Clinical trial results:
A Phase IIIb, multicentre, open-label study of nilotinib in adult patients with newly diagnosed Philadelphia chromosome and/or BCR-ABL positive CML in chronic phase

Summary

EudraCT number	2009-017775-19
Trial protocol	FR NL BE HU ES FI GB PT DE SE CZ DK SK GR AT LT IT LV SI EE BG
Global end of trial date	07 July 2014

Results information

Result version number	v1 (current)
This version publication date	23 July 2016
First version publication date	23 July 2016

Trial information

Trial identification

Sponsor protocol code	CAMN107EIC01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01061177
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	07 July 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 July 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate the rate of molecular response (MR4.0) at 18 months of nilotinib treatment.

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	20 May 2010
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	Austria: 17
Country: Number of subjects enrolled	Belgium: 30
Country: Number of subjects enrolled	Bulgaria: 21
Country: Number of subjects enrolled	Croatia: 4
Country: Number of subjects enrolled	Czech Republic: 16
Country: Number of subjects enrolled	Denmark: 14
Country: Number of subjects enrolled	Estonia: 1
Country: Number of subjects enrolled	Finland: 4
Country: Number of subjects enrolled	France: 150
Country: Number of subjects enrolled	Germany: 258
Country: Number of subjects enrolled	Greece: 10
Country: Number of subjects enrolled	Hungary: 35
Country: Number of subjects enrolled	Italy: 154
Country: Number of subjects enrolled	Latvia: 3
Country: Number of subjects enrolled	Lithuania: 15
Country: Number of subjects enrolled	Netherlands: 28
Country: Number of subjects enrolled	Norway: 12
Country: Number of subjects enrolled	Poland: 66
Country: Number of subjects enrolled	Portugal: 11

Country: Number of subjects enrolled	Romania: 61
Country: Number of subjects enrolled	Slovakia: 10
Country: Number of subjects enrolled	Slovenia: 3
Country: Number of subjects enrolled	Spain: 100
Country: Number of subjects enrolled	Sweden: 33
Country: Number of subjects enrolled	Switzerland: 5
Country: Number of subjects enrolled	United Kingdom: 28
Worldwide total number of subjects	1089
EEA total number of subjects	1084

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)	864
From 65 to 84 years	221
85 years and over	4

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A maximum of 806 patients were planned to be enrolled into the study and were to receive nilotinib 300 mg bid for a duration of up to 24 months.
In order to allow the completion of additional national sub-studies 976 patients were planned to be enrolled.

Period 1

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

Arms

Arm title	Nilotinib

Arm description:

This was a single-arm study; therefore all participants received nilotinib (AMN107) 300 mg bid given as two 150 mg capsules twice daily.

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 300 mg bid given as two 150 mg capsules (to be swallowed whole with a glass of water)

Number of subjects in period 1	Nilotinib
Started	1089
ITT_MR (b2a2 &/or b3a2 +ve pts only)	1056
ITT_CyR (Ph+ patients only)	983
Completed	881
Not completed	208
Adverse event, serious fatal	4
Consent withdrawn by subject	27
Disease progression	17
Abnormal test procedure results	4
Adverse event, non-fatal	117
New cancer therapy	9
Abnormal laboratory values	6
Administratie problems	4

Lost to follow-up	9
Protocol deviation	11

Baseline characteristics

Reporting groups	
Reporting group title	Nilotinib
Reporting group description:	
This was a single-arm study; therefore all participants received nilotinib (AMN107) 300 mg bid given as two 150 mg capsules twice daily.	

Reporting group values	Nilotinib	Total	
Number of subjects	1089	1089	
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)	864	864	
From 65-84 years	221	221	
85 years and over	4	4	
Age Continuous |			
Units: Years			
arithmetic mean	51.6		
standard deviation	± 14.87	-	
Gender, Male/Female			
Units: Participants			
Female	447	447	
Male	642	642	
Race/Ethnicity, Customized			
Units: Subjects			
Caucacian	1045	1045	
Black	6	6	
Oriental	5	5	
Native American	2	2	
Other	31	31	
Study Specific Characteristic			
ECOG = Eastern Cooperative Oncology Group			
Units: Subjects			
No restrictions (0)	867	867	
Only light work (1)	199	199	
Only self care (2)	21	21	
Limited self care (3)	0	0	
Completely disabled (4)	0	0	
Missing	2	2	

Study Specific Characteristic | Units: Kg			
arithmetic mean	77.47		
standard deviation	± 15.73	-	

End points

End points reporting groups

Reporting group title	Nilotinib

Reporting group description:

This was a single-arm study; therefore all participants received nilotinib (AMN107) 300 mg bid given as two 150 mg capsules twice daily.

Primary: Percentage of participants with molecular response (MR4^0) at 18 months

End point title	Percentage of participants with molecular response (MR4^0) at 18 months[1]

End point description:

MR4^0 was defined as either (i) detectable disease ≤ 0.01% BCR-ABL ratio (international scale (IS)) with mean ABL transcripts ≥ 10 000 or (ii) undetectable disease in complementary deoxyribonucleic acid (cDNA) with ≥ 10 000 ABL transcripts.
No statistical analysis was planned for this primary outcome.

End point type	Primary

End point timeframe:

at 18 months

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was planned for this endpoint.

End point values	Nilotinib			
Subject group type	Reporting group			
Number of subjects analysed	1056			
Units: Percentage of Participants				
number (not applicable)	38.3			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants free from progression to accelerated phase/blast crisis (AP/BC) at 12 and 24 months

End point title	Percentage of participants free from progression to accelerated phase/blast crisis (AP/BC) at 12 and 24 months

End point description:

The following events were considered disease progression to AP/BC: Death due to disease under study; AP, as defined by any of the following: ≥ 15% blasts in the peripheral blood or bone marrow, but < 30% blasts in both the peripheral blood and bone marrow, ≥ 30% blasts plus promyelocytes in peripheral blood or bone marrow, ≥ 20% basophils in the peripheral blood, Thrombocytopenia (< 100 × 109/L) that was unrelated to therapy, Evidence of clonal evolution, as determined by medical review with consensus of the SSMC/DMC. BC was defined as: ≥ 30% blasts in peripheral blood or bone marrow, Appearance of extramedullary involvement other than hepatosplenomegaly proven by biopsy

End point type	Secondary

End point timeframe:

at 12 and 24 months

End point values	Nilotinib			
Subject group type	Reporting group			
Number of subjects analysed	1089			
Units: Percentage of participants				
number (not applicable)				
Pts free from progression to AP/BC at 12 months	99.4			
Pts free from progression to AP/BC at 24 months	99.4			

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of event free survival at 12 and 24 months

End point title	Rate of event free survival at 12 and 24 months

End point description:

EFS was defined as the time from the date of Day 1 (first treatment) + 1 day to the first occurrence of any of the following: Loss of complete hematologic response (CHR), Loss of CCyR, Death from any cause, Progression to the AP or BC of CML, Not achieving CHR up to 3 months (ie, 91 + 15 days), Not achieving CCyR up to 18 months (ie, 548 + 15 days), whichever is earlier.

End point type	Secondary

End point timeframe:

at 12 and 24 months

End point values	Nilotinib			
Subject group type	Reporting group			
Number of subjects analysed	1089			
Units: Percentage of participants				
number (not applicable)				
Percentage of participants with EFS at 12 months	71.7			
Percentage of participants with EFS at 24 months	69.1			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with major molecular response (MMR) at, as well as by, 12 and 24 months

End point title	Percentage of participants with major molecular response

	(MMR) at, as well as by, 12 and 24 months

End point description:

MMR was defined as BCR-ABL ratio (IS) ≤ 0.1% in a peripheral blood sample. BCR-ABL1 is an abnormal gene found in chronic myeloid leukemia (CML) and acute lymphoblastic leukemia (ALL). The chromosomal defect in the Philadelphia chromosome is a translocation, in which parts of two chromosomes, 9 and 22, swap places. The result is that a fusion gene is created by juxtapositioning the Abl1 gene on chromosome 9 to a part of the BCR ("breakpoint cluster region") gene on chromosome 22. Depending upon the breakpoints on the BCR gene, there are several forms of fusion proteins.

End point type	Secondary

End point timeframe:

12 months, 24 months

End point values	Nilotinib			
Subject group type	Reporting group			
Number of subjects analysed	1056			
Units: Percentage of participants				
number (not applicable)				
at 12 months	56.2			
at 24 months	61.1			
by 12 months	68.8			
by 24 months	80.3			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with complete cytogenetic response (CCyR) at, as well as by, 12 and 24 months

End point title	Percentage of participants with complete cytogenetic response (CCyR) at, as well as by, 12 and 24 months

End point description:

CCyR parameters were defined as 0% Philadelphia positive (Ph+) metaphases. Loss of CCyR was defined as a patient exceeding the CCyR criteria (ie, > 0% Ph+ metaphases) at a subsequent visit after the patient had achieved CCyR.

End point type	Secondary

End point timeframe:

at 12 and 24 months

End point values	Nilotinib			
Subject group type	Reporting group			
Number of subjects analysed	983			
Units: Percentage of participants				
number (not applicable)				
at 12 months	72.4			
at 24 months	65.6			

By Month 12	82.5			
By Month 24	89			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with major cytogenetic response (MCyR) at, as well as by, 12 and 24 months

End point title	Percentage of participants with major cytogenetic response (MCyR) at, as well as by, 12 and 24 months
End point description:	
MCyR parameters were defined as 0 to 35% Philadelphia positive (Ph+) metaphases.	
End point type	Secondary
End point timeframe:	
at 12 and 24 months	

End point values	Nilotinib			
Subject group type	Reporting group			
Number of subjects analysed	983			
Units: Percentage of participants				
number (not applicable)				
at 12 months	73.8			
at 24 months	66.2			
by 12 months	86.7			
by 24 months	91.4			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants free from progression to AP/BC with MR4^0 at 12 months

End point title	Percentage of participants free from progression to AP/BC with MR4^0 at 12 months
End point description:	
The following events were considered disease progression to AP/BC: Death due to disease under study; AP, as defined by any of the following: ≥ 15% blasts in the peripheral blood or bone marrow, but < 30% blasts in both the peripheral blood and bone marrow, ≥ 30% blasts plus promyelocytes in peripheral blood or bone marrow, ≥ 20% basophils in the peripheral blood, Thrombocytopenia (< 100 × 109/L) that was unrelated to therapy, Evidence of clonal evolution, as determined by medical review with consensus of the SSMC/DMC. BC was defined as: ≥ 30% blasts in peripheral blood or bone marrow, Appearance of extramedullary involvement other than hepatosplenomegaly proven by biopsy	
End point type	Secondary

End point timeframe:

at 12 months

End point values	Nilotinib			
Subject group type	Reporting group			
Number of subjects analysed	1089			
Units: Percentage of participants				
number (not applicable)	100			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with event free survival in participants achieving MR4^0 at 12 months

End point title	Percentage of participants with event free survival in participants achieving MR4^0 at 12 months

End point description:

EFS was defined as the time from the date of Day 1 (first treatment) + 1 day to the first occurrence of any of the following: Loss of complete hematologic response (CHR), Loss of CCyR, Death from any cause, Progression to the AP or BC of CML, Not achieving CHR up to 3 months (ie, 91 + 15 days), Not achieving CCyR up to 18 months (ie, 548 + 15 days), whichever is earlier.

End point type	Secondary

End point timeframe:

at 12 months

End point values	Nilotinib			
Subject group type	Reporting group			
Number of subjects analysed	1089			
Units: Percentage of participants				
number (not applicable)	87			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with Progression Free Survival (PFS) at 12 and 24 months

End point title	Percentage of participants with Progression Free Survival (PFS) at 12 and 24 months

End point description:

PFS was defined by the study protocol as the time from the date of start of study drug to the date of

earliest progression to AP/BC, or the date of death from any cause.

End point type	Secondary

End point timeframe:

12 months, 24 months

End point values	Nilotinib			
Subject group type	Reporting group			
Number of subjects analysed	1089			
Units: Percentage of participants				
number (not applicable)				
at 12 months	99.2			
at 24 months	99			

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of molecular response (MR4^0) at, as well as by, 12 and 24 months

End point title	Rate of molecular response (MR4^0) at, as well as by, 12 and 24 months

End point description:

MR4^0 was defined as either (i) detectable disease ≤ 0.01% BCR-ABL ratio (international scale (IS)) with mean ABL transcripts ≥ 10 000 or (ii) undetectable disease in complementary deoxyribonucleic acid (cDNA) with ≥ 10 000 ABL transcripts.

End point type	Secondary

End point timeframe:

12 and 24 months

End point values	Nilotinib			
Subject group type	Reporting group			
Number of subjects analysed	1056			
Units: Percentage of particiapants				
number (not applicable)				
at 12 months	30.7			
at 24 months	40.2			
by month 12	36.9			
by month 24	55			

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of molecular response (MR4^5) at, as well as by, 12 and 24 months

End point title	Rate of molecular response (MR4^5) at, as well as by, 12 and 24 months

End point description:

MR4^5 was defined as either (i) detectable disease ≤ 0.0032% BCR-ABL ratio (IS) with mean ABL transcripts ≥ 32 000 or (ii) undetectable disease in cDNA with ≥ 32 000 ABL transcripts).

End point type	Secondary

End point timeframe:

12 and 24 months

End point values	Nilotinib			
Subject group type	Reporting group			
Number of subjects analysed	1056			
Units: Percentage of particiapants				
number (not applicable)				
at 12 months	15.2			
at 24 months	21.9			
by 12 months	20.6			
by 24 months	38.4			

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of complete hematologic response (CHR) at, as well as by, 12 and 24 months

End point title	Rate of complete hematologic response (CHR) at, as well as by, 12 and 24 months

End point description:

CHR was defined as all of the following present for ≥ 4 weeks in the peripheral blood: WBC count < 10 x 109/L, Platelet count < 450 x 109/L, No circulating peripheral blood blasts, promyelocytes, myelocytes, or metamyelocytes in the peripheral blood, The presence of < 5% basophils, No evidence of disease-related symptoms and extramedullary disease, including spleen and liver. Loss of CHR was defined as the appearance of any of the following after having achieved a CHR confirmed by a second determination ≥ 4 weeks later (unless associated with progression to AP/BC or death, which was considered to be a confirmed loss of CHR event on its own): WBC count that increased to > 20.0 x 109/L, Platelet count that increased to ≥ 600 x 109/L, Any palpable spleen, defined as size of spleen below costal margin > 5 cm, Appearance of > 5% myelocytes plus metamyelocytes, or any promyelocytes or blasts in the peripheral blood.

End point type	Secondary

End point timeframe:

12 months, 24 months

End point values	Nilotinib			
Subject group type	Reporting group			
Number of subjects analysed	1089			
Units: Percentage of prticipants				
number (not applicable)				
by Month 24	89.1			
at 12 months	82.7			
at 24 months	75.5			
by Month12	86.2			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with Event Free Survival (EFS) at 12 and 24 months

End point title	Percentage of participants with Event Free Survival (EFS) at 12 and 24 months

End point description:

EFS was defined as the time from the date of Day 1 (first treatment) + 1 day to the first occurrence of any of the following: Loss of CHR, Loss of CCyR, Death from any cause, Progression to the AP or BC of CML, Not achieving CHR up to 3 months (ie, 91 + 15 days), Not achieving CCyR up to 18 months (ie, 548 + 15 days), whichever is earlier.

End point type	Secondary

End point timeframe:

12 months, 24 months

End point values	Nilotinib			
Subject group type	Reporting group			
Number of subjects analysed	1089			
Units: Percentage of participants				
number (not applicable)				
at 12 months	71.7			
at 24 months	69.1			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with Overall Survival at 12 and 24 months

End point title	Percentage of participants with Overall Survival at 12 and 24 months

End point description:

OS was defined as the time between the date of Day 1 (first treatment) and the date of death from any cause. Deaths which occurred after the 24-month time window and which were occasionally reported by

some Investigators were excluded from the analysis. This is in agreement with the protocol stating that patients were to be followed for survival and progression to AP/BC up to 24 months after the participants treatment start.

End point type	Secondary

End point timeframe:

12 months, 24 months

End point values	Nilotinib			
Subject group type	Reporting group			
Number of subjects analysed	1089			
Units: Percentage of participants				
number (not applicable)				
at 12 months	99.6			
at 24 months	98.9			

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of molecular response (MR4^0) by 18 months

End point title	Rate of molecular response (MR4^0) by 18 months

End point description:

MR4^0 was defined as either (i) detectable disease ≤ 0.01% BCR-ABL ratio (international scale (IS)) with mean ABL transcripts ≥ 10 000 or (ii) undetectable disease in complementary deoxyribonucleic acid (cDNA) with ≥ 10 000 ABL transcripts. BCR = Breakpoint Cluster Region gene/BCR gene product BCR-ABL is fusion gene formed from the ABL gene from chromosome 9 fusing with the BCR gene on chromosome 22, the gene product is BCR-ABL tyrosine kinase

End point type	Secondary

End point timeframe:

18 months

End point values	Nilotinib			
Subject group type	Reporting group			
Number of subjects analysed	1056			
Units: Percentage of particiapants				
number (not applicable)	48.5			

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of molecular response (MR4^5) by 18 months

End point title	Rate of molecular response (MR4^5) by 18 months

End point description:

MR4^5 was defined as either (i) detectable disease ≤ 0.0032% BCR-ABL ratio (IS) with mean ABL transcripts ≥ 32 000 or (ii) undetectable disease in cDNA with ≥ 32 000 ABL transcripts). BCR = Breakpoint Cluster Region gene/BCR gene product BCR-ABL is fusion gene formed from the ABL gene from chromosome 9 fusing with the BCR gene on chromosome 22, the gene product is BCR-ABL tyrosine kinase

End point type	Secondary

End point timeframe:

18 months

End point values	Nilotinib			
Subject group type	Reporting group			
Number of subjects analysed	1056			
Units: Percentage of particiapants				
number (not applicable)	31.6			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of particiapnts with progression free survival in participants achieving MR4^0 at 12 months

End point title	Percentage of particiapnts with progression free survival in participants achieving MR4^0 at 12 months

End point description:

PFS was defined by the study protocol as the time from the date of start of study drug to the date of earliest progression to AP/BC, or the date of death from any cause.

End point type	Secondary

End point timeframe:

12 months

End point values	Nilotinib			
Subject group type	Reporting group			
Number of subjects analysed	1089			
Units: Percentage of participants				
number (not applicable)	100			

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	17

Reporting groups

Reporting group title	All patients

Reporting group description:

All patients

Serious adverse events	All patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	207 / 1089 (19.01%)		
number of deaths (all causes)	4		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder neoplasm			
subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blast cell crisis			
subjects affected / exposed	2 / 1089 (0.18%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Breast cancer			
subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cervix carcinoma			

subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholangiocarcinoma			
subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Colorectal cancer			
subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Colon adenoma			
subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Duodenal neoplasm			
subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endometrial cancer			
subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Squamous cell carcinoma			
subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin cancer			
subjects affected / exposed	2 / 1089 (0.18%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Retroperitoneal cancer			

subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Prostate cancer				
subjects affected / exposed	2 / 1089 (0.18%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Non-Hodgkin's lymphoma				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Uterine leiomyoma				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary bladder adenoma				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Aneurysm ruptured				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Deep vein thrombosis				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Arterial occlusive disease				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Arterial haemorrhage				

subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Arterial disorder			
subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Aortic stenosis			
subjects affected / exposed	2 / 1089 (0.18%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
Haemorrhage			
subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypertension			
subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Peripheral artery stenosis			
subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peripheral arterial occlusive disease			
subjects affected / exposed	2 / 1089 (0.18%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Leriche syndrome			
subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypertensive crisis			

subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peripheral ischaemia			
subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Raynaud's phenomenon			
subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Hysterectomy			
subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin neoplasm excision			
subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Device dislocation			
subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Drug resistance			
subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Fatigue			
subjects affected / exposed	2 / 1089 (0.18%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Localised oedema			
subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Non-cardiac chest pain			
subjects affected / exposed	4 / 1089 (0.37%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Oedema peripheral			
subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	6 / 1089 (0.55%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Soft tissue inflammation			
subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Genital pain			
subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Genital swelling			
subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metrorrhagia			
subjects affected / exposed	2 / 1089 (0.18%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Menorrhagia			
subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	5 / 1089 (0.46%)		
occurrences causally related to treatment / all	3 / 8		
deaths causally related to treatment / all	0 / 0		
Epistaxis			
subjects affected / exposed	2 / 1089 (0.18%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Hyperventilation			
subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Pneumonitis				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Sleep apnoea syndrome				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Anxiety				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Bipolar disorder				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Confusional state				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Depression				
subjects affected / exposed	4 / 1089 (0.37%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 0			
Depression suicidal				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Suicide attempt				

subjects affected / exposed	3 / 1089 (0.28%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Investigations				
Amylase increased				
subjects affected / exposed	2 / 1089 (0.18%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Blood creatine phosphokinase increased				
subjects affected / exposed	2 / 1089 (0.18%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Blood pressure increased				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
C-reactive protein increased				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Electrocardiogram QT prolonged				
subjects affected / exposed	3 / 1089 (0.28%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Lipase increased				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Platelet count decreased				
subjects affected / exposed	3 / 1089 (0.28%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Transaminases increased				

subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Cervical vertebral fracture			
subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Clavicle fracture			
subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Coronary artery restenosis			
subjects affected / exposed	2 / 1089 (0.18%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Exposure via father			
subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Femoral neck fracture			
subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Overdose			
subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sternal injury			
subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rib fracture			

subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Road traffic accident				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Post procedural inflammation				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tendon rupture				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Congenital, familial and genetic disorders				
Atrial septal defect				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Acute coronary syndrome				
subjects affected / exposed	3 / 1089 (0.28%)			
occurrences causally related to treatment / all	2 / 4			
deaths causally related to treatment / all	0 / 0			
Acute myocardial infarction				
subjects affected / exposed	4 / 1089 (0.37%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 0			
Angina pectoris				
subjects affected / exposed	6 / 1089 (0.55%)			
occurrences causally related to treatment / all	2 / 6			
deaths causally related to treatment / all	0 / 0			

Angina unstable			
subjects affected / exposed	2 / 1089 (0.18%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			
subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Atrial flutter			
subjects affected / exposed	2 / 1089 (0.18%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Arteriosclerosis coronary artery			
subjects affected / exposed	2 / 1089 (0.18%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Aortic valve stenosis			
subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
subjects affected / exposed	13 / 1089 (1.19%)		
occurrences causally related to treatment / all	6 / 13		
deaths causally related to treatment / all	0 / 0		
Mitral valve disease			
subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Coronary artery thrombosis			
subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Coronary artery stenosis			

subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Coronary artery disease			
subjects affected / exposed	7 / 1089 (0.64%)		
occurrences causally related to treatment / all	4 / 9		
deaths causally related to treatment / all	0 / 0		
Mitral valve incompetence			
subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac failure congestive			
subjects affected / exposed	3 / 1089 (0.28%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Pericardial effusion			
subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myocardial ischaemia			
subjects affected / exposed	3 / 1089 (0.28%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction			
subjects affected / exposed	4 / 1089 (0.37%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Pericarditis			
subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Sick sinus syndrome			

subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Prinzmetal angina				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Supraventricular tachycardia				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Carotid artery stenosis				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Carotid artery occlusion				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Aphasia				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Carpal tunnel syndrome				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Facial paresis				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cranial nerve disorder				

subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebrovascular accident				
subjects affected / exposed	2 / 1089 (0.18%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Cerebral ischaemia				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebral haemorrhage				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Headache				
subjects affected / exposed	5 / 1089 (0.46%)			
occurrences causally related to treatment / all	3 / 5			
deaths causally related to treatment / all	0 / 0			
Hyperaesthesia				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Intracranial aneurysm				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ischaemic stroke				
subjects affected / exposed	2 / 1089 (0.18%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Lethargy				

subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Memory impairment				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Motor neurone disease				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Neuropathy peripheral				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Subarachnoid haemorrhage				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sciatica				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Occipital neuralgia				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Transient ischaemic attack				
subjects affected / exposed	2 / 1089 (0.18%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
VIIth nerve paralysis				

subjects affected / exposed	1 / 1089 (0.09%)		
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	5 / 1089 (0.46%)		
occurrences causally related to treatment / all	3 / 5		
deaths causally related to treatment / all	0 / 0		
Haemorrhagic anaemia			
subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Leukopenia			
subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	2 / 1089 (0.18%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Haemolytic anaemia			
subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancytopenia			
subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Splenic infarction			
subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			

subjects affected / exposed	3 / 1089 (0.28%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 1		
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vertigo			
subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Conjunctival disorder			
subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye haemorrhage			
subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Diabetic retinopathy			
subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal pain lower			
subjects affected / exposed	2 / 1089 (0.18%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Abdominal pain			
subjects affected / exposed	4 / 1089 (0.37%)		
occurrences causally related to treatment / all	2 / 6		
deaths causally related to treatment / all	0 / 0		
Colitis			
subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Duodenal ulcer haemorrhage			
subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	2 / 1089 (0.18%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	3 / 1089 (0.28%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Dysphagia			
subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastric ulcer perforation			
subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastritis			
subjects affected / exposed	2 / 1089 (0.18%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrooesophageal reflux disease			

subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrooesophageal sphincter insufficiency			
subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemorrhoids			
subjects affected / exposed	2 / 1089 (0.18%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Haemorrhoids thrombosed			
subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ileus			
subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Inguinal hernia			
subjects affected / exposed	2 / 1089 (0.18%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Intestinal obstruction			
subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatic disorder			

subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				
subjects affected / exposed	6 / 1089 (0.55%)			
occurrences causally related to treatment / all	6 / 6			
deaths causally related to treatment / all	0 / 0			
Pancreatitis acute				
subjects affected / exposed	2 / 1089 (0.18%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Umbilical hernia				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Small intestinal haemorrhage				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	5 / 1089 (0.46%)			
occurrences causally related to treatment / all	2 / 5			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Cholangitis				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cholecystitis				
subjects affected / exposed	2 / 1089 (0.18%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Gallbladder enlargement				

subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatic fibrosis				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatic steatosis				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatotoxicity				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cholelithiasis				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Jaundice				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Diabetic foot				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Dry gangrene				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Photosensitivity reaction				

subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Skin haemorrhage				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Dysuria				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haematuria				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Incontinence				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nephrolithiasis				
subjects affected / exposed	2 / 1089 (0.18%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Renal colic				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal failure				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal cyst				

subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal failure acute				
subjects affected / exposed	2 / 1089 (0.18%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Urinary retention				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal impairment				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Endocrine disorders				
Goitre				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hyperthyroidism				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Inappropriate antidiuretic hormone secretion				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Thyroiditis subacute				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				

Back pain				
subjects affected / exposed	5 / 1089 (0.46%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 0			
Arthropathy				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Arthralgia				
subjects affected / exposed	2 / 1089 (0.18%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Bone pain				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Muscular weakness				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Intervertebral disc protrusion				
subjects affected / exposed	2 / 1089 (0.18%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal pain				
subjects affected / exposed	3 / 1089 (0.28%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Neck pain				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pain in extremity				

subjects affected / exposed	2 / 1089 (0.18%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Rotator cuff syndrome				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Bronchitis				
subjects affected / exposed	2 / 1089 (0.18%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Appendicitis				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Abdominal abscess				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bronchopneumonia				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gangrene				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Epididymitis				

subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diverticulitis				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Corneal abscess				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lung infection				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Perirectal abscess				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Phlebitis infective				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	4 / 1089 (0.37%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 1			
Rectal abscess				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection				

subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection bacterial				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Viral pericarditis				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Diabetes mellitus				
subjects affected / exposed	3 / 1089 (0.28%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Decreased appetite				
subjects affected / exposed	2 / 1089 (0.18%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Hyponatraemia				
subjects affected / exposed	1 / 1089 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hyperglycaemia				
subjects affected / exposed	2 / 1089 (0.18%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Hypercholesterolaemia				

subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Failure to thrive			
subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypophosphataemia			
subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 1089 (0.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	All patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	841 / 1089 (77.23%)		
Investigations			
Blood bilirubin increased			
subjects affected / exposed	80 / 1089 (7.35%)		
occurrences (all)	157		
Alanine aminotransferase increased			
subjects affected / exposed	86 / 1089 (7.90%)		
occurrences (all)	117		
Lipase increased			
subjects affected / exposed	76 / 1089 (6.98%)		
occurrences (all)	95		
Vascular disorders			
Hypertension			

subjects affected / exposed	64 / 1089 (5.88%)		
occurrences (all)	69		
Nervous system disorders			
Headache			
subjects affected / exposed	163 / 1089 (14.97%)		
occurrences (all)	206		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	65 / 1089 (5.97%)		
occurrences (all)	71		
Thrombocytopenia			
subjects affected / exposed	111 / 1089 (10.19%)		
occurrences (all)	162		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	97 / 1089 (8.91%)		
occurrences (all)	113		
Fatigue			
subjects affected / exposed	150 / 1089 (13.77%)		
occurrences (all)	183		
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	88 / 1089 (8.08%)		
occurrences (all)	104		
Abdominal pain			
subjects affected / exposed	79 / 1089 (7.25%)		
occurrences (all)	91		
Vomiting			
subjects affected / exposed	62 / 1089 (5.69%)		
occurrences (all)	72		
Nausea			
subjects affected / exposed	122 / 1089 (11.20%)		
occurrences (all)	147		
Constipation			

subjects affected / exposed	65 / 1089 (5.97%)		
occurrences (all)	72		
Diarrhoea			
subjects affected / exposed	93 / 1089 (8.54%)		
occurrences (all)	115		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	56 / 1089 (5.14%)		
occurrences (all)	65		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	115 / 1089 (10.56%)		
occurrences (all)	127		
Pruritus			
subjects affected / exposed	180 / 1089 (16.53%)		
occurrences (all)	227		
Dry skin			
subjects affected / exposed	93 / 1089 (8.54%)		
occurrences (all)	100		
Rash			
subjects affected / exposed	233 / 1089 (21.40%)		
occurrences (all)	302		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	55 / 1089 (5.05%)		
occurrences (all)	61		
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	93 / 1089 (8.54%)		
occurrences (all)	110		
Back pain			
subjects affected / exposed	78 / 1089 (7.16%)		
occurrences (all)	93		
Arthralgia			

subjects affected / exposed	96 / 1089 (8.82%)		
occurrences (all)	116		
Myalgia			
subjects affected / exposed	99 / 1089 (9.09%)		
occurrences (all)	108		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	113 / 1089 (10.38%)		
occurrences (all)	147		
Metabolism and nutrition disorders			
Hypophosphataemia			
subjects affected / exposed	77 / 1089 (7.07%)		
occurrences (all)	152		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 March 2010	This amendment was a local, country-specific amendment for Germany and Spain. For Germany, the modifications were made in order to allow the switch from study drug to prescription drug in Germany after registration and reimbursement of nilotinib in the study indication. For Spain, a local sub-study to the main protocol was introduced and was described in Post Text Supplement (PTS) 1 which included the rationale and methodology for conducting the sub-study, which aimedto find biological, biochemical and molecular genetics biomarkers, both at the time of diagnosis and during treatment, to allow predicting response to nilotinib in patients with newly diagnosed CML.
11 May 2010	The rationale of Amendment 2 was to specify alternative wording to an existing inclusion
29 June 2010	Amendment 3 clarified a number of definitions, analyses and tests relating to the conduct of the study, specifically addressing the assessments and visits to be performed during the study, and the assessment of the study endpoints.
02 August 2010	Incorporated the changes requested by the German IRB committee into the protocol, Referenced the addition of 10 sub-studies to the core protocol as PTS, which Included biological, biochemical, and molecular genetics biomarkers, Added study the stem cell compartment and analyze the correlation between telomere lengths and response to treatment, Included analysis of nilotinib blood plasma levels during treatment, Added study adherence to treatment and quality of life.
07 October 2010	This local amendment made changes to PTS 4 (a multinational sub-study on the determination of plasma nilotinib levels and single cell quantification of phosphoprotein response during nilotinib treatment in early chronic phase CML). These changes involved: Amendments to the PTS 4 visit schedule table and subsequent alignment of text throughout the document, Amendment of PTS 4 laboratory methodology text.
09 February 2011	The rationale of this substantial global amendment was to Amend the statistical sections to allow for extension of recruitment in order to completethe sub-studies after the completion of the core trial and Clarify the populations for analysis, providing the rationale for the interim analyses and providing further clarity to the analysis of “by” and “at” time points.
25 March 2011	These changes involved: Amendments to the methodology section in PTS 1, Amendments to the sample collection methodology in PTS 6, Removal of reference to a participating country (Belgium) and amendment of text relatingto the validation of samples in PTS 7, Amendments to visit schedule and assessments in PTS 9.
25 July 2011	This substantial local amendment was to allow for prolongation of recruitment in Germany in
23 September 2011	To include the new EUTOS prognostic score in the analysis of prognosis at diagnosis
23 January 2012	This local amendment changes involved: Amendments to multiple sections of PTS 10 to revise the text in line with the new working definition of complete molecular response, as introduced in Amendment 9, Amendments to the data collection and data review sections of PTS 11.

23 April 2012	Amendment 11 provided continued access to nilotinib to patients in study CAMN107EIC01 who a) benefitted from treatment with nilotinib and b) who resided in a country in which nilotinib was not yet reimbursed. Study CAMN107EIC01 was designed to treat patients for a duration of 24 months with nilotinib within the context of the study: following completion of 18 months of study treatment (the primary efficacy analysis time point) all patients were scheduled to receive treatment and be followed up for further 6 months. With this amendment Novartis ensured that patients in countries in which Tasigna 150 mg capsules were not yet reimbursed for the treatment of newly diagnosed patients with Ph+ CML CP had continued access to Tasigna if - according to the Investigator's judgment - they benefitted from it. The amendment applied to the Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, Portugal and Romania. The study duration for patients in these countries was extended beyond 24 months until February 2014, at which time LPLV for study CAMN107EIC01 was scheduled.The patients were to receive commercial drug as soon as the 150 mg capsules were reimbursed in the respective country.
10 January 2013	Amendment 12 provided continued access to nilotinib for patients in study CAMN107EIC01 who a) benefitted from treatment with nilotinib and b) resided in Slovakia or Croatia where nilotinib was not yet reimbursed. Patients were to receive commercial drug as soon as the 150 mg capsules were reimbursed in Slovakia or Croatia. To ensure that legal requirements for prescriptions were met it was added that the prescriptionof nilotinib exclusively followed the assessment of the patient's individual medical need. Finally, the schedule of assessment for patients who resided in Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, Portugal, Slovakia, Croatia and Romania was added.
16 December 2013	To update the efficacy and safety data of nilotinib according to the Investigator's Brochure Edition 9 (June 2013), focusing on the 48 month update of the CAMN107A2303 study in newly diagnosed CML-CP patients and 24 month update of the phase I/II open-label study CAMN107A2101 in CML patients. To prolong the study to guarantee continued access to nilotinib for patients who reside in countries where nilotinib was not reimbursed by end of February 2014 and who were deriving benefit from study treatment according to medical judgment. The overall LPLV was to occur on 30-Jun-2014. In case nilotinib was not yet locally reimbursed by 30-Jun-2014, an alternative program to provide patients with nilotinib was activated in each country according to local regulation.To update the definition of EFS based on the CML management recommendations byEuropean LeukemiaNet (Baccarani et al 2009) and SSMC.To clarify the definition of progression to AP/BC and PFS. Furthermore, changes were made on the statistical sections to better clarify the analysis methods. In addition minor inconsistencies and typos in the protocol were corrected.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported