Clinical trial results:
An Open-Label, Randomized, Multicenter Phase 2 Trial of Dasatinib (SPRYCEL®) vs. Dasatinib plus Smoothen Antagonist (BMS-833923) in the Treatment of Subjects with Newly Diagnosed Chronic Phase Philadelphia Chromosome Positive CML

Summary

EudraCT number	2011-000083-10
Trial protocol	ES DE FI BE
Global end of trial date	25 January 2016

Results information

Result version number	v1 (current)
This version publication date	09 February 2017
First version publication date	09 February 2017

Trial information

Trial identification

Sponsor protocol code	CA180-363

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01357655
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bristol-Myers Squibb
Sponsor organisation address	Parc de l'Alliance, Avenue de Finlande, 8, Braine l'Alleud, Belgium, 1420
Public contact	EU Study Start-up Unit, Bristol-Myers Squibb International Corporation, clinical.trials@bms.com
Scientific contact	EU Study Start-up Unit, Bristol-Myers Squibb International Corporation, 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	25 January 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 January 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to compare response rates in newly diagnosed CP CML subjects treated with dasatinib plus BMS-833923 versus dasatinib alone.

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 subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 July 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 24
Country: Number of subjects enrolled	Spain: 7
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Finland: 4
Country: Number of subjects enrolled	France: 16
Country: Number of subjects enrolled	United States: 13
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Argentina: 3
Worldwide total number of subjects	70
EEA total number of subjects	53

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)	58
From 65 to 84 years	12
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were enrolled at 24 sites worldwide.

Pre-assignment

Screening details:

70 subjects were enrolled, 66 were treated. Reasons for non-treatment include 1 adverse event and 3 no longer met study criteria. Participants enrolled were only treated with Dasatinib. The Dasatinib + SMO antagonist arm did not have participants because a tolerable and recommended phase 2 dose of the SMO antagonist had not been determined.

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	Dasatinib

Arm description:

Subjects received dasatinib, 100 mg, tablet, orally, once daily for approximately 1 year until the study was terminated prematurely.

Arm type	Experimental
Investigational medicinal product name	Dasatinib
Investigational medicinal product code	BMS-354825
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects were administered with dasatinib 20 mg or 50 mg tablets orally once daily (QD) to make the total daily dose of 100 mg for up to 1 year. The study was terminated prematurely.

Number of subjects in period 1[1]	Dasatinib
Started	66
Completed	0
Not completed	66
Consent withdrawn by subject	1
Maximum Clinical Benefit	2
Adverse Event Unrelated to Study Drug	3
Study Drug Toxicity	11
Lost to follow-up	2
Reason Unspecified	1
Administrative Reason by Sponsor	45
Disease Progression	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Out of 70 subjects who were enrolled, 66 subjects received at least 1 dose of dasatinib.

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study

Reporting group description: -

Reporting group values	Overall Study	Total	
Number of subjects	66	66	
Age categorical Units: Subjects			
18-64 years	54	54	
65 years and over	12	12	
Gender categorical Units: Subjects			
Female	27	27	
Male	39	39	

End points

End points reporting groups

Reporting group title	Dasatinib

Reporting group description:

Subjects received dasatinib, 100 mg, tablet, orally, once daily for approximately 1 year until the study was terminated prematurely.

Primary: Number of Subjects With Major Molecular Response

End point title	Number of Subjects With Major Molecular Response[1]

End point description:

Major molecular response (MMR) was assessed using BCR-ABL transcript levels measured by real-time quantitative polymerase chain reaction (qPCR). MMR was defined as a ratio BCR-ABL/ABL ≤0.1% on the international scale (ie, at least 3 log reduction from a standardized baseline value). Efficacy Sample: all treated subjects with at least one assessment on treatment. Number of subjects with MMR by timepoint are cumulative.

Subjects enrolled in this trial could not be randomized to the Dasatinib + SMO antagonist arm because no recommended phase 2 dose of the SMO antagonist could be determined (in a separate trial).

End point type	Primary

End point timeframe:

Baseline up to 12 months

Notes:

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

End point values	Dasatinib			
Subject group type	Reporting group			
Number of subjects analysed	64			
Units: subjects				
Baseline	1			
3 Months	9			
6 Months	30			
12 Months	34			

Statistical analyses

No statistical analyses for this end point

Secondary: Complete Molecular Response at Any Time

End point title	Complete Molecular Response at Any Time

End point description:

The study was terminated prior to data collection for this endpoint.

End point type	Secondary

End point timeframe:

Baseline to End of study (approximately 48 months)

End point values	Dasatinib			
Subject group type	Reporting group			
Number of subjects analysed	0[2]			
Units: participants				

Notes:

[2] - The study was terminated prior to data collection for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival, Measured by the Time From Start of Treatment to Progression or Death

End point title	Progression-free Survival, Measured by the Time From Start of Treatment to Progression or Death

End point description:

The study was terminated prior to data collection for this endpoint.

End point type	Secondary

End point timeframe:

Baseline to End of study (approximately 48 months)

End point values	Dasatinib			
Subject group type	Reporting group			
Number of subjects analysed	0[3]			
Units: months				
number (not applicable)				

Notes:

[3] - The study was terminated prior to data collection for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Event-free Survival, Measured by the Time From Start of Treatment to Progression, Death or Treatment Discontinuation

End point title	Event-free Survival, Measured by the Time From Start of Treatment to Progression, Death or Treatment Discontinuation

End point description:

The study was terminated prior to data collection for this endpoint.

End point type	Secondary

End point timeframe:

Baseline to End of study (approximately 48 months)

End point values	Dasatinib			
Subject group type	Reporting group			
Number of subjects analysed	0[4]			
Units: months				
number (not applicable)				

Notes:

[4] - The study was terminated prior to data collection for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Transformation-free Survival Measured by the Time From Start of Treatment to Criteria for Accelerated or Blast Phase CML Are Met and Death

End point title	Transformation-free Survival Measured by the Time From Start of Treatment to Criteria for Accelerated or Blast Phase CML Are Met and Death

End point description:

The study was terminated prior to data collection for this endpoint.

End point type	Secondary

End point timeframe:

Baseline to End of study (approximately 48 months)

End point values	Dasatinib			
Subject group type	Reporting group			
Number of subjects analysed	0[5]			
Units: months				
number (not applicable)				

Notes:

[5] - The study was terminated prior to data collection for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Experiencing Serious Adverse Events (SAE), Drug-Related Adverse Event (AE), AE Leading to Discontinuation, and Death

End point title	Number of Subjects Experiencing Serious Adverse Events (SAE), Drug-Related Adverse Event (AE), AE Leading to Discontinuation, and Death

End point description:

AE=any new unfavorable symptom, sign, or disease or worsening of a preexisting condition that may not have a causal relationship with treatment. SAE=a medical event that at any dose results in death, persistent or significant disability/ incapacity, or drug dependency/abuse; is life-threatening, an important medical event, or a congenital anomaly/birth defect; or requires or prolongs hospitalization. Drug-related=having certain, probable, possible, or missing relationship to study drug. All Treated

Subjects.

End point type	Secondary

End point timeframe:

From date of first dose of study treatment up to the date of the last dose plus 30 days (approximately 49 months)

End point values	Dasatinib			
Subject group type	Reporting group			
Number of subjects analysed	66			
Units: subjects				
SAE	18			
Drug-Related AE	56			
Death	2			
AE Leading to Discontinuation	14			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

On study adverse events: adverse events with onset on or after the first date of study treatment and on or prior to the last day of study treatment plus 30 days (approximately 49 months). All treated subjects.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Dasatinib

Reporting group description:

Subjects received dasatinib, 100 mg, tablet, orally, once daily for approximately 1 year until the study was terminated prematurely.

Serious adverse events	Dasatinib		
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 66 (27.27%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Ovarian neoplasm			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Prostate cancer			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal cancer			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial fibrillation			

subjects affected / exposed	1 / 66 (1.52%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac failure chronic			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac tamponade			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Myocardial ischaemia			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 66 (3.03%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Amaurosis fugax			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Apical granuloma			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Colitis			
subjects affected / exposed	2 / 66 (3.03%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Gastritis			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Inguinal hernia			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Small intestinal obstruction			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Volvulus			

subjects affected / exposed	1 / 66 (1.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	2 / 66 (3.03%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	5 / 66 (7.58%)		
occurrences causally related to treatment / all	5 / 5		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Liver abscess			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	4 / 66 (6.06%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 1		
Urosepsis			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vaginal abscess			
subjects affected / exposed	1 / 66 (1.52%)		
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	61 / 66 (92.42%)		
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 66 (6.06%)		
occurrences (all)	5		
Weight increased			
subjects affected / exposed	4 / 66 (6.06%)		
occurrences (all)	5		
Vascular disorders			
Hypertension			
subjects affected / exposed	7 / 66 (10.61%)		
occurrences (all)	7		
Nervous system disorders			
Headache			
subjects affected / exposed	27 / 66 (40.91%)		
occurrences (all)	34		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	20 / 66 (30.30%)		
occurrences (all)	35		
Leukopenia			
subjects affected / exposed	8 / 66 (12.12%)		
occurrences (all)	19		
Neutropenia			
subjects affected / exposed	14 / 66 (21.21%)		
occurrences (all)	54		
Thrombocytopenia			
subjects affected / exposed	17 / 66 (25.76%)		
occurrences (all)	45		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	13 / 66 (19.70%)		
occurrences (all)	21		
Chest pain			

subjects affected / exposed	6 / 66 (9.09%)		
occurrences (all)	7		
Fatigue			
subjects affected / exposed	8 / 66 (12.12%)		
occurrences (all)	9		
Peripheral swelling			
subjects affected / exposed	4 / 66 (6.06%)		
occurrences (all)	5		
Pyrexia			
subjects affected / exposed	10 / 66 (15.15%)		
occurrences (all)	13		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	5 / 66 (7.58%)		
occurrences (all)	8		
Abdominal pain upper			
subjects affected / exposed	4 / 66 (6.06%)		
occurrences (all)	4		
Constipation			
subjects affected / exposed	4 / 66 (6.06%)		
occurrences (all)	4		
Diarrhoea			
subjects affected / exposed	18 / 66 (27.27%)		
occurrences (all)	31		
Nausea			
subjects affected / exposed	14 / 66 (21.21%)		
occurrences (all)	21		
Vomiting			
subjects affected / exposed	13 / 66 (19.70%)		
occurrences (all)	14		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	12 / 66 (18.18%)		
occurrences (all)	12		
Dyspnoea			

subjects affected / exposed	10 / 66 (15.15%)		
occurrences (all)	16		
Dyspnoea exertional			
subjects affected / exposed	4 / 66 (6.06%)		
occurrences (all)	4		
Epistaxis			
subjects affected / exposed	4 / 66 (6.06%)		
occurrences (all)	4		
Oropharyngeal pain			
subjects affected / exposed	7 / 66 (10.61%)		
occurrences (all)	9		
Pleural effusion			
subjects affected / exposed	9 / 66 (13.64%)		
occurrences (all)	26		
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	4 / 66 (6.06%)		
occurrences (all)	4		
Rash			
subjects affected / exposed	11 / 66 (16.67%)		
occurrences (all)	13		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	4 / 66 (6.06%)		
occurrences (all)	4		
Insomnia			
subjects affected / exposed	6 / 66 (9.09%)		
occurrences (all)	7		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	7 / 66 (10.61%)		
occurrences (all)	10		
Back pain			
subjects affected / exposed	5 / 66 (7.58%)		
occurrences (all)	5		
Muscle spasms			

subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all)	6 / 66 (9.09%) 10 6 / 66 (9.09%) 7		
Infections and infestations Gastroenteritis subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Pharyngitis subjects affected / exposed occurrences (all) Sinusitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all)	 6 / 66 (9.09%) 6 5 / 66 (7.58%) 7 4 / 66 (6.06%) 6 4 / 66 (6.06%) 4 8 / 66 (12.12%) 8		
Metabolism and nutrition disorders Hypercholesterolaemia subjects affected / exposed occurrences (all) Hypocalcaemia subjects affected / exposed occurrences (all) Hypophosphataemia subjects affected / exposed occurrences (all)	 4 / 66 (6.06%) 5 5 / 66 (7.58%) 9 4 / 66 (6.06%) 13		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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.

The study was terminated early as the overall tolerability of the SMO-antagonist observed in a Phase 1 study of dasatinib plus SMO-antagonist was considered unacceptable in the newly diagnosed CML population.

Notes: