Clinical trial results:
A Phase II, Multicenter, Open Label, Single Arm Study of SAR302503 in Subjects Previously Treated with Ruxolitinib and with a Current Diagnosis of Intermediate or High-Risk Primary Myelofibrosis, Post-Polycythemia Vera Myelofibrosis, or Post-Essential Thrombocythemia Myelofibrosis

Summary

EudraCT number	2011-005226-21
Trial protocol	GB NL AT ES DE IT BE
Global end of trial date	29 April 2014

Results information

Result version number	v1 (current)
This version publication date	23 May 2016
First version publication date	15 July 2015

Trial information

Trial identification

Sponsor protocol code	ARD12181

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01523171
WHO universal trial number (UTN)	U1111-1124-0967

Notes:

Sponsors

Sponsor organisation name	Sanofi aventis recherche & développement
Sponsor organisation address	1 avenue Pierre Brossolette, Chilly-Mazarin, France, 91380
Public contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-us@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-us@sanofi.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	12 June 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 April 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of once daily dose of SAR302503 in subjects previously treated with ruxolitinib and with a current diagnosis of intermediate-1 with symptoms, intermediate-2 or high-risk primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (Post-PV MF), or post-essential thrombocythemia myelofibrosis (Post-ET MF) based on the reduction of spleen volume at the end of 6 treatment cycles.

Protection of trial subjects:

Subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture. During the course of the trial, subjects were provided with individual subject cards indicating the nature of the trial the subject is participating, contact details and any information needed in the event of a medical emergency.
Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 April 2012
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	Netherlands: 15
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Belgium: 6
Country: Number of subjects enrolled	France: 12
Country: Number of subjects enrolled	Germany: 8
Country: Number of subjects enrolled	Italy: 10
Country: Number of subjects enrolled	United States: 33
Country: Number of subjects enrolled	Canada: 1
Worldwide total number of subjects	97
EEA total number of subjects	63

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)	36
From 65 to 84 years	61
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 36 sites in 10 countries. A total of 97 subjects were enrolled between 30 April 2012 and 02 August 2013.

Pre-assignment

Screening details:

All 97 enrolled subjects were treated.

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	Fedratinib

Arm description:

Fedratinib in consecutive 28-day cycles until disease progression or unacceptable toxicity.

Arm type	Experimental
Investigational medicinal product name	Fedratinib
Investigational medicinal product code	SAR302503
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Once daily flexible dosing regimen (200 to 600 mg/day) with starting dose of 400 mg/day.

Number of subjects in period 1	Fedratinib
Started	97
Completed	0
Not completed	97
DP-abdominal pain and progressive leucocytosis	1
Disease progression (DP)	6
Adverse event	18
Study terminated by sponsor	63
Allogenic stem cell transplant	1
Consent withdrawn by subject	8

Baseline characteristics

Reporting groups	
Reporting group title	Fedratinib

Reporting group description:

Fedratinib in consecutive 28-day cycles until disease progression or unacceptable toxicity.

Reporting group values	Fedratinib	Total	
Number of subjects	97	97	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	66.5		
standard deviation	± 8.1	-	
Gender categorical Units: Subjects			
Female	44	44	
Male	53	53	

End points

End points reporting groups

Reporting group title	Fedratinib

Reporting group description:

Fedratinib in consecutive 28-day cycles until disease progression or unacceptable toxicity.

Primary: Response Rate: Percentage of Subjects With >=35% Reduction From Baseline in Spleen Volume at End of Cycle 6

End point title	Response Rate: Percentage of Subjects With >=35% Reduction From Baseline in Spleen Volume at End of Cycle 6[1]

End point description:

Spleen volume was measured by central imaging MRI (CT scan in subjects with contraindications for MRI). Analysis was performed on Per Protocol (PP) population defined as all treated subjects with a baseline and at least one post-baseline MRI/CT scan of spleen volume, and had no important protocol deviations that could impact on efficacy outcome. Last observation carried forward (LOCF) method was used to impute the missing data.

End point type	Primary

End point timeframe:

Baseline, End of Cycle 6

Notes:

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

End point values	Fedratinib			
Subject group type	Reporting group			
Number of subjects analysed	83			
Units: percentage of subjects				
number (confidence interval 95%)	55.4 (44.1 to 66.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Symptom Response Rate: Percentage of Subjects with >=50% Reduction From Baseline in the Total Symptom Score Using MFSAF at End of Cycle 6

End point title	Symptom Response Rate: Percentage of Subjects with >=50% Reduction From Baseline in the Total Symptom Score Using MFSAF at End of Cycle 6

End point description:

The key MF-associated symptoms were assessed using the modified Myelofibrosis Symptom Assessment Form (MFSAF) Diary: night sweats, pruritus, abdominal discomfort, early satiety, pain under ribs on left side, and bone or muscle pain. These were measured on a scale from 0 (absent) to 10 (worst imaginable). Then Total symptom score (range 0 to 60) was defined as the sum of the scores for each of the 6 symptoms of MFSAF. Higher score indicated greater severity of symptoms. Analysis was performed on MFSAF analysis population defined as all treated subjects with baseline and at least 1 post-baseline evaluable assessment of total symptom score.

End point type	Secondary

End point timeframe:

Baseline, End of Cycle 6

End point values	Fedratinib			
Subject group type	Reporting group			
Number of subjects analysed	90			
Units: percentage of subjects				
number (confidence interval 95%)	25.6 (16.9 to 35.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Splenic Response

End point title	Duration of Splenic Response

End point description:

Splenic response was defined as >=35% reduction in volume of spleen from baseline to the end of Cycle 6, measured by MRI/CT scan.

End point type	Secondary

End point timeframe:

Month 6

End point values	Fedratinib			
Subject group type	Reporting group			
Number of subjects analysed	0[2]			
Units: days				
median (full range (min-max))	(to)			

Notes:

[2] - Endpoint not analysed due to SAR302503 clinical program/study termination for safety reasons.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with a ≥50% Reduction From Baseline in Length of Spleen by Palpation at End of Cycle 6

End point title	Percentage of Subjects with a ≥50% Reduction From Baseline in Length of Spleen by Palpation at End of Cycle 6

End point description:

Intent-to-treat population included all enrolled and treated subjects.

End point type	Secondary

End point timeframe:
Baseline, End of Cycle 6

End point values	Fedratinib			
Subject group type	Reporting group			
Number of subjects analysed	97			
Units: percentage of subjects				
number (not applicable)	30.9			

Statistical analyses

No statistical analyses for this end point

Secondary: Response Rate: Percentage of Subjects With ≥35% Reduction From Baseline in Spleen Volume Measured by MRI or CT Scan at End of Cycle 3

End point title	Response Rate: Percentage of Subjects With ≥35% Reduction From Baseline in Spleen Volume Measured by MRI or CT Scan at End of Cycle 3

End point description:
Analysis was performed on PP population.

End point type	Secondary

End point timeframe:
Baseline, End of Cycle 3

End point values	Fedratinib			
Subject group type	Reporting group			
Number of subjects analysed	83			
Units: percentage of subjects				
number (not applicable)	47			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Spleen Volume Measured by MRI or CT Scan at End of Cycle 3 and Cycle 6

End point title	Percent Change From Baseline in Spleen Volume Measured by MRI or CT Scan at End of Cycle 3 and Cycle 6

End point description:
Analysis was performed on PP population.

End point type	Secondary

End point timeframe:

Baseline, End of Cycle 3, 6

End point values	Fedratinib			
Subject group type	Reporting group			
Number of subjects analysed	83			
Units: percent change				
median (full range (min-max))				
End of Cycle 3 (n=20)	-24.3 (-60.6 to 22)			
End of Cycle 6 (n=83)	-34.01 (-72.7 to 114.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration of Fedratinib

End point title	Plasma Concentration of Fedratinib

End point description:

Analysis was performed on pharmacokinetic population defined as all subjects who received at least 1 (even partial) cycle of study treatment and had evaluable drug concentration data.

End point type	Secondary

End point timeframe:

Pre-dose (Hour 0), 0.5, 2.5 hours post-dose on Day 1 of Cycle 1, 2, pre-dose (Hour 0) on Day 1 of Cycle 4

End point values	Fedratinib			
Subject group type	Reporting group			
Number of subjects analysed	97			
Units: ng/mL				
arithmetic mean (standard deviation)				
Cycle 1 Predose (0 hours) (n=94)	1 (± 0)			
Cycle 1 Day 1 (0.5 to 2 hours) (n=93)	924.8 (± 605.4)			
Cycle 1 Day 1 (2.5 to 4 hours) (n=93)	1302.8 (± 708.6)			
Cycle 2 Day 1 Predose (0 hours) (n=85)	1150.1 (± 652.5)			
Cycle 2 Day 1 (0.5 to 2 hours) (n=85)	1873.4 (± 1081)			
Cycle 2 Day 1 (2.5 to 4 hours) (n=87)	2143 (± 906.6)			
Cycle 4 Day 1 Predose (0 hours) (n=69)	1258.7 (± 594.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Janus Kinase 2 (JAK2) V617F Mutation

End point title	Percentage of Subjects With Janus Kinase 2 (JAK2) V617F Mutation

End point description:

End point type	Secondary

End point timeframe:

Day 1 of Cycle 1 and 4, End of Cycle 6

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

Notes:

[3] - Endpoint was not analyzed due to clinical program and study termination for safety reasons.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AE) were collected from signature of the informed consent form up to the final visit (Week 79) regardless of seriousness or relationship to investigational product. Analysis was performed on safety population.

Adverse event reporting additional description:

Reported adverse events and deaths are treatment emergent that is AEs that developed/worsened and death occurred during the 'on treatment period' (from the first dose of study drug to 30 days after last dose of drug).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Fedratinib

Reporting group description:

Fedratinib in consecutive 28-day cycles until disease progression or unacceptable toxicity.

Serious adverse events	Fedratinib		
Total subjects affected by serious adverse events			
subjects affected / exposed	33 / 97 (34.02%)		
number of deaths (all causes)	7		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute Myeloid Leukaemia			
subjects affected / exposed	2 / 97 (2.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Squamous Cell Carcinoma			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Shock			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

Vasculitis				
subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Disease Progression				
subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
General Physical Health Deterioration				
subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Pyrexia				
subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				
Benign Prostatic Hyperplasia				
subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Acute Respiratory Failure				
subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Chronic Obstructive Pulmonary Disease				
subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Epistaxis				

subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypoxia				
subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pleural Disorder				
subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pleural Effusion				
subjects affected / exposed	3 / 97 (3.09%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Pulmonary Embolism				
subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory Failure				
subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Psychiatric disorders				
Panic Attack				
subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Investigations				

Platelet Count Decreased				
subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Post Procedural Haemorrhage				
subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fall				
subjects affected / exposed	2 / 97 (2.06%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Splenic Rupture				
subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Acute Coronary Syndrome				
subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Atrial Fibrillation				
subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac Failure				
subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Myocardial Ischaemia				
subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Sick Sinus Syndrome				
subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ventricular Tachycardia				
subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Encephalopathy				
subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hydrocephalus				
subjects affected / exposed	1 / 97 (1.03%)			
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	1 / 97 (1.03%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Splenomegaly				
subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pancytopenia				
subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Thrombotic Thrombocytopenic Purpura				
subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

Eye disorders			
Photophobia			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hiatus Hernia			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Upper Gastrointestinal Haemorrhage			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oesophageal Varices Haemorrhage			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholestasis			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal Failure Acute			

subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Temporomandibular Joint Syndrome			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Influenza			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung Infection			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	4 / 97 (4.12%)		
occurrences causally related to treatment / all	2 / 4		
deaths causally related to treatment / all	0 / 1		

Sepsis			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Staphylococcal Sepsis			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 97 (2.06%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Hyperkalaemia			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tumour Lysis Syndrome			
subjects affected / exposed	1 / 97 (1.03%)		
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	Fedratinib		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	95 / 97 (97.94%)		
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	6 / 97 (6.19%)		
occurrences (all)	9		
Aspartate Aminotransferase Increased			
subjects affected / exposed	6 / 97 (6.19%)		
occurrences (all)	8		
Blood Creatinine Increased			

subjects affected / exposed	8 / 97 (8.25%)		
occurrences (all)	10		
Lipase Increased			
subjects affected / exposed	7 / 97 (7.22%)		
occurrences (all)	10		
Weight Decreased			
subjects affected / exposed	9 / 97 (9.28%)		
occurrences (all)	9		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	6 / 97 (6.19%)		
occurrences (all)	6		
Nervous system disorders			
Headache			
subjects affected / exposed	13 / 97 (13.40%)		
occurrences (all)	15		
Dizziness			
subjects affected / exposed	11 / 97 (11.34%)		
occurrences (all)	14		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	47 / 97 (48.45%)		
occurrences (all)	86		
Thrombocytopenia			
subjects affected / exposed	26 / 97 (26.80%)		
occurrences (all)	39		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	12 / 97 (12.37%)		
occurrences (all)	12		
Fatigue			
subjects affected / exposed	15 / 97 (15.46%)		
occurrences (all)	16		
Oedema Peripheral			
subjects affected / exposed	6 / 97 (6.19%)		
occurrences (all)	7		

Pain			
subjects affected / exposed	5 / 97 (5.15%)		
occurrences (all)	5		
Pyrexia			
subjects affected / exposed	10 / 97 (10.31%)		
occurrences (all)	10		
Social circumstances			
Blood Product Transfusion Dependent			
subjects affected / exposed	8 / 97 (8.25%)		
occurrences (all)	8		
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	11 / 97 (11.34%)		
occurrences (all)	18		
Abdominal Pain Upper			
subjects affected / exposed	7 / 97 (7.22%)		
occurrences (all)	7		
Constipation			
subjects affected / exposed	20 / 97 (20.62%)		
occurrences (all)	24		
Nausea			
subjects affected / exposed	54 / 97 (55.67%)		
occurrences (all)	74		
Dyspepsia			
subjects affected / exposed	5 / 97 (5.15%)		
occurrences (all)	5		
Diarrhoea			
subjects affected / exposed	59 / 97 (60.82%)		
occurrences (all)	79		
Vomiting			
subjects affected / exposed	40 / 97 (41.24%)		
occurrences (all)	52		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	13 / 97 (13.40%)		
occurrences (all)	14		

Dyspnoea subjects affected / exposed occurrences (all)	12 / 97 (12.37%) 13		
Epistaxis subjects affected / exposed occurrences (all)	7 / 97 (7.22%) 8		
Oropharyngeal Pain subjects affected / exposed occurrences (all)	6 / 97 (6.19%) 7		
Skin and subcutaneous tissue disorders			
Pruritus subjects affected / exposed occurrences (all)	16 / 97 (16.49%) 18		
Night Sweats subjects affected / exposed occurrences (all)	6 / 97 (6.19%) 6		
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	5 / 97 (5.15%) 6		
Back Pain subjects affected / exposed occurrences (all)	5 / 97 (5.15%) 5		
Bone Pain subjects affected / exposed occurrences (all)	7 / 97 (7.22%) 7		
Muscle Spasms subjects affected / exposed occurrences (all)	8 / 97 (8.25%) 9		
Myalgia subjects affected / exposed occurrences (all)	6 / 97 (6.19%) 6		
Pain In Extremity subjects affected / exposed occurrences (all)	6 / 97 (6.19%) 6		
Infections and infestations			

Bronchitis subjects affected / exposed occurrences (all) Respiratory Tract Infection subjects affected / exposed occurrences (all) Upper Respiratory Tract Infection subjects affected / exposed occurrences (all) Urinary Tract Infection subjects affected / exposed occurrences (all)	5 / 97 (5.15%) 5 5 / 97 (5.15%) 5 6 / 97 (6.19%) 6 12 / 97 (12.37%) 15		
Metabolism and nutrition disorders Decreased Appetite subjects affected / exposed occurrences (all)	9 / 97 (9.28%) 9		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 February 2012	It included following statements: 1. Updated exclusion criteria of subjects who may be at risk for liver function test (LFT) abnormalities. 2. Add more frequent monitoring LFTs (ALT, AST and bilirubin [total and direct]) during the first 3 cycles of treatment and in case severe liver enzyme elevations occur at any time during study treatment. 3. Explicit instructions given on dose modifications in case LFT abnormalities are detected. 4. Clarified the concomitant medication section regarding the recommendation to not use oral contraceptives and hormonal replacement therapies that include estrogen (ie, ethinyl estradiol) and progesterone (ie, levonorgestrel) during study treatment.
28 November 2012	It included following statements: Updated to include an interim analysis and interim report performed after approximately one-third of subjects were enrolled and completed 3 cycles of treatment. Increased the study sample size to 70 subjects in an attempt to provide sufficient statistical power (at least 90%) for testing response rate beyond a clinically important threshold: 10% response rate; for this other Janus kinase 2 (JAK2) treatment - refractory population; in addition, the increased sample size was to allow sufficient evaluations for subgroups. Expanded study to include subjects who were intolerant to or allergic to ruxolitinib after receiving ruxolitinib treatment for less than 14 days. Revised to Include subjects categorized as intermediate-1 with symptoms. Changed the risk classification algorithm for myelofibrosis from the original International Prognostic Scoring System to the newer Dynamic International Prognostic Scoring System. Reduced the wash-out period of ruxolitinib before taking the first dose of SAR302503 from 30 to 14 days and the wash-out period of hydroxyurea before taking the first dose of SAR302503 from 14 days to 1 day due to short half-life period of each drug. Updated to allow assessment of bone marrow in <14 days after discontinuing ruxolitinib or hydroxyurea during the screening period. Amended the concomitant medication section to include recent information that SAR302503 is likely a moderate-to-potent inhibitor of CYP3A4. Updated the tumor genomics section to add an additional whole blood sample (6 mL) collection predose at baseline (Cycle 1/Day 1), at Cycle 4 Day 1, and at the end of Cycle 6 to analyze potential molecular pathways associated with response/resistance to JAK2 treatment. Also added that mutation analysis would be performed on MPN-related genes in progenitor cells at single cell level to determine clonal architecture of PMN and its evolution during SAR302503 treatment.

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 clinical program and study termination, for safety reasons, only the primary efficacy endpoint, spleen response (SR) at end of cycle (EOC) 6, SR at EOC 3, the symptom response rate, and spleen size by palpation at EOC 6 were analyzed.

Notes: