants			
Female	33	38	71
Male	71	65	136

End points

End points reporting groups

Reporting group title	Nilotinib
Reporting group description:	
Participants received Nilotinib 400 mg orally twice daily (bid) for 48 months.	
Reporting group title	Imatinib
Reporting group description:	
Participants received Imatinib 400 mg or 600 mg once daily (qd) (based on the participant\'s dose prior to randomization) for 48 months.	

Primary: Rate of confirmed best cumulative complete molecular response (CMR)

End point title	Rate of confirmed best cumulative complete molecular response (CMR)
End point description:	
The rate of confirmed best cumulative CMR was defined as the percentage of participants who had confirmed CMR during the first 12 months of treatment after the randomization date. Participants who achieved confirmed best cumulative CMR during the first 12 months were considered responders. Participants who dropped out early or who did not provide sufficient data for any reason were considered to be non-responders. The definition of CMR is undetectable BCR-ABL (fusion gene formed between bcr gene from chromosome 22 and abl gene from chromosome 9) where BCR-ABL ratio in % international scale (IS) ≤ 0.00001 by real-time quantitative polymerase chain reaction (RQ-PCR) where there was no detectable BCR-ABL and 1) the test had a sensitivity of at least 4.5 logs below the standardized baseline; 2) RQ-PCR negativity was confirmed on the next RQ-PCR sample (usually 3 months later); and 3) the date of confirmed CMR was the date of the first of two negative results with sensitivity >4.5 logs.	
End point type	Primary
End point timeframe:	
12 months	

End point values	Nilotinib	Imatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	104	103		
Units: Number of particiants				
Responders	13	6		
Non-responders	91	97		

Statistical analyses

Statistical analysis title	Rate of confirmed best cumulative CMR
Comparison groups	Nilotinib v Imatinib

Number of subjects included in analysis	207
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.1083
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	2.096
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.766
upper limit	5.738

Notes:

[1] - The null hypothesis for the primary endpoint was that there was no difference in the rate of confirmed best cumulative CMR between the two treatment arms during the first 12 months of treatment. The corresponding alternative hypothesis was that the rate of confirmed best cumulative CMR during the first 12 months of the treatment is different between the nilotinib and imatinib treatment arms.

Secondary: Rate of confirmed best cumulative CMR

End point title	Rate of confirmed best cumulative CMR

End point description:

The rate of confirmed best cumulative CMR was defined as the percentage of participants who had confirmed CMR during the 24, 36 and 48 months post treatment after the randomization date. Participants who achieved confirmed best cumulative CMR during the first 12 months were considered responders. Participants who dropped out early or who did not provide sufficient data for any reason were considered to be non-responders. The definition of CMR is undetectable BCR-ABL (fusion gene formed between bcr gene from chromosome 22 and abl gene from chromosome 9) where BCR-ABL ratio in % international scale (IS) ≤ 0.00001 by RQ-PCR where there was no detectable BCR-ABL and 1) the test had a sensitivity of at least 4.5 logs below the standardized baseline; 2) RQ-PCR negativity was confirmed on the next RQ-PCR sample (usually 3 months later); and 3) the date of confirmed CMR was the date of the first of two negative results with sensitivity >4.5 logs.

End point type	Secondary

End point timeframe:

24 months, 36 month, 48 months

End point values	Nilotinib	Imatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	104	103		
Units: Number of participants				
24 months, Responders	24	11		
24 months, Non-responders	80	92		
36 months, Responders	29	21		
36 months, Non-responders	75	82		
48 months, Responders	32	21		
48 months, Non-responders	72	82		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of cross-over participants with CMR

End point title	Number of cross-over participants with CMR[2]

End point description:

The definition of CMR is undetectable BCR-ABL (fusion gene formed between bcr gene from chromosome 22 and abl gene from chromosome 9) where BCR-ABL ratio in % international scale (IS) ≤ 0.00001 by RQ-PCR where there was no detectable BCR-ABL and 1) the test had a sensitivity of at least 4.5 logs below the standardized baseline; 2) RQ-PCR negativity was confirmed on the next RQ-PCR sample (usually 3 months later); and 3) the date of confirmed CMR was the date of the first of two negative results with sensitivity >4.5 logs.

End point type	Secondary

End point timeframe:

24 months, 36 months, 48 months

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Nilotinib arm (participants who crossed over from Imatinib) only is applicable to this outcome measure.

End point values	Nilotinib			
Subject group type	Reporting group			
Number of subjects analysed	46			
Units: Numner of participants				
24 months	3			
36 months	6			
48 months	9			

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 the earliest documented progression-defining event as follows: transformation to blast crisis or accelerated phase disease, or death from any cause.

End point type	Secondary

End point timeframe:

48 months

End point values	Nilotinib	Imatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	104	103		
Units: months				
median (confidence interval 95%)	9999 (-9999 to 9999)	9999 (-9999 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Event-free survival

End point title	Event-free survival

End point description:

Event-free survival was defined as the time from the date of randomization to the date of first occurrence of any of the following events on study treatment: loss of complete hematological response, confirmed loss of complete cytogenetic response (CCyR), confirmed loss of major molecular response (MMR), death from any cause during treatment, progression to the accelerated phase or blast crisis of chronic myelogenous leukemia (CML) per European Leukemia Network (ELN) criteria, whichever was earliest.

End point type	Secondary

End point timeframe:

48 months

End point values	Nilotinib	Imatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	104	103		
Units: Months				
median (confidence interval 95%)	9999 (-9999 to 9999)	9999 (-9999 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival

End point description:

Overall survival was defined as the time from the date of randomization to the date of death due to any cause at any time during the study, including the follow-up period after discontinuation of treatment.

End point type	Secondary

End point timeframe:

48 months

End point values	Nilotinib	Imatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	104	103		
Units: Months				
median (confidence interval 95%)	9999 (-9999 to 9999)	9999 (-9999 to 9999)		

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	18.0

Reporting groups

Reporting group title	Nilotinib

Reporting group description:

Nilotinib
n=101

Reporting group title	Imatinib subset that crossed over to nilotinib

Reporting group description:

Imatinib subset that crossed over to nilotinib
n=46

Reporting group title	Imatinib

Reporting group description:

Imatinib
Up to crossover, n = 103
After cross over to nilotinib, n = 57

Serious adverse events	Nilotinib	Imatinib subset that crossed over to nilotinib	Imatinib
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 101 (20.79%)	8 / 46 (17.39%)	16 / 103 (15.53%)
number of deaths (all causes)	1	0	1
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
ACUTE MYELOID LEUKAEMIA			
subjects affected / exposed	0 / 101 (0.00%)	0 / 46 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MALIGNANT MELANOMA			

subjects affected / exposed	1 / 101 (0.99%)	0 / 46 (0.00%)	0 / 103 (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
METASTASES TO PERITONEUM			
subjects affected / exposed	0 / 101 (0.00%)	0 / 46 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
NON-SMALL CELL LUNG CANCER METASTATIC			
subjects affected / exposed	0 / 101 (0.00%)	0 / 46 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PROSTATE CANCER			
subjects affected / exposed	0 / 101 (0.00%)	0 / 46 (0.00%)	2 / 103 (1.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RENAL CELL CARCINOMA			
subjects affected / exposed	1 / 101 (0.99%)	0 / 46 (0.00%)	0 / 103 (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
Injury, poisoning and procedural complications			
ANKLE FRACTURE			
subjects affected / exposed	1 / 101 (0.99%)	0 / 46 (0.00%)	0 / 103 (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
BACK INJURY			
subjects affected / exposed	0 / 101 (0.00%)	1 / 46 (2.17%)	0 / 103 (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
DRUG ADMINISTRATION ERROR			
subjects affected / exposed	0 / 101 (0.00%)	1 / 46 (2.17%)	0 / 103 (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
LIGAMENT RUPTURE			

subjects affected / exposed	1 / 101 (0.99%)	0 / 46 (0.00%)	0 / 103 (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
MUSCLE INJURY			
subjects affected / exposed	1 / 101 (0.99%)	0 / 46 (0.00%)	0 / 103 (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
Vascular disorders			
DEEP VEIN THROMBOSIS			
subjects affected / exposed	0 / 101 (0.00%)	0 / 46 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PERIPHERAL ARTERIAL OCCLUSIVE DISEASE			
subjects affected / exposed	1 / 101 (0.99%)	0 / 46 (0.00%)	0 / 103 (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
PERIPHERAL VASCULAR DISORDER			
subjects affected / exposed	0 / 101 (0.00%)	1 / 46 (2.17%)	0 / 103 (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
VASCULITIS			
subjects affected / exposed	1 / 101 (0.99%)	0 / 46 (0.00%)	0 / 103 (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
Cardiac disorders			
ACUTE CORONARY SYNDROME			
subjects affected / exposed	1 / 101 (0.99%)	1 / 46 (2.17%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ACUTE MYOCARDIAL INFARCTION			
subjects affected / exposed	1 / 101 (0.99%)	0 / 46 (0.00%)	0 / 103 (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

ATRIAL FIBRILLATION			
subjects affected / exposed	1 / 101 (0.99%)	0 / 46 (0.00%)	2 / 103 (1.94%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ATRIAL FLUTTER			
subjects affected / exposed	0 / 101 (0.00%)	1 / 46 (2.17%)	0 / 103 (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
CARDIOPULMONARY FAILURE			
subjects affected / exposed	1 / 101 (0.99%)	0 / 46 (0.00%)	0 / 103 (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
CORONARY ARTERY DISEASE			
subjects affected / exposed	1 / 101 (0.99%)	0 / 46 (0.00%)	0 / 103 (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
LEFT VENTRICULAR DYSFUNCTION			
subjects affected / exposed	0 / 101 (0.00%)	0 / 46 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MYOCARDIAL INFARCTION			
subjects affected / exposed	0 / 101 (0.00%)	0 / 46 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PERICARDITIS			
subjects affected / exposed	0 / 101 (0.00%)	0 / 46 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
CEREBRAL ARTERY OCCLUSION			
subjects affected / exposed	1 / 101 (0.99%)	0 / 46 (0.00%)	0 / 103 (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
CEREBRAL ISCHAEMIA			

subjects affected / exposed	1 / 101 (0.99%)	0 / 46 (0.00%)	0 / 103 (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
CEREBROVASCULAR ACCIDENT			
subjects affected / exposed	1 / 101 (0.99%)	1 / 46 (2.17%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
EMBOLIC STROKE			
subjects affected / exposed	1 / 101 (0.99%)	0 / 46 (0.00%)	0 / 103 (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
General disorders and administration site conditions			
INFLUENZA LIKE ILLNESS			
subjects affected / exposed	1 / 101 (0.99%)	0 / 46 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PYREXIA			
subjects affected / exposed	0 / 101 (0.00%)	1 / 46 (2.17%)	0 / 103 (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
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	1 / 101 (0.99%)	0 / 46 (0.00%)	0 / 103 (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
ANAL FISSURE			
subjects affected / exposed	0 / 101 (0.00%)	1 / 46 (2.17%)	0 / 103 (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
CROHN'S DISEASE			
subjects affected / exposed	1 / 101 (0.99%)	0 / 46 (0.00%)	0 / 103 (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

INGUINAL HERNIA			
subjects affected / exposed	0 / 101 (0.00%)	0 / 46 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
CHOLECYSTITIS			
subjects affected / exposed	0 / 101 (0.00%)	1 / 46 (2.17%)	0 / 103 (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
CHOLELITHIASIS			
subjects affected / exposed	1 / 101 (0.99%)	0 / 46 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
LUNG DISORDER			
subjects affected / exposed	1 / 101 (0.99%)	0 / 46 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PLEURAL EFFUSION			
subjects affected / exposed	0 / 101 (0.00%)	0 / 46 (0.00%)	2 / 103 (1.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
BLADDER DILATATION			
subjects affected / exposed	1 / 101 (0.99%)	0 / 46 (0.00%)	0 / 103 (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
NEPHROLITHIASIS			
subjects affected / exposed	0 / 101 (0.00%)	0 / 46 (0.00%)	2 / 103 (1.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URINARY RETENTION			

subjects affected / exposed	0 / 101 (0.00%)	0 / 46 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
INTERVERTEBRAL DISC PROTRUSION			
subjects affected / exposed	0 / 101 (0.00%)	1 / 46 (2.17%)	0 / 103 (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
SPINAL COLUMN STENOSIS			
subjects affected / exposed	1 / 101 (0.99%)	0 / 46 (0.00%)	0 / 103 (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			
CELLULITIS			
subjects affected / exposed	0 / 101 (0.00%)	0 / 46 (0.00%)	2 / 103 (1.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ERYSIPELAS			
subjects affected / exposed	1 / 101 (0.99%)	0 / 46 (0.00%)	0 / 103 (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
INFECTED SKIN ULCER			
subjects affected / exposed	1 / 101 (0.99%)	0 / 46 (0.00%)	0 / 103 (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
LOWER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	1 / 101 (0.99%)	0 / 46 (0.00%)	0 / 103 (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
LUNG INFECTION			

subjects affected / exposed	0 / 101 (0.00%)	0 / 46 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OSTEOMYELITIS			
subjects affected / exposed	1 / 101 (0.99%)	0 / 46 (0.00%)	0 / 103 (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
PNEUMONIA			
subjects affected / exposed	0 / 101 (0.00%)	1 / 46 (2.17%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Nilotinib	Imatinib subset that crossed over to nilotinib	Imatinib
Total subjects affected by non-serious adverse events			
subjects affected / exposed	99 / 101 (98.02%)	39 / 46 (84.78%)	79 / 103 (76.70%)
Vascular disorders			
HYPERTENSION			
subjects affected / exposed	10 / 101 (9.90%)	1 / 46 (2.17%)	6 / 103 (5.83%)
occurrences (all)	10	1	6
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	9 / 101 (8.91%)	5 / 46 (10.87%)	4 / 103 (3.88%)
occurrences (all)	11	6	4
FATIGUE			
subjects affected / exposed	16 / 101 (15.84%)	6 / 46 (13.04%)	8 / 103 (7.77%)
occurrences (all)	19	7	8
INFLUENZA LIKE ILLNESS			
subjects affected / exposed	7 / 101 (6.93%)	2 / 46 (4.35%)	3 / 103 (2.91%)
occurrences (all)	12	2	3
OEDEMA PERIPHERAL			
subjects affected / exposed	6 / 101 (5.94%)	1 / 46 (2.17%)	7 / 103 (6.80%)
occurrences (all)	9	1	9

PAIN			
subjects affected / exposed	7 / 101 (6.93%)	1 / 46 (2.17%)	3 / 103 (2.91%)
occurrences (all)	7	1	3
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	11 / 101 (10.89%)	4 / 46 (8.70%)	9 / 103 (8.74%)
occurrences (all)	13	4	10
DYSPNOEA			
subjects affected / exposed	3 / 101 (2.97%)	3 / 46 (6.52%)	1 / 103 (0.97%)
occurrences (all)	5	3	1
OROPHARYNGEAL PAIN			
subjects affected / exposed	6 / 101 (5.94%)	0 / 46 (0.00%)	6 / 103 (5.83%)
occurrences (all)	6	0	6
Psychiatric disorders			
DEPRESSION			
subjects affected / exposed	6 / 101 (5.94%)	2 / 46 (4.35%)	4 / 103 (3.88%)
occurrences (all)	6	2	4
INSOMNIA			
subjects affected / exposed	12 / 101 (11.88%)	2 / 46 (4.35%)	5 / 103 (4.85%)
occurrences (all)	14	2	5
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	19 / 101 (18.81%)	8 / 46 (17.39%)	5 / 103 (4.85%)
occurrences (all)	34	11	6
AMYLASE INCREASED			
subjects affected / exposed	9 / 101 (8.91%)	2 / 46 (4.35%)	7 / 103 (6.80%)
occurrences (all)	17	3	8
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	14 / 101 (13.86%)	6 / 46 (13.04%)	10 / 103 (9.71%)
occurrences (all)	17	9	13
BILIRUBIN CONJUGATED INCREASED			
subjects affected / exposed	4 / 101 (3.96%)	4 / 46 (8.70%)	0 / 103 (0.00%)
occurrences (all)	8	9	0
BLOOD BILIRUBIN INCREASED			

subjects affected / exposed	10 / 101 (9.90%)	2 / 46 (4.35%)	1 / 103 (0.97%)
occurrences (all)	19	3	1
BLOOD CHOLESTEROL INCREASED			
subjects affected / exposed	8 / 101 (7.92%)	0 / 46 (0.00%)	2 / 103 (1.94%)
occurrences (all)	11	0	2
BLOOD CREATINE PHOSPHOKINASE INCREASED			
subjects affected / exposed	1 / 101 (0.99%)	2 / 46 (4.35%)	9 / 103 (8.74%)
occurrences (all)	1	2	16
BLOOD CREATININE INCREASED			
subjects affected / exposed	6 / 101 (5.94%)	2 / 46 (4.35%)	10 / 103 (9.71%)
occurrences (all)	6	3	17
GAMMA-GLUTAMYLTRANSFERASE INCREASED			
subjects affected / exposed	8 / 101 (7.92%)	2 / 46 (4.35%)	2 / 103 (1.94%)
occurrences (all)	8	2	2
GLOBULINS DECREASED			
subjects affected / exposed	4 / 101 (3.96%)	0 / 46 (0.00%)	8 / 103 (7.77%)
occurrences (all)	8	0	11
HIGH DENSITY LIPOPROTEIN DECREASED			
subjects affected / exposed	2 / 101 (1.98%)	3 / 46 (6.52%)	6 / 103 (5.83%)
occurrences (all)	4	4	8
LIPASE INCREASED			
subjects affected / exposed	19 / 101 (18.81%)	7 / 46 (15.22%)	13 / 103 (12.62%)
occurrences (all)	36	8	18
LOW DENSITY LIPOPROTEIN INCREASED			
subjects affected / exposed	2 / 101 (1.98%)	4 / 46 (8.70%)	3 / 103 (2.91%)
occurrences (all)	3	5	4
WEIGHT DECREASED			
subjects affected / exposed	10 / 101 (9.90%)	2 / 46 (4.35%)	5 / 103 (4.85%)
occurrences (all)	10	2	5
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	5 / 101 (4.95%)	3 / 46 (6.52%)	6 / 103 (5.83%)
occurrences (all)	5	4	6
HEADACHE			

subjects affected / exposed	43 / 101 (42.57%)	8 / 46 (17.39%)	13 / 103 (12.62%)
occurrences (all)	64	11	13
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	6 / 101 (5.94%)	5 / 46 (10.87%)	12 / 103 (11.65%)
occurrences (all)	7	6	13
Eye disorders			
CONJUNCTIVAL HAEMORRHAGE			
subjects affected / exposed	1 / 101 (0.99%)	0 / 46 (0.00%)	6 / 103 (5.83%)
occurrences (all)	1	0	10
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	12 / 101 (11.88%)	5 / 46 (10.87%)	8 / 103 (7.77%)
occurrences (all)	17	6	10
ABDOMINAL PAIN UPPER			
subjects affected / exposed	13 / 101 (12.87%)	5 / 46 (10.87%)	7 / 103 (6.80%)
occurrences (all)	22	7	9
CONSTIPATION			
subjects affected / exposed	15 / 101 (14.85%)	3 / 46 (6.52%)	0 / 103 (0.00%)
occurrences (all)	19	3	0
DIARRHOEA			
subjects affected / exposed	14 / 101 (13.86%)	4 / 46 (8.70%)	19 / 103 (18.45%)
occurrences (all)	16	6	26
NAUSEA			
subjects affected / exposed	22 / 101 (21.78%)	4 / 46 (8.70%)	16 / 103 (15.53%)
occurrences (all)	25	5	18
VOMITING			
subjects affected / exposed	11 / 101 (10.89%)	0 / 46 (0.00%)	6 / 103 (5.83%)
occurrences (all)	16	0	12
Hepatobiliary disorders			
HYPERBILIRUBINAEMIA			
subjects affected / exposed	10 / 101 (9.90%)	6 / 46 (13.04%)	0 / 103 (0.00%)
occurrences (all)	20	7	0
Skin and subcutaneous tissue disorders			
ALOPECIA			
subjects affected / exposed	11 / 101 (10.89%)	4 / 46 (8.70%)	0 / 103 (0.00%)
occurrences (all)	12	4	0

DRY SKIN			
subjects affected / exposed	20 / 101 (19.80%)	3 / 46 (6.52%)	0 / 103 (0.00%)
occurrences (all)	23	3	0
PRURITUS			
subjects affected / exposed	30 / 101 (29.70%)	2 / 46 (4.35%)	0 / 103 (0.00%)
occurrences (all)	41	6	0
RASH			
subjects affected / exposed	30 / 101 (29.70%)	9 / 46 (19.57%)	4 / 103 (3.88%)
occurrences (all)	54	11	4
RASH FOLLICULAR			
subjects affected / exposed	4 / 101 (3.96%)	3 / 46 (6.52%)	0 / 103 (0.00%)
occurrences (all)	4	3	0
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	16 / 101 (15.84%)	6 / 46 (13.04%)	10 / 103 (9.71%)
occurrences (all)	21	7	11
BACK PAIN			
subjects affected / exposed	12 / 101 (11.88%)	7 / 46 (15.22%)	9 / 103 (8.74%)
occurrences (all)	13	7	10
MUSCLE SPASMS			
subjects affected / exposed	15 / 101 (14.85%)	1 / 46 (2.17%)	18 / 103 (17.48%)
occurrences (all)	16	1	22
MUSCULOSKELETAL PAIN			
subjects affected / exposed	10 / 101 (9.90%)	2 / 46 (4.35%)	8 / 103 (7.77%)
occurrences (all)	14	3	8
MYALGIA			
subjects affected / exposed	14 / 101 (13.86%)	6 / 46 (13.04%)	2 / 103 (1.94%)
occurrences (all)	22	7	3
PAIN IN EXTREMITY			
subjects affected / exposed	14 / 101 (13.86%)	8 / 46 (17.39%)	4 / 103 (3.88%)
occurrences (all)	20	8	4
Infections and infestations			
FOLLICULITIS			
subjects affected / exposed	8 / 101 (7.92%)	2 / 46 (4.35%)	0 / 103 (0.00%)
occurrences (all)	9	2	0
INFLUENZA			

subjects affected / exposed	9 / 101 (8.91%)	2 / 46 (4.35%)	9 / 103 (8.74%)
occurrences (all)	11	2	9
NASOPHARYNGITIS			
subjects affected / exposed	9 / 101 (8.91%)	2 / 46 (4.35%)	5 / 103 (4.85%)
occurrences (all)	15	2	6
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	20 / 101 (19.80%)	7 / 46 (15.22%)	14 / 103 (13.59%)
occurrences (all)	30	8	18
URINARY TRACT INFECTION			
subjects affected / exposed	8 / 101 (7.92%)	2 / 46 (4.35%)	1 / 103 (0.97%)
occurrences (all)	10	2	1
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	8 / 101 (7.92%)	1 / 46 (2.17%)	6 / 103 (5.83%)
occurrences (all)	10	3	6
HYPERCHOLESTEROLAEMIA			
subjects affected / exposed	11 / 101 (10.89%)	7 / 46 (15.22%)	6 / 103 (5.83%)
occurrences (all)	13	8	6
HYPERGLYCAEMIA			
subjects affected / exposed	4 / 101 (3.96%)	6 / 46 (13.04%)	6 / 103 (5.83%)
occurrences (all)	7	13	9
HYPERTRIGLYCERIDAEMIA			
subjects affected / exposed	3 / 101 (2.97%)	2 / 46 (4.35%)	7 / 103 (6.80%)
occurrences (all)	3	2	14
HYPOPHOSPHATAEMIA			
subjects affected / exposed	9 / 101 (8.91%)	7 / 46 (15.22%)	13 / 103 (12.62%)
occurrences (all)	15	12	21

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 June 2009	Amendment 1 was a global amendment to include an additional inclusion criterion: To be eligible for the study, patients must now had to have serum calcium levels within normal levels.
20 May 2010	Amendment 2 was a global amendment to correct and clarify two inclusion and one exclusion criterion. Inclusion criterion #4 was modified to remove the example "i.e. BCR-ABL level <1% IS"and to change the time frame between PCR tests to 8 weeks instead of 10 weeks. Inclusion criterion #10, which required phosphorus levels to be within normal limits, was removed. The criterion was also modified to require electrolytes ≥ lower limit of normal rather than within normal limits. Exclusion criterion #4, which states patients must not have had prior stem cell transplantation, was modified: Patients who had received an autologous transplant and were in chronic phase prior to transplant and never in accelerated phase or blast crisis were now eligible. Information regarding study drug and H1N1 vaccinations were also added.
21 March 2012	Amendment 3 was a global amendment to update the safety and to clarify survival follow-up. The protocol was amended in order to reflect what was captured in the case report forms prior to the Month 24 analysis.
15 January 2014	Amendment 4 was a global amendment 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.
05 September 2014	Amendment 5 was a global amendment to remove the requirement for survival follow up for an additional 6 years after the study closure. In addition, the ICF was updated to include language that the biomarker samples that remain after analysis is completed (tumor, blood, plasma, and serum) may be kept for up to 15 years to be used for additi onal studies by Novartis.

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, results of crossover studies and data using 999 as data points are not accurately represented in this record. Please go to https://www.novctrd.com/CtrdWeb/home.nov for complete trial results

Notes: