



Clinical trial results:

Open-Label Single Arm Phase 2 Study Evaluating Dasatinib Therapy Discontinuation In Patients With Chronic Phase Chronic Myeloid Leukemia (CP-CML) With Stable Complete Molecular Response (CMR) DASFREE

Summary

EudraCT number	2012-001421-27
Trial protocol	FI ES IT DE
Global end of trial date	08 October 2021

Results information

Result version number	v1 (current)
This version publication date	21 October 2022
First version publication date	21 October 2022

Trial information

Trial identification

Sponsor protocol code	CA180-406
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bristol-Myers Squibb
Sponsor organisation address	Chaussee de la Hulpe 185, Brussels, Belgium, 1170
Public contact	EU Study Start-Up Unit, Bristol-Myers Squibb International Corporation, Clinical.Trials@bms.com
Scientific contact	Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, Clinical.Trials@bms.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	01 December 2021
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	08 October 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to assess the rate of major molecular response (MMR), defined as the proportion of subjects who maintain MMR (BCR-ABL transcripts < 0.1% on International Scale (IS) at 12 months after dasatinib discontinuation, without re-starting dasatinib treatment.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial participants were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 January 2014
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	Canada: 12
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Germany: 7
Country: Number of subjects enrolled	Italy: 11
Country: Number of subjects enrolled	Spain: 23
Country: Number of subjects enrolled	United States: 26
Worldwide total number of subjects	84
EEA total number of subjects	46

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)	64
From 65 to 84 years	20
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

110 participants were screened. 26 failed to meet eligibility and 84 participants proceeded to receive study treatment.

Period 1

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

Arms

Arm title	Total
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Arm description:

At study entry, dasatinib will be discontinued in all enrolled participants. Dasatinib will be restarted if major molecular response is lost during the off-treatment period at the dose level received before study entry. The participant will remain on treatment for the duration of the study. Dose adjustment for toxicity and response is permitted during the retreatment period based on protocol guidelines. Dosing above 180 mg per day of dasatinib is prohibited.

Arm type	Experimental
Investigational medicinal product name	Dasatinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

20 mg, 50 mg, 80 mg, 100 mg, and 140 mg Tablets

Number of subjects in period 1	Total
Started	84
Restarted Treatment	47 ^[1]
Discontinued Treatment after Restart	47 ^[2]
Completed	60
Not completed	24
Participant No Longer Meets Study Criteria	1
Other Reasons	2
Participant Request to Discontinue Treatment	2
Maximum Clinical Benefit	4
Adverse Event Unrelated to Study Drug	1
Poor/Non-compliance	1

Participant Withdrew Consent	9
Adverse Event Related to Study Drug	4

Notes:

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

Justification: This number reflects the number of participants who restarted treatment after failure to maintain major molecular response.

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

Justification: This number reflects the number of participants who restarted treatment after failure to maintain major molecular response.

Baseline characteristics

Reporting groups

Reporting group title	Total
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Reporting group description:

At study entry, dasatinib will be discontinued in all enrolled participants. Dasatinib will be restarted if major molecular response is lost during the off-treatment period at the dose level received before study entry. The participant will remain on treatment for the duration of the study. Dose adjustment for toxicity and response is permitted during the retreatment period based on protocol guidelines. Dosing above 180 mg per day of dasatinib is prohibited.

Reporting group values	Total	Total	
Number of subjects	84	84	
Age categorical			
Units: Subjects			
Adults (18-64 years)	64	64	
From 65-84 years	20	20	
85 years and over	0	0	
Age Continuous			
Units: Years			
arithmetic mean	52.6		
standard deviation	± 14.57	-	
Sex: Female, Male			
Units:			
Female	37	37	
Male	47	47	
Race/Ethnicity, Customized			
Units: Subjects			
White	75	75	
Black/African American	3	3	
Asian	1	1	
Other	5	5	

End points

End points reporting groups

Reporting group title	Total
Reporting group description: At study entry, dasatinib will be discontinued in all enrolled participants. Dasatinib will be restarted if major molecular response is lost during the off-treatment period at the dose level received before study entry. The participant will remain on treatment for the duration of the study. Dose adjustment for toxicity and response is permitted during the retreatment period based on protocol guidelines. Dosing above 180 mg per day of dasatinib is prohibited.	

Primary: Major Molecular Response (MMR) Rate

End point title	Major Molecular Response (MMR) Rate ^[1]
End point description: Major Molecular Response (MMR) rate at 12 months is the percentage of participants who maintain MMR (BCR-ABL transcripts < 0.1% on the International Scale [IS]) at 12 months after Dasatinib discontinuation without restarting Dasatinib	
End point type	Primary
End point timeframe: At 12 months after Dasatinib discontinuation (assessed up to approximately June 4, 2018)	
Notes: [1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: Only summary statistics were planned for this endpoint	

End point values	Total			
Subject group type	Reporting group			
Number of subjects analysed	84			
Units: Percentage of Participants				
number (confidence interval 95%)	47.6 (36.6 to 58.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Event-Free Survival (EFS) Rate

End point title	Event-Free Survival (EFS) Rate
End point description: Event-free survival (EFS) rate is defined as the percentage of surviving participants with no loss of Major Molecular Response (MMR) at the specified timepoints after dasatinib discontinuation. MMR is defined as BCR-ABL transcripts < 0.1% IS. Loss of MMR is defined per the European LeukemiaNet (ELN) definition of progression. Progression is defined as Transformation to Accelerated Phase or Blast Crisis (AP/BC): Accelerated Phase (AP) Blasts in PB or BM 15–29%; Blast + promyelocytes ≥ 30% with blasts < 30% or ACA in Ph+ cells (clonal progression), or basophils in blood ≥ 20%, or platelets < 100 × 10 ⁹ /L unrelated to therapy Blastic Phase or Crisis (BP/BC) Blasts in PB or BM ≥ 30%, or extramedullary blast cell involvement (with exception of spleen and liver)	

The date of progression is defined as the date any of the above criteria is first met. Participants who have not progressed will be censored on the date of last examination.

End point type	Secondary
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End point timeframe:

From 12 months after Dasatinib treatment discontinuation to every 12 months thereafter (up to approximately 60 months)

End point values	Total			
Subject group type	Reporting group			
Number of subjects analysed	84			
Units: Percentage of participants				
number (confidence interval 95%)				
At 12 months	48.7 (38.0 to 59.4)			
At 24 months	46.3 (35.6 to 57.0)			
At 36 months	45.0 (34.3 to 55.7)			
At 48 months	43.8 (33.1 to 54.4)			
At 60 months	43.8 (33.1 to 54.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Relapse-Free Survival (RFS) Rate

End point title	Relapse-Free Survival (RFS) Rate
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End point description:

RFS is the percentage of participants who did not relapse at the specified timepoints. Participants who did not relapse were censored on the date of their last molecular assessment. Relapse is defined as any of the following events while on study: the loss of Major Molecular Response (MMR), loss of Complete Cytogenetic Response (CCyR), loss of Complete Hematologic Response (CHR) or progression to advanced/blastic phase.

MMR is defined as BCR-ABL transcripts < 0.1% IS. Cytogenetic response (CyR) is based on the prevalence of Ph+ cells in metaphase from bone marrow (BM) sample based on evaluation of at least 20 metaphases. CCyR is defined as 0% Ph+ cells in metaphase in BM. CHR is obtained when all the following criteria are met in peripheral blood (PB) sampling: white blood cell ≤10,000/mm³; Platelets < 450,000/mm³; PB basophils <5%; No blasts or promyelocytes in PB; <5% myelocytes plus metamyelocytes in PB; No extramedullary involvement (including no hepatomegaly or splenomegaly).

End point type	Secondary
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End point timeframe:

From 12 months after Dasatinib treatment discontinuation to every 6 months thereafter (up to approximately 60 months)

End point values	Total			
Subject group type	Reporting group			
Number of subjects analysed	84			
Units: Percentage of Participants				
number (confidence interval 95%)				
At 6 Months	61.9 (51.5 to 72.3)			
At 12 Months	48.7 (38.0 to 59.4)			
At 18 Months	47.5 (36.8 to 58.2)			
At 24 months	46.3 (35.6 to 57.0)			
At 30 months	46.3 (35.6 to 57.0)			
At 36 months	45.0 (34.4 to 55.7)			
At 42 months	43.8 (33.1 to 54.4)			
At 48 months	43.8 (33.1 to 54.4)			
At 54 months	43.8 (33.1 to 54.4)			
At 60 months	43.8 (33.1 to 54.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS) Rate

End point title	Progression Free Survival (PFS) Rate
End point description:	
Progression free survival (PFS) is defined as the percentage of participants who experienced death (due to any cause) or accelerated phase, or blast crisis. Participants who neither progress nor die will be censored on the date of their last molecular assessment. Progression is defined as Transformation to Accelerated Phase or Blast Crisis (AP/BC) Accelerated Phase (AP) Blasts in PB or BM 15–29%; Blast + promyelocytes \geq 30% with blasts $<$ 30% or ACA in Ph+ cells (clonal progression), or basophils in blood \geq 20%, or platelets $<$ 100 x 10 ⁹ /L unrelated to therapy Blastic Phase or Crisis (BP/BC) Blasts in PB or BM \geq 30%, or extramedullary blast cell involvement (with the exception of spleen and liver)	
End point type	Secondary
End point timeframe:	
From 12 months after Dasatinib treatment discontinuation to every 6 months thereafter (up to approximately 60 months)	

End point values	Total			
Subject group type	Reporting group			
Number of subjects analysed	84			
Units: Percentage of participants				
number (confidence interval 95%)				

At 6 months	100.0 (100.0 to 100.0)			
At 12 months	100.0 (100.0 to 100.0)			
At 18 months	100.0 (100.0 to 100.0)			
At 24 months	98.7 (96.2 to 100.0)			
At 30 months	98.7 (96.2 to 100.0)			
At 36 months	98.7 (96.2 to 100.0)			
At 42 months	98.7 (96.2 to 100.0)			
At 48 months	98.7 (96.2 to 100.0)			
At 54 months	98.7 (96.2 to 100.0)			
At 60 months	98.7 (96.2 to 100.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants who experience intermittent loss of complete molecular response (CMR) (MR4.5) but no loss of major molecular response (MMR)

End point title	Number of participants who experience intermittent loss of complete molecular response (CMR) (MR4.5) but no loss of major molecular response (MMR)
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End point description:

The number of participants who did not lose major molecular response (MMR) 60 months after discontinuing study treatment who were in MR4.5 at the time of discontinuation and lost MR4.5. Molecular response will be assessed using BCR-ABL transcript levels measurement by real-time quantitative polymerase chain reaction (Q-PCR). MMR is defined as BCR-ABL transcripts < 0.1% Internal Standard (IS). CMR (MR4.5) defined as $\leq 0.0032\%$ (IS) or ≥ 4.5 log reduction of BCR-ABL transcript levels molecular response.

End point type	Secondary
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End point timeframe:

60 months after last dose

End point values	Total			
Subject group type	Reporting group			
Number of subjects analysed	31			
Units: Participants	19			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants who did not experience loss of complete molecular response (CMR) (MR4.5) and major molecular response (MMR)

End point title	Number of participants who did not experience loss of complete molecular response (CMR) (MR4.5) and major molecular response (MMR)
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End point description:

Assessment of BCR-ABL kinetics in patients who are in CMR (MR4.5) or less when transcript levels are still measurable. CMR (MR4.5) defined as $\leq 0.0032\%$ (IS) or ≥ 4.5 log reduction of BCR-ABL transcript levels molecular response.

End point type	Secondary
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End point timeframe:

From 12 months after Dasatinib treatment discontinuation to 5 years after the first visit of the last enrolled participant (up to approximately 82 months)

End point values	Total			
Subject group type	Reporting group			
Number of subjects analysed	31			
Units: Participants	12			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to transformation to accelerated phase/blast crisis (AP/BC)

End point title	Time to transformation to accelerated phase/blast crisis (AP/BC)
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End point description:

Time to Transformation to AP/BC is defined as the rate at which participants experienced transformation to accelerated phase/blast crisis (AP/BC) since discontinuation. Participants who did not develop to AP, late phase, or BC phase were censored on their last molecular measurement date.

"99999"=N/A

End point type	Secondary
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End point timeframe:

From 12 months after Dasatinib treatment discontinuation to 5 years after the first visit of the last enrolled participant (up to approximately 82 months)

End point values	Total			
Subject group type	Reporting group			
Number of subjects analysed	84			
Units: Months				
median (confidence interval 95%)	99999 (99999 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)
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End point description:

Time to Transformation to AP/BC is defined as the rate at which participants experienced transformation to accelerated phase/blast crisis (AP/BC) since discontinuation. Participants who did not develop to AP, late phase, or BC phase were censored on their last molecular measurement date.

"99999"=N/A

End point type	Secondary
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End point timeframe:

From 12 months after Dasatinib treatment discontinuation to the date of death or last known alive date (up to approximately 82 months)

End point values	Total			
Subject group type	Reporting group			
Number of subjects analysed	84			
Units: Months				
median (confidence interval 95%)	99999 (99999 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival

End point title	Progression Free Survival
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End point description:

Progression-free survival (PFS) is defined as the time from treatment discontinuation to the date of progression or death (due to any cause), whichever occurs first. Participants who neither progress nor die will be censored on the date of their last molecular assessment.

"99999"=N/A

End point type	Secondary
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End point timeframe:

From treatment discontinuation to the date of progression or death due to any cause, whichever occurs first (up to 82 months)

End point values	Total			
Subject group type	Reporting group			
Number of subjects analysed	84			
Units: Months				
median (confidence interval 95%)	99999 (99999 to 99999)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Participants were assessed for all-cause mortality from their enrollment to study completion, (up to approximately 87 months). SAEs and Other AEs were assessed from first dose to 30 days following last dose (up to approximately 85 months).

Adverse event reporting additional description:

The number at Risk for All-Cause Mortality represents all enrolled Participants. The number at Risk for Serious Adverse Events and Other (Not Including Serious) Adverse Events represents all participants that received at least 1 dose of study medication during re-treatment.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	24.1
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Reporting groups

Reporting group title	DASATINIB
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Reporting group description:

At study entry, dasatinib will be discontinued in all enrolled participants. Dasatinib will be restarted if major molecular response is lost during the off-treatment period at the dose level received before study entry. The participant will remain on treatment for the duration of the study. Dose adjustment for toxicity and response is permitted during the retreatment period based on protocol guidelines. Dosing above 180 mg per day of dasatinib is prohibited.

Serious adverse events	DASATINIB		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 47 (17.02%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ovarian cancer metastatic			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Prostate cancer			

subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Myocardial ischaemia			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pericarditis			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Polychondritis			

subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
External ear cellulitis			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	DASATINIB		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	42 / 47 (89.36%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 47 (8.51%)		
occurrences (all)	5		
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 47 (6.38%)		
occurrences (all)	4		
Headache			
subjects affected / exposed	6 / 47 (12.77%)		
occurrences (all)	8		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	3 / 47 (6.38%)		
occurrences (all)	5		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	5 / 47 (10.64%)		
occurrences (all)	5		
Pyrexia			
subjects affected / exposed	4 / 47 (8.51%)		
occurrences (all)	4		

Oedema peripheral subjects affected / exposed occurrences (all)	3 / 47 (6.38%) 5		
Fatigue subjects affected / exposed occurrences (all)	10 / 47 (21.28%) 12		
Gastrointestinal disorders			
Constipation subjects affected / exposed occurrences (all)	6 / 47 (12.77%) 7		
Diarrhoea subjects affected / exposed occurrences (all)	4 / 47 (8.51%) 9		
Dry mouth subjects affected / exposed occurrences (all)	3 / 47 (6.38%) 3		
Haemorrhoids subjects affected / exposed occurrences (all)	4 / 47 (8.51%) 4		
Vomiting subjects affected / exposed occurrences (all)	3 / 47 (6.38%) 3		
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	4 / 47 (8.51%) 4		
Dyspnoea subjects affected / exposed occurrences (all)	3 / 47 (6.38%) 3		
Pleural effusion subjects affected / exposed occurrences (all)	4 / 47 (8.51%) 10		
Skin and subcutaneous tissue disorders			
Rash subjects affected / exposed occurrences (all)	5 / 47 (10.64%) 7		

Psychiatric disorders			
Depression			
subjects affected / exposed	3 / 47 (6.38%)		
occurrences (all)	3		
Insomnia			
subjects affected / exposed	3 / 47 (6.38%)		
occurrences (all)	3		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	7 / 47 (14.89%)		
occurrences (all)	8		
Back pain			
subjects affected / exposed	4 / 47 (8.51%)		
occurrences (all)	5		
Myalgia			
subjects affected / exposed	6 / 47 (12.77%)		
occurrences (all)	8		
Pain in extremity			
subjects affected / exposed	3 / 47 (6.38%)		
occurrences (all)	3		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	7 / 47 (14.89%)		
occurrences (all)	11		
Sinusitis			
subjects affected / exposed	4 / 47 (8.51%)		
occurrences (all)	4		
Upper respiratory tract infection			
subjects affected / exposed	4 / 47 (8.51%)		
occurrences (all)	5		
Viral infection			
subjects affected / exposed	3 / 47 (6.38%)		
occurrences (all)	3		
Metabolism and nutrition disorders			
Hypercholesterolaemia			

subjects affected / exposed	3 / 47 (6.38%)		
occurrences (all)	4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 November 2013	Edits to requirements for women of childbearing age; correction of EudraCT number
02 March 2015	Updates to eligibility criteria; second level of dose escalation to 180 mg dasatinib added; updates to ECG monitoring; bone marrow biopsy or aspirate or peripheral blood (FISH) for cytogenetic assessment no longer required as part of the baseline assessments; changes in the study stopping rule incorporated; corrections to assessment of response free survival and frequency of safety and efficacy review.
22 March 2016	Hepatitis B serology status now required; revised method of contraception guidelines; destruction of study drug now permitted per protocol requirements
24 July 2017	Added new exploratory endpoint; updated event free survival definition and timeframe; BCR-ABL kinetics analysis updated; clarification in the frequency of complete blood count (CBC) and platelet assessments; statistical section updated for consistency with the statistical analysis plan

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported