Clinical trial results:
A prospective, randomized, open-label, two-arm Phase III study to evaluate treatment-free remission (TFR) rate in patients with Philadelphia chromosome-positive CML after two different durations of consolidation treatment with nilotinib 300 mg BID

Summary

EudraCT number	2012-005124-15
Trial protocol	AT SK SE HU IT DE NO PT FI ES IE CZ BG BE GR DK SI HR
Global end of trial date	08 July 2020

Results information

Result version number	v1 (current)
This version publication date	09 July 2021
First version publication date	09 July 2021

Trial information

Trial identification

Sponsor protocol code	CAMN107AIC05

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01743989
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, novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, novartis.email@novartis.com

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	08 July 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 July 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to assess the optimal duration of consolidation treatment with nilotinib 300 mg twice daily (BID) in order that patients remained in treatment free remission (TFR) (≥MR4.0) without molecular relapse 12 months after entering the TFR phase.

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	15 April 2013
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: 15
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Bulgaria: 17
Country: Number of subjects enrolled	Czechia: 9
Country: Number of subjects enrolled	Denmark: 6
Country: Number of subjects enrolled	Finland: 2
Country: Number of subjects enrolled	France: 54
Country: Number of subjects enrolled	Germany: 65
Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	Greece: 14
Country: Number of subjects enrolled	Hungary: 17
Country: Number of subjects enrolled	Italy: 182
Country: Number of subjects enrolled	Norway: 5
Country: Number of subjects enrolled	Poland: 54
Country: Number of subjects enrolled	Portugal: 27
Country: Number of subjects enrolled	Romania: 19
Country: Number of subjects enrolled	Serbia: 27
Country: Number of subjects enrolled	Slovakia: 6
Country: Number of subjects enrolled	Slovenia: 2

Country: Number of subjects enrolled	Spain: 85
Country: Number of subjects enrolled	Sweden: 4
Worldwide total number of subjects	620
EEA total number of subjects	585

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)	512
From 65 to 84 years	108
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

For one participant randomized to Nilotinib 36-month treatment arm, the informed consent was not obtained prior to any study specific procedure. This participant discontinued the study before entering the TFR phase.

Period 1

Period 1 title	Treatment phase
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Nilotinib 24-month treatment

Arm description:

Participants were treated with nilotinib 300mg BID for 24 months and, thereafter, entered the 36-month TFR phase

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

Dosage and administration details:

Nilotinib daily oral dose of 300 mg BID, supplied as 150 mg hard gelatin capsules.

Arm title	Nilotinib 36-month treatment

Arm description:

Participants were treated with nilotinib 300mg BID for 36 months and, thereafter, entered the 24-month TFR phase

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

Dosage and administration details:

Nilotinib daily oral dose of 300 mg BID, supplied as 150 mg hard gelatin capsules.

Arm title	Not randomized

Arm description:

Participants were treated with nilotinib 300mg BID for 24 months, but did not achieve a sustained molecular response after 24 months of treatment and were not randomized.

Arm type	Experimental

Investigational medicinal product name	Nilotinib
Investigational medicinal product code	AMN107
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Nilotinib daily oral dose of 300 mg BID, supplied as 150 mg hard gelatin capsules.

Number of subjects in period 1	Nilotinib 24-month treatment	Nilotinib 36-month treatment	Not randomized
Started	120	119	381
Participants who signed informed consent	120	118	381
Completed	119	104	0
Not completed	1	15	381
Adverse event, serious fatal	-	1	3
New cancer (CML) therapy	-	1	-
Abnormal laboratory value(s)	-	-	3
Physician decision	-	-	3
Unstable MR4.0	-	6	263
Patient non-compliance to treatment	-	-	3
Not randomized by mistake	-	-	1
Administrative problems	-	-	1
Abnormal test procedure result(s)	-	-	1
Included by mistake	-	-	1
Consent withdrawn by subject	1	3	28
Adverse event, non-fatal	-	4	67
Protocol deviation	-	-	3
Pregnancy	-	-	2
Lost to follow-up	-	-	2

Period 2

Period 2 title	TFR phase
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes

Arm title	Nilotinib 24-month treatment

Arm description:

Participants were treated with nilotinib 300mg BID for 24 months and, thereafter, entered the 36-month TFR phase

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

Dosage and administration details:

Nilotinib daily oral dose of 300 mg BID, supplied as 150 mg hard gelatin capsules.

Arm title	Nilotinib 36-month treatment

Arm description:

Participants were treated with nilotinib 300mg BID for 36 months and, thereafter, entered the 24-month TFR phase

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

Dosage and administration details:

Nilotinib daily oral dose of 300 mg BID, supplied as 150 mg hard gelatin capsules.

Number of subjects in period 2	Nilotinib 24-month treatment	Nilotinib 36-month treatment
Started	119	104
Participants who were re-treated	74	55
Completed	37	36
Not completed	82	68
Physician decision	-	1
Logistical problems	-	2
Consent withdrawn by subject	-	2
Adverse event, non-fatal	-	1
Relapse (Loss of MMR/Confirmed loss of MR4.0)	82	59
Protocol deviation	-	1
Lost to follow-up	-	2

Baseline characteristics

Reporting groups	
Reporting group title	Nilotinib 24-month treatment
Reporting group description:	
Participants were treated with nilotinib 300mg BID for 24 months and, thereafter, entered the 36-month TFR phase	
Reporting group title	Nilotinib 36-month treatment
Reporting group description:	
Participants were treated with nilotinib 300mg BID for 36 months and, thereafter, entered the 24-month TFR phase	
Reporting group title	Not randomized
Reporting group description:	
Participants were treated with nilotinib 300mg BID for 24 months, but did not achieve a sustained molecular response after 24 months of treatment and were not randomized.	

Reporting group values	Nilotinib 24-month treatment	Nilotinib 36-month treatment	Not randomized
Number of subjects	120	119	381
Age Categorical Units: Participants			
<=18 years	0	0	0
Between 18 and 65 years	106	98	308
>=65 years	14	21	73
Sex: Female, Male Units: Participants			
Female	48	49	129
Male	72	70	252
Race/Ethnicity, Customized Units: Subjects			
Caucasian	114	112	355
Black	0	1	4
Asian	0	0	2
Native American	0	1	1
North African descent	1	0	1
Unknown	0	1	5
Other	5	4	13

Reporting group values	Total		
Number of subjects	620		
Age Categorical Units: Participants			
<=18 years	0		
Between 18 and 65 years	512		
>=65 years	108		
Sex: Female, Male Units: Participants			
Female	226		
Male	394		

Race/Ethnicity, Customized Units: Subjects			
Caucasian	581		
Black	5		
Asian	2		
Native American	2		
North African descent	2		
Unknown	6		
Other	22		

End points

End points reporting groups

Reporting group title	Nilotinib 24-month treatment
Reporting group description:	
Participants were treated with nilotinib 300mg BID for 24 months and, thereafter, entered the 36-month TFR phase	
Reporting group title	Nilotinib 36-month treatment
Reporting group description:	
Participants were treated with nilotinib 300mg BID for 36 months and, thereafter, entered the 24-month TFR phase	
Reporting group title	Not randomized
Reporting group description:	
Participants were treated with nilotinib 300mg BID for 24 months, but did not achieve a sustained molecular response after 24 months of treatment and were not randomized.	
Reporting group title	Nilotinib 24-month treatment
Reporting group description:	
Participants were treated with nilotinib 300mg BID for 24 months and, thereafter, entered the 36-month TFR phase	
Reporting group title	Nilotinib 36-month treatment
Reporting group description:	
Participants were treated with nilotinib 300mg BID for 36 months and, thereafter, entered the 24-month TFR phase	

Primary: Percentage of participants who remained in treatment free remission (TFR) without molecular relapse 12 months after entering the TFR phase

End point title	Percentage of participants who remained in treatment free remission (TFR) without molecular relapse 12 months after entering the TFR phase

End point description:

Number of participants who remained in TFR (≥molecular response (MR) 4.0) without molecular relapse 12 months after entering the TFR phase (without re-starting nilotinib therapy) divided by the number of participants who entered the TFR phase and multiplied by 100.
Molecular relapse during TFR is defined as the loss of major molecular response (MMR), or the confirmed loss of MR4.0 (defined by 3 consecutive tests less than MR4.0 assessed at 3 consecutive visits during TFR phase). Participants dropping out early from the study during the TFR phase were considered as unsuccessful TFR.
Confidence intervals were calculated based on the Exact Clopper-Pearson method.
MMR is defined as≥3.0 log reduction in BCR-ABL transcripts compared to the standardized baseline or ≤0.1% BCR-ABL.
MR4.0 is defined as either detectable disease≤0.01% BCR-ABL or undetectable disease in cDNA with≥10,000 ABL transcripts

End point type	Primary

End point timeframe:

12 months after entering the TFR phase, which is after 36 months from study treatment start for Nilotinib 24-month treatment arm and after 48 months from study treatment start for Nilotinib 36-month treatment arm

End point values	Nilotinib 24-month treatment	Nilotinib 36-month treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119	104		
Units: Percentage of participants				
number (confidence interval 95%)	31.9 (23.7 to 41.1)	37.5 (28.2 to 47.5)		

Statistical analyses

Statistical analysis title	Nilotinib 24-month vs Nilotinib 36-month treatment
Comparison groups	Nilotinib 24-month treatment v Nilotinib 36-month treatment
Number of subjects included in analysis	223
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.383
Method	Chi-squared

Secondary: Cumulative incidence of MMR during the pre-randomization induction/consolidation phase among participants without that response at study entry

End point title	Cumulative incidence of MMR during the pre-randomization induction/consolidation phase among participants without that response at study entry

End point description:

Number of participants who were in MMR during pre-randomization induction/consolidation phase divided by the number of participants without that response at baseline and multiplied by 100.
Confidence intervals were calculated based on the Exact Clopper-Pearson method.
MMR is defined as ≥3.0 log reduction in BCR-ABL transcripts compared to the standardized baseline or ≤0.1% BCR-ABL.

End point type	Secondary

End point timeframe:

From baseline up to 24 months after study treatment start

End point values	Nilotinib 24-month treatment	Nilotinib 36-month treatment	Not randomized	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	23	16	98	
Units: Percentage of participants				
number (confidence interval 95%)				
Up to 3 months after study treatment start	69.6 (47.1 to 86.8)	37.5 (15.2 to 64.6)	29.6 (20.8 to 39.7)	
Up to 6 months after study treatment start	100 (85.2 to 100.0)	100.0 (79.4 to 100.0)	64.3 (54.0 to 73.7)	
Up to 9 months after study treatment start	100 (85.2 to 100.0)	100.0 (79.4 to 100.0)	71.4 (61.4 to 80.1)	

Up to 12 months after study treatment start	100 (85.2 to 100.0)	100.0 (79.4 to 100.0)	77.6 (68.0 to 85.4)	
Up to 15 months after study treatment start	100 (85.2 to 100.0)	100.0 (79.4 to 100.0)	80.6 (71.4 to 87.9)	
Up to 18 months after study treatment start	100 (85.2 to 100.0)	100.0 (79.4 to 100.0)	82.7 (73.7 to 89.6)	
Up to 21 months after study treatment start	100 (85.2 to 100.0)	100.0 (79.4 to 100.0)	85.7 (77.2 to 92.0)	
Up to 24 months after study treatment start	100 (85.2 to 100.0)	100.0 (79.4 to 100.0)	86.7 (78.4 to 92.7)	

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulative incidence of MMR during the post-randomization consolidation phase among participants without that response at study entry

End point title	Cumulative incidence of MMR during the post-randomization consolidation phase among participants without that response at study entry[1]

End point description:

Number of participants who were in MMR during post-randomization consolidation phase divided by the number of participants without that response at baseline and multiplied by 100. Post-randomization consolidation phase corresponded to the 12-month additional treatment (after randomization) for Nilotinib 36-month treatment arm.
Confidence intervals were calculated based on the Exact Clopper-Pearson method.
MMR is defined as ≥3.0 log reduction in BCR-ABL transcripts compared to the standardized baseline or ≤0.1% BCR-ABL.

End point type	Secondary

End point timeframe:

From randomization (month 24 after study treatment start) up to 36 months after study treatment start

Notes:

[1] - 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: Only participants randomized to Nilotinib 36-month treatment arm entered the post-randomization consolidation phase.

End point values	Nilotinib 36-month treatment			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: Percentage of participants				
number (confidence interval 95%)				
Up to 27 months after study treatment start	100.0 (79.4 to 100.0)			
Up to 30 months after study treatment start	100.0 (79.4 to 100.0)			
Up to 33 months after study treatment start	100.0 (79.4 to 100.0)			
Up to 36 months after study treatment start	100.0 (79.4 to 100.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulative incidence of MR4.0 during the pre-randomization induction/consolidation phase among participants without that response at study entry

End point title	Cumulative incidence of MR4.0 during the pre-randomization induction/consolidation phase among participants without that response at study entry

End point description:

Number of participants who were in MR4.0 during the pre-randomization induction/consolidation phase divided by the number of participants without that response at baseline and multiplied by 100.
Confidence intervals were calculated based on the Exact Clopper-Pearson method.
MR4.0 is defined as either detectable disease ≤0.01% BCR-ABL IS or undetectable disease in cDNA with ≥10,000 ABL transcripts (numbers of ABL transcripts in the same volume of cDNA used to test for BCR-ABL)

End point type	Secondary

End point timeframe:

From baseline up to 24 months after study treatment start

End point values	Nilotinib 24-month treatment	Nilotinib 36-month treatment	Not randomized	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	92	94	357	
Units: Percentage of participants				
number (confidence interval 95%)				
Up to 3 months after study treatment start	48.9 (38.3 to 59.6)	38.3 (28.5 to 48.9)	12.9 (9.6 to 16.8)	
Up to 6 months after study treatment start	85.9 (77.1 to 92.3)	81.9 (72.6 to 89.1)	26.6 (22.1 to 31.5)	
Up to 9 months after study treatment start	94.6 (87.8 to 98.2)	92.6 (85.3 to 97.0)	34.5 (29.5 to 39.6)	
Up to 12 months after study treatment start	96.7 (90.8 to 99.3)	98.9 (94.2 to 100.0)	39.2 (34.1 to 44.5)	
Up to 15 months after study treatment start	100.0 (96.1 to 100.0)	98.9 (94.2 to 100.0)	42.0 (36.8 to 47.3)	
Up to 18 months after study treatment start	100.0 (96.1 to 100.0)	100.0 (96.2 to 100.0)	45.1 (39.9 to 50.4)	
Up to 21 months after study treatment start	100.0 (96.1 to 100.0)	100.0 (96.2 to 100.0)	48.7 (43.4 to 54.1)	
Up to 24 months after study treatment start	100.0 (96.1 to 100.0)	100.0 (96.2 to 100.0)	52.1 (46.8 to 57.4)	

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulative incidence of MR4.0 during the post-randomization consolidation phase among participants without that response at study entry

End point title	Cumulative incidence of MR4.0 during the post-randomization consolidation phase among participants without that response

	at study entry[2]

End point description:

Number of participants who were in MR4.0 during the post-randomization consolidation phase divided by the number of participants without that response at baseline and multiplied by 100. Post-randomization consolidation phase corresponded to the 12-month additional treatment (after randomization) for Nilotinib 36-month treatment arm.
Confidence intervals were calculated based on the Exact Clopper-Pearson method.
MR4.0 is defined as either detectable disease ≤0.01% BCR-ABL IS or undetectable disease in cDNA with ≥10,000 ABL transcripts (numbers of ABL transcripts in the same volume of cDNA used to test for BCR-ABL)

End point type	Secondary

End point timeframe:

From randomization (month 24 after study treatment start) up to 36 months after study treatment start

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: Only participants randomized to Nilotinib 36-month treatment arm entered the post-randomization consolidation phase.

End point values	Nilotinib 36-month treatment			
Subject group type	Reporting group			
Number of subjects analysed	94			
Units: Percentage of participants				
number (confidence interval 95%)				
Up to 27 months after study treatment start	97.9 (92.5 to 99.7)			
Up to 30 months after study treatment start	97.9 (92.5 to 99.7)			
Up to 33 months after study treatment start	97.9 (92.5 to 99.7)			
Up to 36 months after study treatment start	97.9 (92.5 to 99.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulative incidence of MR4.5 during the pre-randomization induction/consolidation phase among participants without that response at study entry

End point title	Cumulative incidence of MR4.5 during the pre-randomization induction/consolidation phase among participants without that response at study entry

End point description:

Number of participants who were in MR4.5 during the pre-randomization induction/consolidation phase divided by the number of participants without that response at baseline and multiplied by 100.
Confidence intervals were calculated based on the Exact Clopper-Pearson method.
MR4.5 is defined as either detectable disease ≤ 0.0032% BCR-ABL IS; or undetectable disease within cDNA with ≥ 32,000 ABL transcripts (numbers of ABL transcripts in the same volume of cDNA used to test for BCR-ABL)

End point type	Secondary

End point timeframe:

From baseline up to 24 months after study treatment start

End point values	Nilotinib 24-month treatment	Nilotinib 36-month treatment	Not randomized	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	109	109	374	
Units: Percentage of participants				
number (confidence interval 95%)				
Up to 3 months after study treatment start	21.1 (13.9 to 30.0)	17.4 (10.8 to 25.9)	4.0 (2.3 to 6.5)	
Up to 6 months after study treatment start	38.5 (29.4 to 48.3)	38.5 (29.4 to 48.3)	8.6 (5.9 to 11.9)	
Up to 9 months after study treatment start	57.8 (48.0 to 67.2)	54.1 (44.3 to 63.7)	10.7 (7.8 to 14.3)	
Up to 12 months after study treatment start	70.6 (61.2 to 79.0)	65.1 (55.4 to 74.0)	14.2 (10.8 to 18.1)	
Up to 15 months after study treatment start	79.8 (71.1 to 86.9)	76.1 (67.0 to 83.8)	15.2 (11.8 to 19.3)	
Up to 18 months after study treatment start	83.5 (75.2 to 89.9)	80.7 (72.1 to 87.7)	16.6 (13.0 to 20.7)	
Up to 21 months after study treatment start	85.3 (77.3 to 91.4)	84.4 (76.2 to 90.6)	18.4 (14.7 to 22.8)	
Up to 24 months after study treatment start	89.0 (81.6 to 94.2)	89.0 (81.6 to 94.2)	20.3 (16.4 to 24.8)	

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulative incidence of MR4.5 during the post-randomization consolidation phase among participants without that response at study entry

End point title	Cumulative incidence of MR4.5 during the post-randomization consolidation phase among participants without that response at study entry[3]

End point description:

Number of participants who were in MR4.5 during the post-randomization consolidation phase divided by the number of participants without that response at baseline and multiplied by 100. Post-randomization consolidation phase corresponded to the 12-month additional treatment (after randomization) for Nilotinib 36-month treatment arm.
Confidence intervals were calculated based on the Exact Clopper-Pearson method.
MR4.5 is defined as either detectable disease ≤ 0.0032% BCR-ABL IS; or undetectable disease within cDNA with ≥ 32,000 ABL transcripts (numbers of ABL transcripts in the same volume of cDNA used to test for BCR-ABL)

End point type	Secondary

End point timeframe:

From randomization (month 24 after study treatment start) up to 36 months after study treatment start

Notes:

[3] - 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: Only participants randomized to Nilotinib 36-month treatment arm entered the post-randomization consolidation phase.

End point values	Nilotinib 36-month treatment			
Subject group type	Reporting group			
Number of subjects analysed	109			
Units: Percentage of participants				
number (confidence interval 95%)				
Up to 27 months after study treatment start	70.6 (61.2 to 79.0)			
Up to 30 months after study treatment start	76.1 (67.0 to 83.8)			
Up to 33 months after study treatment start	84.4 (76.2 to 90.6)			
Up to 36 months after study treatment start	87.2 (79.4 to 92.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulative incidence of MMR during the pre-randomization induction/consolidation phase

End point title	Cumulative incidence of MMR during the pre-randomization induction/consolidation phase

End point description:

Number of participants who were in MMR during the pre-randomization induction/consolidation phase divided by the number of enrolled participants and multiplied by 100.
Confidence intervals were calculated based on the Exact Clopper-Pearson method.
MMR is defined as ≥3.0 log reduction in BCR-ABL transcripts compared to the standardized baseline or ≤0.1% BCR-ABL.

End point type	Secondary

End point timeframe:

From baseline up to 24 months after study treatment start

End point values	Nilotinib 24-month treatment	Nilotinib 36-month treatment	Not randomized	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	120	118	381	
Units: Percentage of participants				
number (confidence interval 95%)				
Baseline	80.8 (72.6 to 87.4)	86.4 (78.9 to 92.1)	74.3 (69.6 to 78.6)	
Up to 3 months after study treatment start	94.2 (88.4 to 97.6)	91.5 (85.0 to 95.9)	81.9 (77.7 to 85.6)	
Up to 6 months after study treatment start	100.0 (97.0 to 100.0)	100.0 (96.9 to 100.0)	90.8 (87.5 to 93.5)	
Up to 9 months after study treatment start	100.0 (97.0 to 100.0)	100.0 (96.9 to 100.0)	92.7 (89.6 to 95.1)	
Up to 12 months after study treatment start	100.0 (97.0 to 100.0)	100.0 (96.9 to 100.0)	94.2 (91.4 to 96.4)	

Up to 15 months after study treatment start	100.0 (97.0 to 100.0)	100.0 (96.9 to 100.0)	95.0 (92.3 to 97.0)	
Up to 18 months after study treatment start	100.0 (97.0 to 100.0)	100.0 (96.9 to 100.0)	95.5 (93.0 to 97.4)	
Up to 21 months after study treatment start	100.0 (97.0 to 100.0)	100.0 (96.9 to 100.0)	96.3 (93.9 to 98.0)	
Up to 24 months after study treatment start	100.0 (97.0 to 100.0)	100.0 (96.9 to 100.0)	96.6 (94.2 to 98.2)	

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulative incidence of MMR during the post-randomization consolidation phase

End point title	Cumulative incidence of MMR during the post-randomization consolidation phase[4]

End point description:

Number of participants who were in MMR during the post-randomization consolidation phase divided by the number of enrolled participants and multiplied by 100. Post-randomization consolidation phase corresponded to the 12-month additional treatment (after randomization) for Nilotinib 36-month treatment arm.
Confidence intervals were calculated based on the Exact Clopper-Pearson method.
MMR is defined as ≥3.0 log reduction in BCR-ABL transcripts compared to the standardized baseline or ≤0.1% BCR-ABL.

End point type	Secondary

End point timeframe:

From randomization (month 24 after study treatment start) up to 36 months after study treatment start

Notes:

[4] - 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: Only participants randomized to Nilotinib 36-month treatment arm entered the post-randomization consolidation phase.

End point values	Nilotinib 36-month treatment			
Subject group type	Reporting group			
Number of subjects analysed	118			
Units: Percentage of participants				
number (confidence interval 95%)				
Up to 27 months after study treatment start	98.3 (94.0 to 99.8)			
Up to 30 months after study treatment start	98.3 (94.0 to 99.8)			
Up to 33 months after study treatment start	98.3 (94.0 to 99.8)			
Up to 36 months after study treatment start	98.3 (94.0 to 99.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulative incidence of MR4.0 during the pre-randomization induction/consolidation phase

End point title	Cumulative incidence of MR4.0 during the pre-randomization induction/consolidation phase

End point description:

Number of participants who were in MR4.0 during the pre-randomization induction/consolidation phase divided by the number of enrolled participants and multiplied by 100.
Confidence intervals were calculated based on the Exact Clopper-Pearson method.
MR4.0 is defined as either detectable disease ≤0.01% BCR-ABL IS or undetectable disease in cDNA with ≥10,000 ABL transcripts (numbers of ABL transcripts in the same volume of cDNA used to test for BCR-ABL)

End point type	Secondary

End point timeframe:

From baseline up to 24 months after study treatment start

End point values	Nilotinib 24-month treatment	Nilotinib 36-month treatment	Not randomized	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	120	118	381	
Units: Percentage of participants				
number (confidence interval 95%)				
Baseline	23.3 (16.1 to 31.9)	20.3 (13.5 to 28.7)	6.3 (4.1 to 9.2)	
Up to 3 months after study treatment start	60.8 (51.5 to 69.6)	50.8 (41.5 to 60.2)	18.4 (14.6 to 22.6)	
Up to 6 months after study treatment start	89.2 (82.2 to 94.1)	85.6 (77.9 to 91.4)	31.2 (26.6 to 36.2)	
Up to 9 months after study treatment start	95.8 (90.5 to 98.6)	94.1 (88.2 to 97.6)	38.6 (33.7 to 43.7)	
Up to 12 months after study treatment start	97.5 (92.9 to 99.5)	99.2 (95.4 to 100.0)	43.0 (38.0 to 48.2)	
Up to 15 months after study treatment start	100.0 (97.0 to 100.0)	99.2 (95.4 to 100.0)	45.7 (40.6 to 50.8)	
Up to 18 months after study treatment start	100.0 (97.0 to 100.0)	100.0 (96.9 to 100.0)	48.6 (43.4 to 53.7)	
Up to 21 months after study treatment start	100.0 (97.0 to 100.0)	100.0 (96.9 to 100.0)	52.0 (46.8 to 57.1)	
Up to 24 months after study treatment start	100.0 (97.0 to 100.0)	100.0 (96.9 to 100.0)	55.1 (50.0 to 60.2)	

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulative incidence of MR4.0 during the post-randomization consolidation phase

End point title	Cumulative incidence of MR4.0 during the post-randomization consolidation phase[5]

End point description:

Number of participants who were in MR4.0 during the post-randomization consolidation phase divided by the number of enrolled participants and multiplied by 100. Post-randomization consolidation phase corresponded to the 12-month additional treatment (after randomization) for Nilotinib 36-month treatment arm.
Confidence intervals were calculated based on the Exact Clopper-Pearson method.
MR4.0 is defined as either detectable disease ≤0.01% BCR-ABL IS or undetectable disease in cDNA with ≥10,000 ABL transcripts (numbers of ABL transcripts in the same volume of cDNA used to test for BCR-ABL)

End point type	Secondary

End point timeframe:

From randomization (month 24 after study treatment start) up to 36 months after study treatment start

Notes:

[5] - 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: Only participants randomized to Nilotinib 36-month treatment arm entered the post-randomization consolidation phase.

End point values	Nilotinib 36-month treatment			
Subject group type	Reporting group			
Number of subjects analysed	118			
Units: Percentage of participants				
number (confidence interval 95%)				
Up to 27 months after study treatment start	98.3 (94.0 to 99.8)			
Up to 30 months after study treatment start	98.3 (94.0 to 99.8)			
Up to 33 months after study treatment start	98.3 (94.0 to 99.8)			
Up to 36 months after study treatment start	98.3 (94.0 to 99.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulative incidence of MR4.5 during the pre-randomization induction/consolidation phase

End point title	Cumulative incidence of MR4.5 during the pre-randomization induction/consolidation phase

End point description:

Number of participants who were in MR4.5 during the pre-randomization induction/consolidation phase divided by the number of enrolled participants and multiplied by 100.
Confidence intervals were calculated based on the Exact Clopper-Pearson method.
MR4.5 is defined as either detectable disease ≤ 0.0032% BCR-ABL IS; or undetectable disease within cDNA with ≥ 32,000 ABL transcripts (numbers of ABL transcripts in the same volume of cDNA used to test for BCR-ABL)

End point type	Secondary

End point timeframe:

From baseline up to 24 months after study treatment start

End point values	Nilotinib 24-month treatment	Nilotinib 36-month treatment	Not randomized	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	120	118	381	
Units: Percentage of participants				
number (confidence interval 95%)				
Baseline	9.2 (4.7 to 15.8)	7.6 (3.6 to 14.0)	1.8 (0.7 to 3.8)	
Up to 3 months after study treatment start	28.3 (20.5 to 37.3)	23.7 (16.4 to 32.4)	5.8 (3.7 to 8.6)	
Up to 6 months after study treatment start	44.2 (35.1 to 53.5)	43.2 (34.1 to 52.7)	10.2 (7.4 to 13.7)	
Up to 9 months after study treatment start	61.7 (52.4 to 70.4)	57.6 (48.2 to 66.7)	12.3 (9.2 to 16.1)	
Up to 12 months after study treatment start	73.3 (64.5 to 81.0)	67.8 (58.6 to 76.1)	15.7 (12.2 to 19.8)	
Up to 15 months after study treatment start	81.7 (73.6 to 88.1)	78.0 (69.4 to 85.1)	16.8 (13.2 to 20.9)	
Up to 18 months after study treatment start	85.0 (77.3 to 90.9)	82.2 (74.1 to 88.6)	18.1 (14.4 to 22.4)	
Up to 21 months after study treatment start	86.7 (79.3 to 92.2)	85.6 (77.9 to 91.4)	19.9 (16.1 to 24.3)	
Up to 24 months after study treatment start	90.0 (83.2 to 94.7)	89.8 (82.9 to 94.6)	21.8 (17.7 to 26.3)	

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulative incidence of MR4.5 during the post-randomization consolidation phase

End point title	Cumulative incidence of MR4.5 during the post-randomization consolidation phase[6]

End point description:

Number of participants who were in MR4.5 during the post-randomization consolidation phase divided by the number of enrolled participants and multiplied by 100. Post-randomization consolidation phase corresponded to the 12-month additional treatment (after randomization) for Nilotinib 36-month treatment arm.
Confidence intervals were calculated based on the Exact Clopper-Pearson method.
MR4.5 is defined as either detectable disease ≤ 0.0032% BCR-ABL IS; or undetectable disease within cDNA with ≥ 32,000 ABL transcripts (numbers of ABL transcripts in the same volume of cDNA used to test for BCR-ABL)

End point type	Secondary

End point timeframe:

From randomization (month 24 after study treatment start) up to 36 months after study treatment start

Notes:

[6] - 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: Only participants randomized to Nilotinib 36-month treatment arm entered the post-randomization consolidation phase.

End point values	Nilotinib 36-month treatment			
Subject group type	Reporting group			
Number of subjects analysed	118			
Units: Percentage of participants				
number (confidence interval 95%)				
Up to 27 months after study treatment start	72.9 (63.9 to 80.7)			
Up to 30 months after study treatment start	78.0 (69.4 to 85.1)			
Up to 33 months after study treatment start	85.6 (77.9 to 91.4)			
Up to 36 months after study treatment start	88.1 (80.9 to 93.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants who were in MMR during TFR phase

End point title	Percentage of participants who were in MMR during TFR phase

End point description:

Number of participants who were in MMR at selected timepoints divided by the number of participants in the TFR phase and multiplied by 100. Participants randomized in Nilotinib 36-month treatment arm had a maximum of 24 months of TFR phase, whereas participants randomized in Nilotinib 24-month treatment arm had a maximum of 36 months of TFR phase.
Confidence intervals were calculated based on the Exact Clopper-Pearson method.
MMR is defined as ≥3.0 log reduction in BCR-ABL transcripts compared to the standardized baseline or ≤0.1% BCR-ABL.
Note: 999 indicates value is not applicable.

End point type	Secondary

End point timeframe:

From Month 1 after entering TFR phase up to 24 months after entering TFR phase for Nilotinib 36-month treatment arm and up to 36 months after entering TFR phase for Nilotinib 24-month treatment arm

End point values	Nilotinib 24-month treatment	Nilotinib 36-month treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119	104		
Units: Percentage of participants				
number (confidence interval 95%)				
Month 1 after entering TFR phase	97.5 (92.8 to 99.5)	94.2 (87.9 to 97.9)		
Month 2 after entering TFR phase	84.9 (77.2 to 90.8)	80.8 (71.9 to 87.8)		
Month 3 after entering TFR phase	62.2 (52.8 to 70.9)	61.5 (51.5 to 70.9)		
Month 4 after entering TFR phase	51.3 (41.9 to 60.5)	53.8 (43.8 to 63.7)		
Month 5 after entering TFR phase	45.4 (36.2 to 54.8)	46.2 (36.3 to 56.2)		

Month 6 after entering TFR phase	42.9 (33.8 to 52.3)	43.3 (33.6 to 53.4)		
Month 8 after entering TFR phase	40.3 (31.5 to 49.7)	43.3 (33.6 to 53.4)		
Month 10 after entering TFR phase	38.7 (29.9 to 48.0)	42.3 (32.7 to 52.4)		
Month 12 after entering TFR phase	36.1 (27.5 to 45.5)	39.4 (30.0 to 49.5)		
Month 15 after entering TFR phase	35.3 (26.8 to 44.6)	39.4 (30.0 to 49.5)		
Month 18 after entering TFR phase	35.3 (26.8 to 44.6)	39.4 (30.0 to 49.5)		
Month 21 after entering TFR phase	34.5 (26.0 to 43.7)	38.5 (29.1 to 48.5)		
Month 24 after entering TFR phase	31.9 (23.7 to 41.1)	35.6 (26.4 to 45.6)		
Month 27 after entering TFR phase	31.9 (23.7 to 41.1)	999 (999 to 999)		
Month 30 after entering TFR phase	31.9 (23.7 to 41.1)	999 (999 to 999)		
Month 33 after entering TFR phase	30.3 (22.2 to 39.4)	999 (999 to 999)		
Month 36 after entering TFR phase	23.5 (16.2 to 32.2)	999 (999 to 999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants who were in MR4.0 during the TFR phase

End point title	Percentage of participants who were in MR4.0 during the TFR phase

End point description:

Number of participants who were in MR4.0 at selected timepoints divided by the number of participants in the TFR phase and multiplied by 100. Participants randomized in Nilotinib 36-month treatment arm had a maximum of 24 months of TFR phase, whereas participants randomized in Nilotinib 24-month treatment arm had a maximum of 36 months of TFR phase.
Confidence intervals were calculated based on the Exact Clopper-Pearson method.
MR4.0 is defined as either detectable disease ≤0.01% BCR-ABL IS or undetectable disease in cDNA with ≥10,000 ABL transcripts (numbers of ABL transcripts in the same volume of cDNA used to test for BCR-ABL).
Note: 999 indicates value is not applicable.

End point type	Secondary

End point timeframe:

From Month 1 after entering TFR phase up to 24 months after entering TFR phase for Nilotinib 36-month treatment arm and up to 36 months after entering TFR phase for Nilotinib 24-month treatment arm

End point values	Nilotinib 24-month treatment	Nilotinib 36-month treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119	104		
Units: Percentage of participants				
number (confidence interval 95%)				
Month 1 after entering TFR phase	87.4 (80.1 to 92.8)	83.7 (75.1 to 90.2)		
Month 2 after entering TFR phase	58.0 (48.6 to 67.0)	56.7 (46.7 to 66.4)		
Month 3 after entering TFR phase	39.5 (30.7 to 48.9)	42.3 (32.7 to 52.4)		
Month 4 after entering TFR phase	36.1 (27.5 to 45.5)	42.3 (32.7 to 52.4)		
Month 5 after entering TFR phase	32.8 (24.5 to 42.0)	41.3 (31.8 to 51.4)		
Month 6 after entering TFR phase	33.6 (25.2 to 42.9)	38.5 (29.1 to 48.5)		
Month 8 after entering TFR phase	34.5 (26.0 to 43.7)	40.4 (30.9 to 50.5)		
Month 10 after entering TFR phase	35.3 (26.8 to 44.6)	38.5 (29.1 to 48.5)		
Month 12 after entering TFR phase	31.9 (23.7 to 41.1)	37.5 (28.2 to 47.5)		
Month 15 after entering TFR phase	34.5 (26.0 to 43.7)	34.6 (25.6 to 44.6)		
Month 18 after entering TFR phase	33.6 (25.2 to 42.9)	38.5 (29.1 to 48.5)		
Month 21 after entering TFR phase	30.3 (22.2 to 39.4)	32.7 (23.8 to 42.6)		
Month 24 after entering TFR phase	29.4 (21.4 to 38.5)	30.8 (22.1 to 40.6)		
Month 27 after entering TFR phase	31.1 (22.9 to 40.2)	999 (999 to 999)		
Month 30 after entering TFR phase	30.3 (22.2 to 39.4)	999 (999 to 999)		
Month 33 after entering TFR phase	27.7 (19.9 to 36.7)	999 (999 to 999)		
Month 36 after entering TFR phase	26.1 (18.4 to 34.9)	999 (999 to 999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants who were in MR4.5 during the TFR phase

End point title	Percentage of participants who were in MR4.5 during the TFR phase

End point description:

Number of participants who were in MR4.5 at selected timepoints divided by the number of participants in the TFR phase and multiplied by 100. Participants randomized in Nilotinib 36-month treatment arm had a maximum of 24 months of TFR phase, whereas participants randomized in Nilotinib 24-month treatment arm had a maximum of 36 months of TFR phase.
Confidence intervals were calculated based on the Exact Clopper-Pearson method.
MR4.5 is defined as either detectable disease ≤ 0.0032% BCR-ABL IS; or undetectable disease within cDNA with ≥ 32,000 ABL transcripts (numbers of ABL transcripts in the same volume of cDNA used to test for BCR-ABL).

Note: 999 indicates value is not applicable.

End point type	Secondary

End point timeframe:

From Month 1 after entering TFR phase up to 24 months after entering TFR phase for Nilotinib 36-month treatment arm and up to 36 months after entering TFR phase for Nilotinib 24-month treatment arm

End point values	Nilotinib 24-month treatment	Nilotinib 36-month treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119	104		
Units: Percentage of participants				
number (confidence interval 95%)				
Month 3 after entering TFR phase	21.8 (14.8 to 30.4)	26.9 (18.7 to 36.5)		
Month 6 after entering TFR phase	17.6 (11.3 to 25.7)	28.8 (20.4 to 38.6)		
Month 12 after entering TFR phase	20.2 (13.4 to 28.5)	26.9 (18.7 to 36.5)		
Month 15 after entering TFR phase	18.5 (12.0 to 26.6)	23.1 (15.4 to 32.4)		
Month 18 after entering TFR phase	25.2 (17.7 to 34.0)	26.9 (18.7 to 36.5)		
Month 21 after entering TFR phase	22.7 (15.5 to 31.3)	22.1 (14.6 to 31.3)		
Month 24 after entering TFR phase	24.4 (17.0 to 33.1)	20.2 (13.0 to 29.2)		
Month 27 after entering TFR phase	21.8 (14.8 to 30.4)	999 (999 to 999)		
Month 30 after entering TFR phase	22.7 (15.5 to 31.3)	999 (999 to 999)		
Month 33 after entering TFR phase	19.3 (12.7 to 27.6)	999 (999 to 999)		
Month 36 after entering TFR phase	16.8 (10.6 to 24.8)	999 (999 to 999)		

Statistical analyses

No statistical analyses for this end point

Secondary: BCR-ABL ratio (expressed as a percentage) during the induction/consolidation phase

End point title	BCR-ABL ratio (expressed as a percentage) during the induction/consolidation phase

End point description:

BCR-ABL transcript ratio by international scale (IS) (expressed as a percentage) during the induction/consolidation phase. Participants randomized to Nilotinib 36-month treatment arm had 12-month additional consolidation phase (post-randomization).Only those participants with evaluable data at the specified time points for this outcome measure were analyzed (represented by n=X / Y / Z in the category titles).
Note: 999 indicates value is not applicable.

End point type	Secondary

End point timeframe:

From baseline up to 24 months after study treatment start for Nilotinib 24-month treatment arm and Not randomized participants; and up to 36 months after study treatment start for Nilotinib 36-month treatment arm.

End point values	Nilotinib 24-month treatment	Nilotinib 36-month treatment	Not randomized	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	120	118	381	
Units: Percentage				
arithmetic mean (standard deviation)				
Baseline (n= 120/ 117/ 380)	0.1367 (± 0.55144)	0.0633 (± 0.12790)	0.5509 (± 3.94256)	
Month 3 after treatment start(n=117/117/343)	0.0106 (± 0.02660)	0.0086 (± 0.01155)	0.0728 (± 0.22537)	
Month 6 after treatment start (n=118/115/327)	0.0052 (± 0.00631)	0.0124 (± 0.05508)	0.0530 (± 0.09587)	
Month 9 after treatment start (n=116/117/312)	0.0049 (± 0.00809)	0.0046 (± 0.00544)	0.0573 (± 0.13905)	
Month 12 after treatment start (n=117/117/298)	0.0044 (± 0.00611)	0.0037 (± 0.00440)	0.0772 (± 0.56398)	
Month 15 after treatment start (n=117/116/286)	0.0035 (± 0.00591)	0.0034 (± 0.00389)	0.0669 (± 0.37209)	
Month 18 after treatment start (n=117/115/269)	0.0029 (± 0.00354)	0.0034 (± 0.00409)	0.0462 (± 0.12284)	
Month 21 after treatment start (n=115/114/246)	0.0028 (± 0.00319)	0.0031 (± 0.00288)	0.0390 (± 0.08271)	
Month 24 after treatment start (n=113/113/153)	0.0027 (± 0.00424)	0.0029 (± 0.00319)	0.0325 (± 0.05140)	
Month 27 after treatment start (n=0/112/0)	999 (± 999)	0.0089 (± 0.06119)	999 (± 999)	
Month 30 after treatment start (n=0/112/0)	999 (± 999)	0.0111 (± 0.08672)	999 (± 999)	
Month 33 after treatment start (n=0/111/0)	999 (± 999)	0.0025 (± 0.00439)	999 (± 999)	
Month 36 after treatment start (n=0/103/0)	999 (± 999)	0.0025 (± 0.00338)	999 (± 999)	

Statistical analyses

No statistical analyses for this end point

Secondary: BCR-ABL ratio (expressed as a percentage) during the TFR phase

End point title	BCR-ABL ratio (expressed as a percentage) during the TFR phase

End point description:

BCR-ABL/control gene (ABL) transcript ratio by international scale (IS) (expressed as a percentage) during the TFR phase. BCR-ABL is the fusion gene from breakpoint cluster region and Abelson genes. Participants randomized in Nilotinib 36-month treatment arm had a maximum of 24 months of TFR phase, whereas participants randomized in Nilotinib 24-month treatment arm had a maximum of 36 months of TFR phase.
Only those participants with evaluable data at the specified time points for this outcome measure were analyzed (represented by n=X / Y in the category titles).

Note: 999 indicates value is not applicable.

End point type	Secondary

End point timeframe:

From Month 1 after entering TFR phase up to 24 months after entering TFR phase for Nilotinib 36-month treatment arm and up to 36 months after entering TFR phase for Nilotinib 24-month treatment arm

End point values	Nilotinib 24-month treatment	Nilotinib 36-month treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119	104		
Units: Percentage				
arithmetic mean (standard deviation)				
Month 1 after entering the TFR phase (n=116/ 99)	0.0042 (± 0.00621)	0.0074 (± 0.02130)		
Month 2 after entering the TFR phase (n=112/ 100)	0.1162 (± 0.35606)	0.2122 (± 0.99372)		
Month 3 after entering the TFR phase (n=81/ 64)	1.3774 (± 9.71909)	0.4754 (± 1.84649)		
Month 4 after entering the TFR phase (n=112/ 100)	0.2667 (± 0.80336)	0.2506 (± 0.91197)		
Month 5 after entering the TFR phase (n=62/ 52)	0.1740 (± 0.76123)	0.0801 (± 0.26739)		
Month 6 after entering the TFR phase (n=51/ 43)	0.2219 (± 1.51808)	0.1095 (± 0.66322)		
Month 8 after entering the TFR phase (n=47/ 42)	0.0075 (± 0.01403)	0.0042 (± 0.00742)		
Month 10 after entering the TFR phase (n=45/ 43)	0.0062 (± 0.01295)	0.0039 (± 0.00680)		
Month 12 after entering the TFR phase (n=41/ 39)	0.0047 (± 0.00665)	0.0027 (± 0.00357)		
Month 15 after entering the TFR phase (n=42/ 39)	0.0030 (± 0.00317)	0.0043 (± 0.00555)		
Month 18 after entering the TFR phase (n=40/ 40)	0.0030 (± 0.00384)	0.0027 (± 0.00330)		
Month 21 after entering the TFR phase (n=38/ 40)	0.0036 (± 0.00484)	0.0041 (± 0.00495)		
Month 24 after entering the TFR phase (n=38/ 35)	0.0077 (± 0.02910)	0.0047 (± 0.00691)		
Month 27 after entering the TFR phase (n=112/ 100)	0.0024 (± 0.00246)	999 (± 999)		
Month 30 after entering the TFR phase (n=36/ 0)	0.0023 (± 0.00281)	999 (± 999)		
Month 33 after entering the TFR phase (n=35/ 0)	0.0079 (± 0.02376)	999 (± 999)		
Month 36 after entering the TFR phase (n=28/ 0)	0.0041 (± 0.00767)	999 (± 999)		

Statistical analyses

No statistical analyses for this end point

Secondary: BCR-ABL ratio (expressed as a percentage) during the nilotinib re-

treatment phase

End point title	BCR-ABL ratio (expressed as a percentage) during the nilotinib re-treatment phase

End point description:

BCR-ABL/control gene (ABL) transcript ratio by international scale (IS) (expressed as a percentage) during the nilotinib re-treatment phase. BCR-ABL is the fusion gene from breakpoint cluster region and Abelson genes.
Only those participants who entered the re-treatment phase with evaluable data at the specified time points for this outcome measure were analyzed (represented by n=X / Y in the category titles).
Note: 999 indicates value is not applicable.

End point type	Secondary

End point timeframe:

From Day 1 after entering the re-treatment phase up to 24 months after entering re-treatment phase for Nilotinib 36-month treatment arm and 36 months after entering the re-treatment phase for Nilotinib 24-month treatment arm

End point values	Nilotinib 24-month treatment	Nilotinib 36-month treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	55		
Units: Percentage				
arithmetic mean (standard deviation)				
Day 1 re-treatment phase (n=2/ 2)	2.8246 (± 2.39596)	0.6301 (± 0.74388)		
Week 6 re-treatment phase (n=70/ 54)	0.6276 (± 2.34231)	0.3112 (± 0.60279)		
Month 3 re-treatment phase (n=70/ 52)	0.0311 (± 0.07265)	0.0131 (± 0.02359)		
Month 6 re-treatment phase (n=70/ 53)	0.0095 (± 0.03296)	0.0070 (± 0.01330)		
Month 9 re-treatment phase (n=71/ 51)	0.0259 (± 0.17766)	0.0065 (± 0.01099)		
Month 12 re-treatment phase (n=64/ 45)	0.0088 (± 0.03190)	0.0047 (± 0.00839)		
Month 15 re-treatment phase (n=64/ 48)	0.0061 (± 0.01322)	0.0045 (± 0.01176)		
Month 18 re-treatment phase (n=64/ 48)	0.0105 (± 0.05205)	0.0039 (± 0.00581)		
Month 21 re-treatment phase (n=59/ 21)	0.0051 (± 0.01699)	0.0031 (± 0.00342)		
Month 24 re-treatment phase (n=55/ 2)	0.0038 (± 0.00756)	0.0014 (± 0.00197)		
Month 27 re-treatment phase (n=52/ 0)	0.0033 (± 0.00439)	999 (± 999)		
Month 30 re-treatment phase (n=43/ 0)	0.0113 (± 0.04446)	999 (± 999)		
Month 33 re-treatment phase (n=11/ 0)	0.0029 (± 0.00541)	999 (± 999)		
Month 36 re-treatment phase (n=1/ 0)	0.0005 (± 999)	999 (± 999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival (PFS) during the TFR phase of the study.

End point title	Progression-free survival (PFS) during the TFR phase of the study.

End point description:

PFS is defined as the time from the date of start of the nilotinib TFR phase to the date of acelerated phase/blast crisis (AP/BC) or death, whichever came first. Participants randomized in Nilotinib 36-month treatment arm had a maximum of 24 months of TFR phase, whereas participants randomized in Nilotinib 24-month treatment arm had a maximum of 36 months of TFR phase.
Patients not known to have recurred or died on or before the cut-off date for PFS analysis were censored at the date of their last assessment (cytogenetic, hematology or extramedullary) for patients who were on study, and at the date of last contact for patients who were in follow-up.
Note: 999 indicates value is not applicable.

End point type	Secondary

End point timeframe:

From the start of the TFR phase to progression to AP/BC or death up to 24 months after entering TFR phase for Nilotininb 36-month treatment arm and up to 36 months after entering TFR phase for Nilotinib 24-month treatment arm

End point values	Nilotinib 24-month treatment	Nilotinib 36-month treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119	104		
Units: Months				
median (confidence interval 95%)	999 (999 to 999)	999 (999 to 999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment -free survival (TFS) during the TFR phase of the study

End point title	Treatment -free survival (TFS) during the TFR phase of the study

End point description:

TFS is defined as the time from the start of the TFR phase to the date of the earliest of the following: loss of MMR, confirmed loss of MR4.0, re-start of nilotinib treatment, progression to AP/BC,or death from any cause. Patients not known to have had any of the events on or before the cut-off date were censored at the earlier of the date of their last assessment for patients who were still on study and the date of last contact for patients who were in follow-up. Participants randomized in Nilotinib 36-month treatment arm had a maximum of 24 months of TFR phase, whereas participants randomized in Nilotinib 24-month treatment arm had a maximum of 36 months of TFR phase.
MMR is defined as ≥3.0 log reduction in BCR-ABL transcripts compared to the standardized baseline or ≤0.1%BCR-ABL.
MR4.0 is defined as either detectable disease ≤0.01%BCR-ABL IS or undetectable disease in cDNA with ≥10,000 ABL transcripts (numbers of ABL transcripts in the same volume of cDNA used to test for BCR-ABL)

End point type	Secondary

End point timeframe:

From the start of the TFR phase to the date of occurrence of treatment-free survival event, up to 24 months after entering TFR phase for Nilotinib 36-month treatment arm and up to 36 months after

End point values	Nilotinib 24-month treatment	Nilotinib 36-month treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119	104		
Units: Months				
median (confidence interval 95%)	4.1 (3.7 to 5.5)	4.2 (3.7 to 19.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS) rate during the TFR phase of the study.

End point title	Overall survival (OS) rate during the TFR phase of the study.[7]

End point description:

OS is defined as the time from start of the TFR phase to the time of death due to any cause. Participants randomized in Nilotinib 36-month treatment arm had a maximum of 24 months of TFR phase, whereas participants randomized in Nilotinib 24-month treatment arm had a maximum of 36 months of TFR phase.
For participants without any event on or before the cut-off date, survival time will be censored at the date of their last assessment for patients who are still on study, and at the date of last contact for patients who are in follow-up.
Note: 999 indicates value is not applicable.

End point type	Secondary

End point timeframe:

From the start of the TFR phase to death due to any cause, assessed up to 24 months after entering TFR phase for Nilotinib 36-month treatment arm and up to 36 months after entering TFR phase for Nilotinib 24-month treatment arm

Notes:

[7] - 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: This endpoint refers to TFR phase not the baseline period

End point values	Nilotinib 24-month treatment	Nilotinib 36-month treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120	119		
Units: Months				
median (confidence interval 95%)	999 (999 to 999)	999 (999 to 999)		

Statistical analyses

No statistical analyses for this end point

Post-hoc: All Collected Deaths

End point title	All Collected Deaths

End point description:

Deaths on-treatment were collected during the induction/consolidation phase (from the first dose of study drug to 30 days after study treatment discontinuation, assessed up to 24 months for Nilotinib 24-month treatment arm and Not randomized, and up to 36 months for Nilotinib 36-month treatment arm) and during the re-treatment phase (from the start date of the re-treatment phase to 30 days after study treatment discontinuation, assessed up to 36 months for Nilotinib 24-month treatment arm and up to 24 months for Nilotinib 36-month treatment arm).
Total deaths were collected from first dose of study drug until end of study, up to maximum duration of 5 years

End point type	Post-hoc

End point timeframe:

On-treatment deaths: induction/consolidation phase (up to 24 months or 36 months from treatment start, depending on arm) and re-treatment phase (up to 36 months or up to 24 months from re-treatment start, depending on arm). All deaths: up to 5 years

End point values	Nilotinib 24-month treatment	Nilotinib 36-month treatment	Not randomized	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	120	118	381	
Units: Participants				
On-treatment deaths	1	1	3	
Total deaths	1	3	10	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were collected during:
-Induction/consolidation phase, up to 24 months (or 36 months for Nilotinib 36-month treatment arm)
-Re-treatment phase, up to 36 months for Nilotinib 24-month treatment arm (or 24 months for Nilotinib 36-month treatment arm)

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	23.1

Reporting groups

Reporting group title	Nilotinib 24-month treatment

Reporting group description:

Participants were treated with nilotinib 300mg BID for 24 months and, thereafter, entered the 36-month TFR phase

Reporting group title	Nilotinib 36-month treatment

Reporting group description:

Participants were treated with nilotinib 300mg BID for 36 months and, thereafter, entered the 24-month TFR phase

Reporting group title	Not Randomized

Reporting group description:

Participants were treated with nilotinib 300mg BID for 24 months, but did not achieve a sustained molecular response after 24 months of treatment and were not randomized

Reporting group title	Total

Reporting group description:

Total

Serious adverse events	Nilotinib 24-month treatment	Nilotinib 36-month treatment	Not Randomized
Total subjects affected by serious adverse events			
subjects affected / exposed	33 / 120 (27.50%)	27 / 118 (22.88%)	76 / 381 (19.95%)
number of deaths (all causes)	1	1	3
number of deaths resulting from adverse events	0	0	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 120 (0.83%)	0 / 118 (0.00%)	0 / 381 (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
Glioblastoma			

subjects affected / exposed	0 / 120 (0.00%)	1 / 118 (0.85%)	0 / 381 (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
Lung adenocarcinoma			
subjects affected / exposed	0 / 120 (0.00%)	0 / 118 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myelofibrosis			
subjects affected / exposed	0 / 120 (0.00%)	1 / 118 (0.85%)	0 / 381 (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
Non-Hodgkin's lymphoma			
subjects affected / exposed	0 / 120 (0.00%)	0 / 118 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian cancer			
subjects affected / exposed	0 / 120 (0.00%)	0 / 118 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Arterial disorder			
subjects affected / exposed	0 / 120 (0.00%)	0 / 118 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arterial occlusive disease			
subjects affected / exposed	0 / 120 (0.00%)	0 / 118 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Extremity necrosis			
subjects affected / exposed	0 / 120 (0.00%)	1 / 118 (0.85%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematoma			

subjects affected / exposed	1 / 120 (0.83%)	0 / 118 (0.00%)	0 / 381 (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
Hypertensive crisis			
subjects affected / exposed	0 / 120 (0.00%)	0 / 118 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intermittent claudication			
subjects affected / exposed	0 / 120 (0.00%)	0 / 118 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemia			
subjects affected / exposed	1 / 120 (0.83%)	0 / 118 (0.00%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 120 (0.00%)	1 / 118 (0.85%)	2 / 381 (0.52%)
occurrences causally related to treatment / all	0 / 0	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery stenosis			
subjects affected / exposed	0 / 120 (0.00%)	0 / 118 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral ischaemia			
subjects affected / exposed	1 / 120 (0.83%)	1 / 118 (0.85%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	2 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thromboangiitis obliterans			
subjects affected / exposed	0 / 120 (0.00%)	0 / 118 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery occlusion			

subjects affected / exposed	1 / 120 (0.83%)	0 / 118 (0.00%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Pregnancy			
subjects affected / exposed	0 / 120 (0.00%)	0 / 118 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 120 (0.83%)	0 / 118 (0.00%)	0 / 381 (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
Hyperplasia			
subjects affected / exposed	1 / 120 (0.83%)	0 / 118 (0.00%)	0 / 381 (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
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 120 (0.00%)	0 / 118 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Necrosis			
subjects affected / exposed	1 / 120 (0.83%)	0 / 118 (0.00%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 120 (0.00%)	0 / 118 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden death			
subjects affected / exposed	0 / 120 (0.00%)	0 / 118 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

General physical health deterioration			
subjects affected / exposed	0 / 120 (0.00%)	0 / 118 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Sarcoidosis			
subjects affected / exposed	0 / 120 (0.00%)	1 / 118 (0.85%)	0 / 381 (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
Reproductive system and breast disorders			
Acquired hydrocele			
subjects affected / exposed	0 / 120 (0.00%)	0 / 118 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Menorrhagia			
subjects affected / exposed	0 / 120 (0.00%)	0 / 118 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian cyst			
subjects affected / exposed	0 / 120 (0.00%)	1 / 118 (0.85%)	0 / 381 (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
Adnexa uteri mass			
subjects affected / exposed	1 / 120 (0.83%)	0 / 118 (0.00%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 120 (0.00%)	0 / 118 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			

subjects affected / exposed	0 / 120 (0.00%)	1 / 118 (0.85%)	0 / 381 (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
Pleural effusion			
subjects affected / exposed	0 / 120 (0.00%)	0 / 118 (0.00%)	2 / 381 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 120 (0.00%)	0 / 118 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	1 / 120 (0.83%)	0 / 118 (0.00%)	0 / 381 (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
Psychiatric disorders			
Adjustment disorder			
subjects affected / exposed	0 / 120 (0.00%)	1 / 118 (0.85%)	0 / 381 (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
Mental disorder			
subjects affected / exposed	0 / 120 (0.00%)	1 / 118 (0.85%)	0 / 381 (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
Investigations			
Amylase increased			
subjects affected / exposed	1 / 120 (0.83%)	0 / 118 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrocardiogram abnormal			
subjects affected / exposed	0 / 120 (0.00%)	0 / 118 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lipase increased			

subjects affected / exposed	0 / 120 (0.00%)	0 / 118 (0.00%)	2 / 381 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Troponin increased			
subjects affected / exposed	1 / 120 (0.83%)	0 / 118 (0.00%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Humerus fracture			
subjects affected / exposed	0 / 120 (0.00%)	1 / 118 (0.85%)	0 / 381 (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
Injury			
subjects affected / exposed	0 / 120 (0.00%)	1 / 118 (0.85%)	0 / 381 (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
Limb injury			
subjects affected / exposed	0 / 120 (0.00%)	0 / 118 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower limb fracture			
subjects affected / exposed	1 / 120 (0.83%)	0 / 118 (0.00%)	0 / 381 (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
Tendon rupture			
subjects affected / exposed	1 / 120 (0.83%)	0 / 118 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye contusion			
subjects affected / exposed	1 / 120 (0.83%)	0 / 118 (0.00%)	0 / 381 (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
Femoral neck fracture			

subjects affected / exposed	0 / 120 (0.00%)	0 / 118 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose			
subjects affected / exposed	0 / 120 (0.00%)	0 / 118 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	2 / 120 (1.67%)	0 / 118 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed	0 / 120 (0.00%)	1 / 118 (0.85%)	2 / 381 (0.52%)
occurrences causally related to treatment / all	0 / 0	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	0 / 120 (0.00%)	0 / 118 (0.00%)	5 / 381 (1.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	6 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arrhythmia supraventricular			
subjects affected / exposed	0 / 120 (0.00%)	0 / 118 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	3 / 120 (2.50%)	2 / 118 (1.69%)	4 / 381 (1.05%)
occurrences causally related to treatment / all	3 / 5	2 / 2	3 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	0 / 120 (0.00%)	0 / 118 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			

subjects affected / exposed	0 / 120 (0.00%)	1 / 118 (0.85%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure acute			
subjects affected / exposed	0 / 120 (0.00%)	0 / 118 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiac failure congestive			
subjects affected / exposed	0 / 120 (0.00%)	0 / 118 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Coronary artery disease			
subjects affected / exposed	0 / 120 (0.00%)	0 / 118 (0.00%)	4 / 381 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery stenosis			
subjects affected / exposed	0 / 120 (0.00%)	0 / 118 (0.00%)	3 / 381 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive cardiomyopathy			
subjects affected / exposed	0 / 120 (0.00%)	0 / 118 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	2 / 120 (1.67%)	0 / 118 (0.00%)	4 / 381 (1.05%)
occurrences causally related to treatment / all	2 / 2	0 / 0	4 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	1 / 120 (0.83%)	0 / 118 (0.00%)	2 / 381 (0.52%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocarditis			

subjects affected / exposed	1 / 120 (0.83%)	0 / 118 (0.00%)	0 / 381 (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
Tachyarrhythmia			
subjects affected / exposed	0 / 120 (0.00%)	0 / 118 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular arrhythmia			
subjects affected / exposed	0 / 120 (0.00%)	0 / 118 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	1 / 120 (0.83%)	0 / 118 (0.00%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus bradycardia			
subjects affected / exposed	1 / 120 (0.83%)	0 / 118 (0.00%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral artery thrombosis			
subjects affected / exposed	1 / 120 (0.83%)	0 / 118 (0.00%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral infarction			
subjects affected / exposed	1 / 120 (0.83%)	0 / 118 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral ischaemia			
subjects affected / exposed	1 / 120 (0.83%)	0 / 118 (0.00%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			

subjects affected / exposed	1 / 120 (0.83%)	0 / 118 (0.00%)	3 / 381 (0.79%)
occurrences causally related to treatment / all	1 / 1	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	2 / 120 (1.67%)	0 / 118 (0.00%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	0 / 120 (0.00%)	1 / 118 (0.85%)	0 / 381 (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
Facial paralysis			
subjects affected / exposed	0 / 120 (0.00%)	0 / 118 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 120 (0.00%)	1 / 118 (0.85%)	0 / 381 (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
Hypoaesthesia			
subjects affected / exposed	0 / 120 (0.00%)	1 / 118 (0.85%)	0 / 381 (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
Ischaemic stroke			
subjects affected / exposed	0 / 120 (0.00%)	0 / 118 (0.00%)	2 / 381 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mononeuropathy			
subjects affected / exposed	0 / 120 (0.00%)	0 / 118 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			

subjects affected / exposed	1 / 120 (0.83%)	0 / 118 (0.00%)	0 / 381 (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
Syncope			
subjects affected / exposed	1 / 120 (0.83%)	1 / 118 (0.85%)	2 / 381 (0.52%)
occurrences causally related to treatment / all	0 / 3	1 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	0 / 120 (0.00%)	0 / 118 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphadenopathy mediastinal			
subjects affected / exposed	0 / 120 (0.00%)	1 / 118 (0.85%)	0 / 381 (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
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 120 (0.00%)	1 / 118 (0.85%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Retinal detachment			
subjects affected / exposed	1 / 120 (0.83%)	0 / 118 (0.00%)	0 / 381 (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
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 120 (0.00%)	0 / 118 (0.00%)	2 / 381 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal fissure			

subjects affected / exposed	0 / 120 (0.00%)	0 / 118 (0.00%)	2 / 381 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal fistula			
subjects affected / exposed	0 / 120 (0.00%)	1 / 118 (0.85%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 120 (0.00%)	0 / 118 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer			
subjects affected / exposed	1 / 120 (0.83%)	0 / 118 (0.00%)	0 / 381 (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
Gastritis			
subjects affected / exposed	0 / 120 (0.00%)	0 / 118 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 120 (0.83%)	0 / 118 (0.00%)	0 / 381 (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
Haematochezia			
subjects affected / exposed	0 / 120 (0.00%)	0 / 118 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoids			
subjects affected / exposed	0 / 120 (0.00%)	1 / 118 (0.85%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			

subjects affected / exposed	1 / 120 (0.83%)	1 / 118 (0.85%)	0 / 381 (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
Intestinal obstruction			
subjects affected / exposed	0 / 120 (0.00%)	0 / 118 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar hernia			
subjects affected / exposed	0 / 120 (0.00%)	0 / 118 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 120 (0.00%)	0 / 118 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 120 (0.00%)	0 / 118 (0.00%)	3 / 381 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	0 / 120 (0.00%)	0 / 118 (0.00%)	2 / 381 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Umbilical hernia			
subjects affected / exposed	0 / 120 (0.00%)	1 / 118 (0.85%)	0 / 381 (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
Vomiting			
subjects affected / exposed	0 / 120 (0.00%)	0 / 118 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholangitis			

subjects affected / exposed	0 / 120 (0.00%)	0 / 118 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	0 / 120 (0.00%)	1 / 118 (0.85%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	1 / 120 (0.83%)	0 / 118 (0.00%)	0 / 381 (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
Cholelithiasis			
subjects affected / exposed	0 / 120 (0.00%)	1 / 118 (0.85%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 120 (0.00%)	1 / 118 (0.85%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperhidrosis			
subjects affected / exposed	0 / 120 (0.00%)	1 / 118 (0.85%)	0 / 381 (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
Hyperkeratosis			
subjects affected / exposed	0 / 120 (0.00%)	0 / 118 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 120 (0.00%)	1 / 118 (0.85%)	0 / 381 (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
Urinary retention			

subjects affected / exposed	0 / 120 (0.00%)	0 / 118 (0.00%)	2 / 381 (0.52%)
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 failure			
subjects affected / exposed	0 / 120 (0.00%)	1 / 118 (0.85%)	0 / 381 (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
Musculoskeletal and connective tissue disorders			
Arthropathy			
subjects affected / exposed	0 / 120 (0.00%)	0 / 118 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	0 / 120 (0.00%)	0 / 118 (0.00%)	2 / 381 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bursitis			
subjects affected / exposed	0 / 120 (0.00%)	0 / 118 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc disorder			
subjects affected / exposed	0 / 120 (0.00%)	1 / 118 (0.85%)	0 / 381 (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
Intervertebral disc protrusion			
subjects affected / exposed	1 / 120 (0.83%)	0 / 118 (0.00%)	2 / 381 (0.52%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metatarsalgia			
subjects affected / exposed	1 / 120 (0.83%)	0 / 118 (0.00%)	0 / 381 (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
Musculoskeletal pain			

subjects affected / exposed	0 / 120 (0.00%)	0 / 118 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	2 / 120 (1.67%)	0 / 118 (0.00%)	0 / 381 (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
Pain in extremity			
subjects affected / exposed	0 / 120 (0.00%)	0 / 118 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal stenosis			
subjects affected / exposed	1 / 120 (0.83%)	0 / 118 (0.00%)	0 / 381 (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
Spondylitis			
subjects affected / exposed	1 / 120 (0.83%)	0 / 118 (0.00%)	0 / 381 (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			
Anal abscess			
subjects affected / exposed	0 / 120 (0.00%)	1 / 118 (0.85%)	0 / 381 (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
Bacterial pyelonephritis			
subjects affected / exposed	1 / 120 (0.83%)	0 / 118 (0.00%)	0 / 381 (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
Bronchitis			
subjects affected / exposed	0 / 120 (0.00%)	0 / 118 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			

subjects affected / exposed	1 / 120 (0.83%)	2 / 118 (1.69%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	1 / 120 (0.83%)	0 / 118 (0.00%)	0 / 381 (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
Enterocolitis infectious			
subjects affected / exposed	1 / 120 (0.83%)	0 / 118 (0.00%)	0 / 381 (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
Gallbladder empyema			
subjects affected / exposed	1 / 120 (0.83%)	0 / 118 (0.00%)	0 / 381 (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
Gangrene			
subjects affected / exposed	0 / 120 (0.00%)	1 / 118 (0.85%)	0 / 381 (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
Influenza			
subjects affected / exposed	0 / 120 (0.00%)	1 / 118 (0.85%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngitis			
subjects affected / exposed	0 / 120 (0.00%)	1 / 118 (0.85%)	0 / 381 (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
Neuroborreliosis			
subjects affected / exposed	0 / 120 (0.00%)	0 / 118 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orchitis			

subjects affected / exposed	0 / 120 (0.00%)	0 / 118 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 120 (0.00%)	1 / 118 (0.85%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia legionella			
subjects affected / exposed	1 / 120 (0.83%)	0 / 118 (0.00%)	0 / 381 (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 streptococcal			
subjects affected / exposed	1 / 120 (0.83%)	0 / 118 (0.00%)	0 / 381 (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
Sepsis			
subjects affected / exposed	0 / 120 (0.00%)	0 / 118 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 120 (0.00%)	0 / 118 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vestibular neuronitis			
subjects affected / exposed	1 / 120 (0.83%)	0 / 118 (0.00%)	0 / 381 (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	0 / 120 (0.00%)	1 / 118 (0.85%)	0 / 381 (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
Metabolism and nutrition disorders			
Diabetes mellitus			

subjects affected / exposed	0 / 120 (0.00%)	0 / 118 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	1 / 120 (0.83%)	0 / 118 (0.00%)	0 / 381 (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
Hyponatraemia			
subjects affected / exposed	1 / 120 (0.83%)	0 / 118 (0.00%)	0 / 381 (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
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 120 (0.00%)	1 / 118 (0.85%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Total		
Total subjects affected by serious adverse events			
subjects affected / exposed	136 / 619 (21.97%)		
number of deaths (all causes)	5		
number of deaths resulting from adverse events	1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 619 (0.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Glioblastoma			
subjects affected / exposed	1 / 619 (0.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung adenocarcinoma			
subjects affected / exposed	1 / 619 (0.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Myelofibrosis				
subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Non-Hodgkin's lymphoma				
subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ovarian cancer				
subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Arterial disorder				
subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Arterial occlusive disease				
subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Extremity necrosis				
subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Haematoma				
subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypertensive crisis				
subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Intermittent claudication				

subjects affected / exposed	1 / 619 (0.16%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Ischaemia			
subjects affected / exposed	1 / 619 (0.16%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Peripheral arterial occlusive disease			
subjects affected / exposed	3 / 619 (0.48%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Peripheral artery stenosis			
subjects affected / exposed	1 / 619 (0.16%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Peripheral ischaemia			
subjects affected / exposed	2 / 619 (0.32%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Thromboangiitis obliterans			
subjects affected / exposed	1 / 619 (0.16%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Peripheral artery occlusion			
subjects affected / exposed	1 / 619 (0.16%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			
Pregnancy			
subjects affected / exposed	1 / 619 (0.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			

Death				
subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Hyperplasia				
subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Multiple organ dysfunction syndrome				
subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Necrosis				
subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Sudden death				
subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
General physical health deterioration				
subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				
Sarcoidosis				
subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast				

disorders				
Acquired hydrocele				
subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Menorrhagia				
subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ovarian cyst				
subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Adnexa uteri mass				
subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Chronic obstructive pulmonary disease				
subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	2 / 619 (0.32%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				

subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Adjustment disorder				
subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Mental disorder				
subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Investigations				
Amylase increased				
subjects affected / exposed	2 / 619 (0.32%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Electrocardiogram abnormal				
subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Lipase increased				
subjects affected / exposed	2 / 619 (0.32%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Troponin increased				
subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural				

complications			
Humerus fracture			
subjects affected / exposed	1 / 619 (0.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury			
subjects affected / exposed	1 / 619 (0.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Limb injury			
subjects affected / exposed	1 / 619 (0.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lower limb fracture			
subjects affected / exposed	1 / 619 (0.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tendon rupture			
subjects affected / exposed	2 / 619 (0.32%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Eye contusion			
subjects affected / exposed	1 / 619 (0.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Femoral neck fracture			
subjects affected / exposed	1 / 619 (0.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Overdose			
subjects affected / exposed	1 / 619 (0.16%)		
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 / 619 (0.48%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Acute myocardial infarction				
subjects affected / exposed	3 / 619 (0.48%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Angina pectoris				
subjects affected / exposed	5 / 619 (0.81%)			
occurrences causally related to treatment / all	6 / 6			
deaths causally related to treatment / all	0 / 0			
Arrhythmia supraventricular				
subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				
subjects affected / exposed	9 / 619 (1.45%)			
occurrences causally related to treatment / all	8 / 12			
deaths causally related to treatment / all	0 / 0			
Atrial flutter				
subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac failure				
subjects affected / exposed	2 / 619 (0.32%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Cardiac failure acute				
subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Cardiac failure congestive				

subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Coronary artery disease				
subjects affected / exposed	4 / 619 (0.65%)			
occurrences causally related to treatment / all	4 / 4			
deaths causally related to treatment / all	0 / 0			
Coronary artery stenosis				
subjects affected / exposed	3 / 619 (0.48%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Hypertensive cardiomyopathy				
subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				
subjects affected / exposed	6 / 619 (0.97%)			
occurrences causally related to treatment / all	6 / 7			
deaths causally related to treatment / all	0 / 0			
Myocardial ischaemia				
subjects affected / exposed	3 / 619 (0.48%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Myocarditis				
subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tachyarrhythmia				
subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ventricular arrhythmia				

subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Angina unstable				
subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Sinus bradycardia				
subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Cerebral artery thrombosis				
subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebral infarction				
subjects affected / exposed	2 / 619 (0.32%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Cerebral ischaemia				
subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebrovascular accident				
subjects affected / exposed	4 / 619 (0.65%)			
occurrences causally related to treatment / all	4 / 4			
deaths causally related to treatment / all	0 / 0			
Dizziness				
subjects affected / exposed	2 / 619 (0.32%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Epilepsy				

subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Facial paralysis				
subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Headache				
subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypoaesthesia				
subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ischaemic stroke				
subjects affected / exposed	2 / 619 (0.32%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Mononeuropathy				
subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Seizure				
subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	4 / 619 (0.65%)			
occurrences causally related to treatment / all	1 / 6			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Febrile neutropenia				

subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lymphadenopathy mediastinal				
subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ear and labyrinth disorders				
Vertigo				
subjects affected / exposed	2 / 619 (0.32%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Eye disorders				
Retinal detachment				
subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal pain upper				
subjects affected / exposed	2 / 619 (0.32%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Anal fissure				
subjects affected / exposed	2 / 619 (0.32%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Anal fistula				
subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Constipation				
subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Duodenal ulcer			
subjects affected / exposed	1 / 619 (0.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastritis			
subjects affected / exposed	1 / 619 (0.16%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 619 (0.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haematochezia			
subjects affected / exposed	1 / 619 (0.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemorrhoids			
subjects affected / exposed	1 / 619 (0.16%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Inguinal hernia			
subjects affected / exposed	2 / 619 (0.32%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Intestinal obstruction			
subjects affected / exposed	1 / 619 (0.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lumbar hernia			
subjects affected / exposed	1 / 619 (0.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea			

subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				
subjects affected / exposed	3 / 619 (0.48%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Pancreatitis acute				
subjects affected / exposed	2 / 619 (0.32%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Umbilical hernia				
subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Cholangitis				
subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cholecystitis				
subjects affected / exposed	2 / 619 (0.32%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Cholecystitis acute				
subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cholelithiasis				

subjects affected / exposed	2 / 619 (0.32%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 619 (0.16%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperhidrosis			
subjects affected / exposed	1 / 619 (0.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperkeratosis			
subjects affected / exposed	1 / 619 (0.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 619 (0.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary retention			
subjects affected / exposed	2 / 619 (0.32%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Renal failure			
subjects affected / exposed	1 / 619 (0.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthropathy			
subjects affected / exposed	1 / 619 (0.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Back pain			
subjects affected / exposed	2 / 619 (0.32%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Bursitis			
subjects affected / exposed	1 / 619 (0.16%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Intervertebral disc disorder			
subjects affected / exposed	1 / 619 (0.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intervertebral disc protrusion			
subjects affected / exposed	3 / 619 (0.48%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Metatarsalgia			
subjects affected / exposed	1 / 619 (0.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal pain			
subjects affected / exposed	1 / 619 (0.16%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Osteoarthritis			
subjects affected / exposed	2 / 619 (0.32%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pain in extremity			
subjects affected / exposed	1 / 619 (0.16%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Spinal stenosis			

subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spondylitis				
subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Anal abscess				
subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bacterial pyelonephritis				
subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bronchitis				
subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
subjects affected / exposed	3 / 619 (0.48%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Cystitis				
subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Enterocolitis infectious				
subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gallbladder empyema				

subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gangrene				
subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Influenza				
subjects affected / exposed	2 / 619 (0.32%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Laryngitis				
subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Neuroborreliosis				
subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Orchitis				
subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	2 / 619 (0.32%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pneumonia legionella				
subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia streptococcal				

subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vestibular neuronitis				
subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lower respiratory tract infection				
subjects affected / exposed	1 / 619 (0.16%)			
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	1 / 619 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hyperkalaemia				
subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hyponatraemia				
subjects affected / exposed	1 / 619 (0.16%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Diabetes mellitus inadequate control				

subjects affected / exposed	1 / 619 (0.16%)		
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	Nilotinib 24-month treatment	Nilotinib 36-month treatment	Not Randomized
Total subjects affected by non-serious adverse events			
subjects affected / exposed	97 / 120 (80.83%)	104 / 118 (88.14%)	280 / 381 (73.49%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	10 / 120 (8.33%)	18 / 118 (15.25%)	27 / 381 (7.09%)
occurrences (all)	14	29	32
Aspartate aminotransferase increased			
subjects affected / exposed	8 / 120 (6.67%)	12 / 118 (10.17%)	11 / 381 (2.89%)
occurrences (all)	13	18	15
Blood bilirubin increased			
subjects affected / exposed	8 / 120 (6.67%)	13 / 118 (11.02%)	30 / 381 (7.87%)
occurrences (all)	12	20	48
Blood cholesterol increased			
subjects affected / exposed	15 / 120 (12.50%)	14 / 118 (11.86%)	24 / 381 (6.30%)
occurrences (all)	17	26	26
Blood triglycerides increased			
subjects affected / exposed	3 / 120 (2.50%)	8 / 118 (6.78%)	6 / 381 (1.57%)
occurrences (all)	3	13	7
Gamma-glutamyltransferase increased			
subjects affected / exposed	4 / 120 (3.33%)	6 / 118 (5.08%)	9 / 381 (2.36%)
occurrences (all)	5	6	10
Lipase increased			
subjects affected / exposed	21 / 120 (17.50%)	10 / 118 (8.47%)	34 / 381 (8.92%)
occurrences (all)	31	20	56
Weight increased			
subjects affected / exposed	5 / 120 (4.17%)	6 / 118 (5.08%)	3 / 381 (0.79%)
occurrences (all)	7	8	3
Vascular disorders			

Hypertension			
subjects affected / exposed	20 / 120 (16.67%)	25 / 118 (21.19%)	27 / 381 (7.09%)
occurrences (all)	21	30	27
Nervous system disorders			
Headache			
subjects affected / exposed	17 / 120 (14.17%)	12 / 118 (10.17%)	34 / 381 (8.92%)
occurrences (all)	25	12	39
Sciatica			
subjects affected / exposed	5 / 120 (4.17%)	7 / 118 (5.93%)	9 / 381 (2.36%)
occurrences (all)	5	9	10
Paraesthesia			
subjects affected / exposed	6 / 120 (5.00%)	4 / 118 (3.39%)	9 / 381 (2.36%)
occurrences (all)	7	4	9
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	16 / 120 (13.33%)	14 / 118 (11.86%)	27 / 381 (7.09%)
occurrences (all)	20	18	28
Fatigue			
subjects affected / exposed	13 / 120 (10.83%)	7 / 118 (5.93%)	17 / 381 (4.46%)
occurrences (all)	15	8	17
Pyrexia			
subjects affected / exposed	5 / 120 (4.17%)	10 / 118 (8.47%)	23 / 381 (6.04%)
occurrences (all)	8	11	26
Influenza like illness			
subjects affected / exposed	2 / 120 (1.67%)	6 / 118 (5.08%)	2 / 381 (0.52%)
occurrences (all)	2	6	2
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	7 / 120 (5.83%)	6 / 118 (5.08%)	15 / 381 (3.94%)
occurrences (all)	8	7	16
Abdominal pain upper			
subjects affected / exposed	12 / 120 (10.00%)	14 / 118 (11.86%)	19 / 381 (4.99%)
occurrences (all)	14	17	22
Constipation			
subjects affected / exposed	19 / 120 (15.83%)	14 / 118 (11.86%)	25 / 381 (6.56%)
occurrences (all)	21	16	26

Dyspepsia			
subjects affected / exposed	4 / 120 (3.33%)	7 / 118 (5.93%)	6 / 381 (1.57%)
occurrences (all)	5	7	7
Nausea			
subjects affected / exposed	13 / 120 (10.83%)	5 / 118 (4.24%)	11 / 381 (2.89%)
occurrences (all)	17	8	13
Vomiting			
subjects affected / exposed	10 / 120 (8.33%)	3 / 118 (2.54%)	9 / 381 (2.36%)
occurrences (all)	10	3	9
Diarrhoea			
subjects affected / exposed	6 / 120 (5.00%)	5 / 118 (4.24%)	11 / 381 (2.89%)
occurrences (all)	6	5	13
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	9 / 120 (7.50%)	15 / 118 (12.71%)	13 / 381 (3.41%)
occurrences (all)	11	18	15
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	6 / 120 (5.00%)	9 / 118 (7.63%)	18 / 381 (4.72%)
occurrences (all)	6	9	18
Dry skin			
subjects affected / exposed	9 / 120 (7.50%)	15 / 118 (12.71%)	17 / 381 (4.46%)
occurrences (all)	13	22	19
Pruritus			
subjects affected / exposed	15 / 120 (12.50%)	23 / 118 (19.49%)	57 / 381 (14.96%)
occurrences (all)	20	28	66
Rash			
subjects affected / exposed	21 / 120 (17.50%)	10 / 118 (8.47%)	41 / 381 (10.76%)
occurrences (all)	26	12	46
Psychiatric disorders			
Insomnia			
subjects affected / exposed	4 / 120 (3.33%)	6 / 118 (5.08%)	3 / 381 (0.79%)
occurrences (all)	4	7	3
Musculoskeletal and connective tissue disorders			
Arthralgia			

subjects affected / exposed	17 / 120 (14.17%)	18 / 118 (15.25%)	27 / 381 (7.09%)
occurrences (all)	21	23	33
Back pain			
subjects affected / exposed	16 / 120 (13.33%)	11 / 118 (9.32%)	21 / 381 (5.51%)
occurrences (all)	19	12	23
Muscle spasms			
subjects affected / exposed	10 / 120 (8.33%)	16 / 118 (13.56%)	12 / 381 (3.15%)
occurrences (all)	12	18	13
Musculoskeletal pain			
subjects affected / exposed	4 / 120 (3.33%)	11 / 118 (9.32%)	6 / 381 (1.57%)
occurrences (all)	4	13	7
Myalgia			
subjects affected / exposed	12 / 120 (10.00%)	15 / 118 (12.71%)	26 / 381 (6.82%)
occurrences (all)	14	20	31
Pain in extremity			
subjects affected / exposed	12 / 120 (10.00%)	21 / 118 (17.80%)	26 / 381 (6.82%)
occurrences (all)	14	30	30
Infections and infestations			
Bronchitis			
subjects affected / exposed	8 / 120 (6.67%)	9 / 118 (7.63%)	14 / 381 (3.67%)
occurrences (all)	11	11	15
Gastroenteritis			
subjects affected / exposed	10 / 120 (8.33%)	3 / 118 (2.54%)	4 / 381 (1.05%)
occurrences (all)	10	6	4
Influenza			
subjects affected / exposed	6 / 120 (5.00%)	9 / 118 (7.63%)	15 / 381 (3.94%)
occurrences (all)	6	9	16
Nasopharyngitis			
subjects affected / exposed	4 / 120 (3.33%)	12 / 118 (10.17%)	14 / 381 (3.67%)
occurrences (all)	5	17	15
Upper respiratory tract infection			
subjects affected / exposed	8 / 120 (6.67%)	8 / 118 (6.78%)	11 / 381 (2.89%)
occurrences (all)	8	13	16
Folliculitis			
subjects affected / exposed	6 / 120 (5.00%)	4 / 118 (3.39%)	4 / 381 (1.05%)
occurrences (all)	7	4	5

Metabolism and nutrition disorders			
Dyslipidaemia			
subjects affected / exposed	0 / 120 (0.00%)	7 / 118 (5.93%)	5 / 381 (1.31%)
occurrences (all)	0	10	5
Hypercholesterolaemia			
subjects affected / exposed	23 / 120 (19.17%)	20 / 118 (16.95%)	65 / 381 (17.06%)
occurrences (all)	26	26	74
Hyperglycaemia			
subjects affected / exposed	5 / 120 (4.17%)	16 / 118 (13.56%)	16 / 381 (4.20%)
occurrences (all)	8	23	22
Hypertriglyceridaemia			
subjects affected / exposed	10 / 120 (8.33%)	2 / 118 (1.69%)	14 / 381 (3.67%)
occurrences (all)	16	2	15
Hypophosphataemia			
subjects affected / exposed	7 / 120 (5.83%)	13 / 118 (11.02%)	13 / 381 (3.41%)
occurrences (all)	15	22	17
Decreased appetite			
subjects affected / exposed	6 / 120 (5.00%)	1 / 118 (0.85%)	5 / 381 (1.31%)
occurrences (all)	7	1	5

Non-serious adverse events	Total		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	481 / 619 (77.71%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	55 / 619 (8.89%)		
occurrences (all)	75		
Aspartate aminotransferase increased			
subjects affected / exposed	31 / 619 (5.01%)		
occurrences (all)	46		
Blood bilirubin increased			
subjects affected / exposed	51 / 619 (8.24%)		
occurrences (all)	80		
Blood cholesterol increased			
subjects affected / exposed	53 / 619 (8.56%)		
occurrences (all)	69		
Blood triglycerides increased			

subjects affected / exposed	17 / 619 (2.75%)		
occurrences (all)	23		
Gamma-glutamyltransferase increased			
subjects affected / exposed	19 / 619 (3.07%)		
occurrences (all)	21		
Lipase increased			
subjects affected / exposed	65 / 619 (10.50%)		
occurrences (all)	107		
Weight increased			
subjects affected / exposed	14 / 619 (2.26%)		
occurrences (all)	18		
Vascular disorders			
Hypertension			
subjects affected / exposed	72 / 619 (11.63%)		
occurrences (all)	78		
Nervous system disorders			
Headache			
subjects affected / exposed	63 / 619 (10.18%)		
occurrences (all)	76		
Sciatica			
subjects affected / exposed	21 / 619 (3.39%)		
occurrences (all)	24		
Paraesthesia			
subjects affected / exposed	19 / 619 (3.07%)		
occurrences (all)	20		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	57 / 619 (9.21%)		
occurrences (all)	66		
Fatigue			
subjects affected / exposed	37 / 619 (5.98%)		
occurrences (all)	40		
Pyrexia			
subjects affected / exposed	38 / 619 (6.14%)		
occurrences (all)	45		
Influenza like illness			

subjects affected / exposed occurrences (all)	10 / 619 (1.62%) 10		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Dyspepsia subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all)	 28 / 619 (4.52%) 31 45 / 619 (7.27%) 53 58 / 619 (9.37%) 63 17 / 619 (2.75%) 19 29 / 619 (4.68%) 38 22 / 619 (3.55%) 22 22 / 619 (3.55%) 24		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	 37 / 619 (5.98%) 44		
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all) Dry skin subjects affected / exposed occurrences (all) Pruritus	 33 / 619 (5.33%) 33 41 / 619 (6.62%) 54		

subjects affected / exposed	95 / 619 (15.35%)		
occurrences (all)	114		
Rash			
subjects affected / exposed	72 / 619 (11.63%)		
occurrences (all)	84		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	13 / 619 (2.10%)		
occurrences (all)	14		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	62 / 619 (10.02%)		
occurrences (all)	77		
Back pain			
subjects affected / exposed	48 / 619 (7.75%)		
occurrences (all)	54		
Muscle spasms			
subjects affected / exposed	38 / 619 (6.14%)		
occurrences (all)	43		
Musculoskeletal pain			
subjects affected / exposed	21 / 619 (3.39%)		
occurrences (all)	24		
Myalgia			
subjects affected / exposed	53 / 619 (8.56%)		
occurrences (all)	65		
Pain in extremity			
subjects affected / exposed	59 / 619 (9.53%)		
occurrences (all)	74		
Infections and infestations			
Bronchitis			
subjects affected / exposed	31 / 619 (5.01%)		
occurrences (all)	37		
Gastroenteritis			
subjects affected / exposed	17 / 619 (2.75%)		
occurrences (all)	20		
Influenza			

subjects affected / exposed	30 / 619 (4.85%)		
occurrences (all)	31		
Nasopharyngitis			
subjects affected / exposed	30 / 619 (4.85%)		
occurrences (all)	37		
Upper respiratory tract infection			
subjects affected / exposed	27 / 619 (4.36%)		
occurrences (all)	37		
Folliculitis			
subjects affected / exposed	14 / 619 (2.26%)		
occurrences (all)	16		
Metabolism and nutrition disorders			
Dyslipidaemia			
subjects affected / exposed	12 / 619 (1.94%)		
occurrences (all)	15		
Hypercholesterolaemia			
subjects affected / exposed	108 / 619 (17.45%)		
occurrences (all)	126		
Hyperglycaemia			
subjects affected / exposed	37 / 619 (5.98%)		
occurrences (all)	53		
Hypertriglyceridaemia			
subjects affected / exposed	26 / 619 (4.20%)		
occurrences (all)	33		
Hypophosphataemia			
subjects affected / exposed	33 / 619 (5.33%)		
occurrences (all)	54		
Decreased appetite			
subjects affected / exposed	12 / 619 (1.94%)		
occurrences (all)	13		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 April 2014	The main purpose for this substantial amendment was the inclusion of the optional Stem cells ENESTpath substudy "Leukemic stem cells quantification in patients with chronic myeloid leukemia included in the ENESTpath trial"; the purpose of this substudy was to evaluate the importance of leukemic stem cells (LSC) in the long-term maintenance of the disease and their role in the relapse of patients during the TFR phase.
10 February 2015	The main purposes for this substantial amendment were: 1. To modify the study sample size based on new data from the ENESTcmr and STIM studies and a number of published clinical trials 2. To amend the secondary objectives of the study and related endpoints 3. To incorporate the safety recommendations provided by the DMC on patients with severe cardiovascular ischemic events experienced before entering the study or while on study
23 September 2015	To update the protocol including the 'CML patient's voice' Italian substudy to evaluate the emotional aspects in patients participating to a nilotinib Treatment-free remission (TFR) trial. This substudy aims to examine patients' psycho-emotional characteristics, quality of life and experiences of being involved in CAMN107AIC05 trial and its discontinuation using a qualitative-quantitative mixed method. The 'CML patient's voice' Italian substudy will be conducted in Italy only.
01 June 2016	To include hepatitis B virus testing as one of the study procedures, to identify study patients who may be at risk of hepatitis B reactivation. Reactivation of hepatitis B virus can occur in patients who are chronic carriers of this virus and are receiving a drug of the BCR-ABL TKI class such as nilotinib. Some cases involving BCR-ABL TKI resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

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

Notes: