



Clinical trial results:

A Randomized Phase II, Open-Label study of the Efficacy and Safety of Orally Administered SAR302503 in patients with polycythemia vera (PV) or essential thrombocythemia (ET) who are resistant or intolerant to hydroxyurea

Summary

EudraCT number	2011-001847-58
Trial protocol	FR GB ES IT
Global end of trial date	19 May 2014

Results information

Result version number	v1 (current)
This version publication date	01 April 2016
First version publication date	15 July 2015

Trial information

Trial identification

Sponsor protocol code	ARD12042
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01420783
WHO universal trial number (UTN)	U1111-1121-4203

Notes:

Sponsors

Sponsor organisation name	Sanofi aventis recherche & développement
Sponsor organisation address	1 avenue Pierre Brossolette, Chilly-Mazarin, France, 91380
Public contact	Sanofi aventis recherche & développement, Trial Transparency Team, Contact-us@sanofi.com
Scientific contact	Sanofi aventis recherche & développement, Trial Transparency Team, 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	26 June 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 May 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of daily oral doses of 100, 200 and 400 mg fedratinib in subjects with polycythemia vera (PV) or essential thrombocythemia (ET) who are resistant or intolerant to hydroxyurea (per European Leukemia Net Consensus criteria):

- Inducing the absence of phlebotomy and a hematocrit below 45% for a minimum of 3 months in subjects with PV, and Reduction of platelet count to $\leq 400 \times 10^9/L$ for a minimum of 3 months in subjects with ET.

Polycythemia vera (PV) Dose Expansion Phase and ET Dose Ranging Phase (only 600 mg dose group):

To evaluate the efficacy of daily oral SAR302503 in subjects with PV and ET who are resistant or intolerant to hydroxyurea (per European LeukemiaNet criteria) for:

-Inducing absence of phlebotomy eligibility beginning at Day 1 of Cycle 4 and continuing through Day 1 of Cycle 6 in subjects with PV, and Reduction of platelet count to $\leq 400 \times 10^9/L$ beginning at Day 1 of Cycle 4 and continuing through Day 1 of Cycle 6 in subjects with ET.

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	17 October 2011
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	Spain: 10
Country: Number of subjects enrolled	United Kingdom: 12
Country: Number of subjects enrolled	France: 8
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Italy: 12
Country: Number of subjects enrolled	Australia: 6
Country: Number of subjects enrolled	United States: 21
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 4
Country: Number of subjects enrolled	Canada: 6

Worldwide total number of subjects	81
EEA total number of subjects	44

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)	47
From 65 to 84 years	32
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 30 sites in 9 countries. A total of 81 subjects were screened between 17 October 2011 to 26 August 2013.

Pre-assignment

Screening details:

Of 81 screened subjects, 80 subjects were randomized and treated. The enrollment of additional ET subjects at 600 mg dose level was stopped prior to the termination of the SAR302503 program.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Fedratinib 100 mg

Arm description:

Fedratinib for a minimum of 8 cycles (each cycle of 28 days) in the absence of disease progression or unacceptable toxicity. Subjects who completed 8 cycles of therapy and who tolerated study treatment and benefited clinically were allowed to continue treatment.

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:

Fedratinib 100 mg once daily.

Arm title	Fedratinib 200 mg
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Arm description:

Fedratinib for a minimum of 8 cycles (each cycle of 28 days) in the absence of disease progression or unacceptable toxicity. Subjects who completed 8 cycles of therapy and who tolerated study treatment and benefited clinically were allowed to continue treatment.

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:

Fedratinib 200 mg once daily.

Arm title	Fedratinib $\geq$ 400 mg
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Arm description:

Fedratinib for a minimum of 8 cycles (each cycle of 28 days) in the absence of disease progression or unacceptable toxicity. Subjects who completed 8 cycles of therapy and who tolerated study treatment and benefited clinically were allowed to continue treatment.

Arm type	Experimental
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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:

Fedratinib 400 mg once daily. The study drug dose was titrated up or down in a 100 mg step to optimize efficacy and to minimize drug toxicity for individual subjects. The maximum allowable dose was 600 mg/day.

Number of subjects in period 1^[1]	Fedratinib 100 mg	Fedratinib 200 mg	Fedratinib $\geq$ 400 mg
Started	22	24	34
Completed	0	0	0
Not completed	22	24	34
Consent withdrawn by subject	-	-	12
Disease progression	-	1	1
Adverse event	3	4	10
Unspecified	19	19	11

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: One subject was randomized but not treated.

Baseline characteristics

Reporting groups

Reporting group title	Fedratinib 100 mg
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Reporting group description:

Fedratinib for a minimum of 8 cycles (each cycle of 28 days) in the absence of disease progression or unacceptable toxicity. Subjects who completed 8 cycles of therapy and who tolerated study treatment and benefited clinically were allowed to continue treatment.

Reporting group title	Fedratinib 200 mg
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Reporting group description:

Fedratinib for a minimum of 8 cycles (each cycle of 28 days) in the absence of disease progression or unacceptable toxicity. Subjects who completed 8 cycles of therapy and who tolerated study treatment and benefited clinically were allowed to continue treatment.

Reporting group title	Fedratinib $\geq$ 400 mg
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Reporting group description:

Fedratinib for a minimum of 8 cycles (each cycle of 28 days) in the absence of disease progression or unacceptable toxicity. Subjects who completed 8 cycles of therapy and who tolerated study treatment and benefited clinically were allowed to continue treatment.

Reporting group values	Fedratinib 100 mg	Fedratinib 200 mg	Fedratinib $\geq$ 400 mg
Number of subjects	22	24	34
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	62.7 $\pm$ 13.8	52.6 $\pm$ 16	61.7 $\pm$ 12.9
Gender categorical Units: Subjects			
Female	12	16	17
Male	10	8	17

Reporting group values	Total		
Number of subjects	80		
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	-		
Gender categorical Units: Subjects			
Female	45		
Male	35		

End points

End points reporting groups

Reporting group title	Fedratinib 100 mg
Reporting group description: Fedratinib for a minimum of 8 cycles (each cycle of 28 days) in the absence of disease progression or unacceptable toxicity. Subjects who completed 8 cycles of therapy and who tolerated study treatment and benefited clinically were allowed to continue treatment.	
Reporting group title	Fedratinib 200 mg
Reporting group description: Fedratinib for a minimum of 8 cycles (each cycle of 28 days) in the absence of disease progression or unacceptable toxicity. Subjects who completed 8 cycles of therapy and who tolerated study treatment and benefited clinically were allowed to continue treatment.	
Reporting group title	Fedratinib $\geq$ 400 mg
Reporting group description: Fedratinib for a minimum of 8 cycles (each cycle of 28 days) in the absence of disease progression or unacceptable toxicity. Subjects who completed 8 cycles of therapy and who tolerated study treatment and benefited clinically were allowed to continue treatment.	

Primary: Percentage of Polycythemia Vera (PV) Subjects With Absence of Phlebotomy and Hematocrit Below 45% for a Minimum of 3 Months

End point title	Percentage of Polycythemia Vera (PV) Subjects With Absence of Phlebotomy and Hematocrit Below 45% for a Minimum of 3 Months ^[1]
End point description:	
End point type	Primary
End point timeframe: Baseline up to Cycle 8	
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: Due to termination of the study (when the SAR302503 clinical program was terminated due to safety reason), no analysis was performed.	

End point values	Fedratinib 100 mg	Fedratinib 200 mg	Fedratinib $\geq$ 400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0 ^[2]	0 ^[3]	0 ^[4]	
Units: percentage of subjects				
number (not applicable)				

Notes:

[2] - The study was terminated when the SAR302503 clinical program was terminated due to safety reason.

[3] - The study was terminated when the SAR302503 clinical program was terminated due to safety reason.

[4] - The study was terminated when the SAR302503 clinical program was terminated due to safety reason.

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of PV Subjects With Absence of Phlebotomy Eligibility

End point title	Percentage of PV Subjects With Absence of Phlebotomy Eligibility ^[5]
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End point description:

End point type	Primary
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End point timeframe:

Day 1 of Cycle 4 up to Day 1 of Cycle 6

Notes:

[5] - 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: Due to termination of the study (when the SAR302503 clinical program was terminated due to safety reason), no analysis was performed.

End point values	Fedratinib 100 mg	Fedratinib 200 mg	Fedratinib >= 400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0 ^[6]	0 ^[7]	0 ^[8]	
Units: percentage of subjects				
number (not applicable)				

Notes:

[6] - The study was terminated when the SAR302503 clinical program was terminated due to safety reason.

[7] - The study was terminated when the SAR302503 clinical program was terminated due to safety reason.

[8] - The study was terminated when the SAR302503 clinical program was terminated due to safety reason.

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Essential Thrombocythemia (ET) Subjects With Platelet Count $\leq 400 \times 10^9/L$ for a Minimum of 3 Months

End point title	Percentage of Essential Thrombocythemia (ET) Subjects With Platelet Count $\leq 400 \times 10^9/L$ for a Minimum of 3 Months ^[9]
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End point description:

End point type	Primary
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End point timeframe:

Day 1 of Cycle 4 up to Day 1 of Cycle 6

Notes:

[9] - 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: Due to termination of the study (when the SAR302503 clinical program was terminated due to safety reason), no analysis was performed.

End point values	Fedratinib 100 mg	Fedratinib 200 mg	Fedratinib >= 400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0 ^[10]	0 ^[11]	0 ^[12]	
Units: percentage of subjects				
number (not applicable)				

Notes:

[10] - The study was terminated when the SAR302503 clinical program was terminated due to safety reason.

[11] - The study was terminated when the SAR302503 clinical program was terminated due to safety

reason.

[12] - The study was terminated when the SAR302503 clinical program was terminated due to safety reason.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of PV Subjects With Absence of Phlebotomy From Cycle 4 to Cycle 8

End point title	Percentage of PV Subjects With Absence of Phlebotomy From Cycle 4 to Cycle 8
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End point description:

End point type	Secondary
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End point timeframe:

Day 1 of Cycle 4 up to End of Cycle 8

End point values	Fedratinib 100 mg	Fedratinib 200 mg	Fedratinib $\geq$ 400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0 ^[13]	0 ^[14]	0 ^[15]	
Units: percentage of subjects				
number (not applicable)				

Notes:

[13] - The study was terminated when the SAR302503 clinical program was terminated due to safety reason.

[14] - The study was terminated when the SAR302503 clinical program was terminated due to safety reason.

[15] - The study was terminated when the SAR302503 clinical program was terminated due to safety reason.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of ET Subjects With Platelet Count of $\leq 400 \times 10^9/L$ From Cycle 4 to Cycle 8

End point title	Percentage of ET Subjects With Platelet Count of $\leq 400 \times 10^9/L$ From Cycle 4 to Cycle 8
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End point description:

End point type	Secondary
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End point timeframe:

Day 1 of Cycle 4 up to End of Cycle 8

End point values	Fedratinib 100 mg	Fedratinib 200 mg	Fedratinib >= 400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0 ^[16]	0 ^[17]	0 ^[18]	
Units: percentage of subjects				
number (not applicable)				

Notes:

[16] - The study was terminated when the SAR302503 clinical program was terminated due to safety reason.

[17] - The study was terminated when the SAR302503 clinical program was terminated due to safety reason.

[18] - The study was terminated when the SAR302503 clinical program was terminated due to safety reason.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Clinicohematologic Response From Cycle 6 to Cycle 8

End point title	Percentage of Subjects With Clinicohematologic Response From Cycle 6 to Cycle 8
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End point description:

End point type	Secondary
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End point timeframe:

Day 1 of Cycle 6 up to End of Cycle 8 (Up to Day 224)

End point values	Fedratinib 100 mg	Fedratinib 200 mg	Fedratinib >= 400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0 ^[19]	0 ^[20]	0 ^[21]	
Units: percentage of subjects				
number (not applicable)				

Notes:

[19] - The study was terminated when the SAR302503 clinical program was terminated due to safety reason.

[20] - The study was terminated when the SAR302503 clinical program was terminated due to safety reason.

[21] - The study was terminated when the SAR302503 clinical program was terminated due to safety reason.

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Spleen Volume at End of Cycle 4, 8 and End of Treatment

End point title	Percent Change From Baseline in Spleen Volume at End of Cycle 4, 8 and End of Treatment
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End point description:

End point type	Secondary
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End point timeframe:

Baseline, End of Cycle 4, 8 and End of Treatment

End point values	Fedratinib 100 mg	Fedratinib 200 mg	Fedratinib $\geq$ 400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0 ^[22]	0 ^[23]	0 ^[24]	
Units: percent change				
arithmetic mean (standard deviation)	()	()	()	

Notes:

[22] - The study was terminated when the SAR302503 clinical program was terminated due to safety reason.

[23] - The study was terminated when the SAR302503 clinical program was terminated due to safety reason.

[24] - The study was terminated when the SAR302503 clinical program was terminated due to safety reason.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with a $\geq$ 35% Reduction From Baseline in Spleen Volume

End point title	Percentage of Subjects with a $\geq$ 35% Reduction From Baseline in Spleen Volume
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End point description:

End point type	Secondary
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End point timeframe:

Baseline, End of Cycle 4, 8 and End of Treatment

End point values	Fedratinib 100 mg	Fedratinib 200 mg	Fedratinib $\geq$ 400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0 ^[25]	0 ^[26]	0 ^[27]	
Units: percentage of subjects				
number (not applicable)				

Notes:

[25] - The study was terminated when the SAR302503 clinical program was terminated due to safety reason.

[26] - The study was terminated when the SAR302503 clinical program was terminated due to safety reason.

[27] - The study was terminated when the SAR302503 clinical program was terminated due to safety reason.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Who Had Changes in Histological, Cytogenetic, and Molecular Responses in Bone Marrow

End point title	Number of Subjects Who Had Changes in Histological, Cytogenetic, and Molecular Responses in Bone Marrow
End point description:	
End point type	Secondary
End point timeframe:	
Up to end of treatment	

End point values	Fedratinib 100 mg	Fedratinib 200 mg	Fedratinib >= 400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0 ^[28]	0 ^[29]	0 ^[30]	
Units: subjects				

Notes:

[28] - The study was terminated when the SAR302503 clinical program was terminated due to safety reason.

[29] - The study was terminated when the SAR302503 clinical program was terminated due to safety reason.

[30] - The study was terminated when the SAR302503 clinical program was terminated due to safety reason.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Response Measured by The Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF)

End point title	Percentage of Subjects With Response Measured by The Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF)
End point description:	
End point type	Secondary
End point timeframe:	
Baseline, End of Cycle 1, 4, and 8	

End point values	Fedratinib 100 mg	Fedratinib 200 mg	Fedratinib >= 400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0 ^[31]	0 ^[32]	0 ^[33]	
Units: percentage of subjects				
number (not applicable)				

Notes:

[31] - The study was terminated when the SAR302503 clinical program was terminated due to safety reason.

[32] - The study was terminated when the SAR302503 clinical program was terminated due to safety reason.

[33] - The study was terminated when the SAR302503 clinical program was terminated due to safety reason.

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulative Distribution Function of Response on the MPN-SAF

End point title	Cumulative Distribution Function of Response on the MPN-SAF
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End point description:

End point type	Secondary
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End point timeframe:

End of Cycles1, 4, 8 and End of Treatment

End point values	Fedratinib 100 mg	Fedratinib 200 mg	Fedratinib >= 400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0 ^[34]	0 ^[35]	0 ^[36]	
Units: units on a scale				
arithmetic mean (standard deviation)	()	()	()	

Notes:

[34] - The study was terminated when the SAR302503 clinical program was terminated due to safety reason.

[35] - The study was terminated when the SAR302503 clinical program was terminated due to safety reason.

[36] - The study was terminated when the SAR302503 clinical program was terminated due to safety reason.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Resolution of Symptoms on MPN-SAF

End point title	Percentage of Subjects With Resolution of Symptoms on MPN-SAF
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End point description:

End point type	Secondary
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End point timeframe:

Baseline, End of Cycle 1, 4, and 8 (up to Day 224)

End point values	Fedratinib 100 mg	Fedratinib 200 mg	Fedratinib >= 400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0 ^[37]	0 ^[38]	0 ^[39]	
Units: percentage of subjects				
number (not applicable)				

Notes:

[37] - The study was terminated when the SAR302503 clinical program was terminated due to safety reason.

[38] - The study was terminated when the SAR302503 clinical program was terminated due to safety reason.

[39] - The study was terminated when the SAR302503 clinical program was terminated due to safety reason.

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of Life and Utility Values Using the EuroQoL (EQ)-5D Questionnaire

End point title	Quality of Life and Utility Values Using the EuroQoL (EQ)-5D Questionnaire
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End point description:

End point type	Secondary
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End point timeframe:

Baseline, End of Cycle 8

End point values	Fedratinib 100 mg	Fedratinib 200 mg	Fedratinib >= 400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0 ^[40]	0 ^[41]	0 ^[42]	
Units: units on a scale				
arithmetic mean (standard deviation)	()	()	()	

Notes:

[40] - The study was terminated when the SAR302503 clinical program was terminated due to safety reason.

[41] - The study was terminated when the SAR302503 clinical program was terminated due to safety reason.

[42] - The study was terminated when the SAR302503 clinical program was terminated due to safety reason.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Who Experienced TEAEs, Grade 3-4 TEAEs, SAEs and Discontinued

End point title	Number of Subjects Who Experienced TEAEs, Grade 3-4 TEAEs, SAEs and Discontinued
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End point description:

Treatment-emergent adverse event (TEAE) defined as any adverse event that is new, gets worse, or becomes serious during the treatment period. Clinical and laboratory AEs were assessed and reported using terminology of the National Cancer Institute (NCI) – CTCAE version 4.03. Grade 3 TEAE are severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living. Grade 4 TEAE are Life-threatening consequences, urgent intervention indicated. Analysis was done on safety population defined as all randomized and treated subjects.

End point type	Secondary
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End point timeframe:

Up to Week 32

End point values	Fedratinib 100 mg	Fedratinib 200 mg	Fedratinib >= 400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22	24	34	
Units: subjects				
Subjects with any TEAE	21	24	34	
Subjects with any Grade 3-4 TEAE	10	10	18	
Subjects with any treatment-emergent SAE	7	7	8	
Subjects with any TEAE leading to discontinuation	3	4	10	

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 (up to 27 cycles) regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Reported adverse events are treatment-emergent adverse events that is AEs that developed/worsened during the 'on treatment period' (from first dose of the study drug up to end of treatment). Analysis was done on safety population.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Fedratinib 100 mg
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Reporting group description:

Fedratinib for a minimum of 8 cycles (each cycle of 28 days) in the absence of disease progression or unacceptable toxicity. Subjects who completed 8 cycles of therapy and who tolerated study treatment and benefited clinically were allowed to continue treatment.

Reporting group title	Fedratinib >= 400 mg
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Reporting group description:

Fedratinib for a minimum of 8 cycles (each cycle of 28 days) in the absence of disease progression or unacceptable toxicity. Subjects who completed 8 cycles of therapy and who tolerated study treatment and benefited clinically were allowed to continue treatment.

Reporting group title	Fedratinib 200 mg
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Reporting group description:

Fedratinib for a minimum of 8 cycles (each cycle of 28 days) in the absence of disease progression or unacceptable toxicity. Subjects who completed 8 cycles of therapy and who tolerated study treatment and benefited clinically were allowed to continue treatment.

Serious adverse events	Fedratinib 100 mg	Fedratinib >= 400 mg	Fedratinib 200 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 22 (31.82%)	8 / 34 (23.53%)	7 / 24 (29.17%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous Cell Carcinoma Of Skin			
subjects affected / exposed	1 / 22 (4.55%)	0 / 34 (0.00%)	0 / 24 (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
Vascular disorders			
Deep Vein Thrombosis			

subjects affected / exposed	0 / 22 (0.00%)	1 / 34 (2.94%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematoma			
subjects affected / exposed	0 / 22 (0.00%)	0 / 34 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Pregnancy			
subjects affected / exposed	0 / 22 (0.00%)	0 / 34 (0.00%)	1 / 24 (4.17%)
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			
Influenza Like Illness			
subjects affected / exposed	0 / 22 (0.00%)	1 / 34 (2.94%)	0 / 24 (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
Psychiatric disorders			
Suicide Attempt			
subjects affected / exposed	1 / 22 (4.55%)	0 / 34 (0.00%)	0 / 24 (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
Investigations			
Lipase Increased			
subjects affected / exposed	1 / 22 (4.55%)	1 / 34 (2.94%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Pericarditis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 34 (2.94%)	0 / 24 (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
Ventricular Arrhythmia			

subjects affected / exposed	0 / 22 (0.00%)	0 / 34 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Haemorrhage Intracranial			
subjects affected / exposed	1 / 22 (4.55%)	0 / 34 (0.00%)	0 / 24 (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
Headache			
subjects affected / exposed	0 / 22 (0.00%)	1 / 34 (2.94%)	0 / 24 (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
Migraine			
subjects affected / exposed	0 / 22 (0.00%)	1 / 34 (2.94%)	0 / 24 (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
Wernicke's Encephalopathy			
subjects affected / exposed	0 / 22 (0.00%)	0 / 34 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Splenic Infarction			
subjects affected / exposed	0 / 22 (0.00%)	1 / 34 (2.94%)	0 / 24 (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
Thrombocytosis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 34 (2.94%)	0 / 24 (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
Ear and labyrinth disorders			
Vertigo Positional			
subjects affected / exposed	1 / 22 (4.55%)	0 / 34 (0.00%)	0 / 24 (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			
subjects affected / exposed	0 / 22 (0.00%)	0 / 34 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 22 (0.00%)	1 / 34 (2.94%)	0 / 24 (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
Ileus			
subjects affected / exposed	1 / 22 (4.55%)	0 / 34 (0.00%)	0 / 24 (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
Inguinal Hernia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 34 (2.94%)	0 / 24 (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
Melaena			
subjects affected / exposed	0 / 22 (0.00%)	1 / 34 (2.94%)	0 / 24 (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
Vomiting			
subjects affected / exposed	0 / 22 (0.00%)	0 / 34 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Soft Tissue Mass			
subjects affected / exposed	0 / 22 (0.00%)	0 / 34 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Diverticulitis			

subjects affected / exposed	0 / 22 (0.00%)	0 / 34 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis Viral			
subjects affected / exposed	0 / 22 (0.00%)	0 / 34 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 34 (2.94%)	0 / 24 (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			
Hyponatraemia			
subjects affected / exposed	1 / 22 (4.55%)	0 / 34 (0.00%)	0 / 24 (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

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

Non-serious adverse events	Fedratinib 100 mg	Fedratinib >= 400 mg	Fedratinib 200 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 22 (90.91%)	34 / 34 (100.00%)	23 / 24 (95.83%)
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 22 (0.00%)	1 / 34 (2.94%)	2 / 24 (8.33%)
occurrences (all)	0	2	2
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 22 (9.09%)	5 / 34 (14.71%)	6 / 24 (25.00%)
occurrences (all)	2	5	8
Fatigue			
subjects affected / exposed	6 / 22 (27.27%)	7 / 34 (20.59%)	4 / 24 (16.67%)
occurrences (all)	6	8	6
Influenza Like Illness			

subjects affected / exposed	1 / 22 (4.55%)	2 / 34 (5.88%)	0 / 24 (0.00%)
occurrences (all)	1	2	0
Malaise			
subjects affected / exposed	0 / 22 (0.00%)	2 / 34 (5.88%)	0 / 24 (0.00%)
occurrences (all)	0	3	0
Oedema Peripheral			
subjects affected / exposed	3 / 22 (13.64%)	5 / 34 (14.71%)	2 / 24 (8.33%)
occurrences (all)	3	6	2
Pain			
subjects affected / exposed	0 / 22 (0.00%)	1 / 34 (2.94%)	3 / 24 (12.50%)
occurrences (all)	0	1	4
Pyrexia			
subjects affected / exposed	1 / 22 (4.55%)	5 / 34 (14.71%)	3 / 24 (12.50%)
occurrences (all)	1	7	4
Reproductive system and breast disorders			
Erectile Dysfunction			
subjects affected / exposed	1 / 22 (4.55%)	2 / 34 (5.88%)	0 / 24 (0.00%)
occurrences (all)	1	2	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 22 (0.00%)	4 / 34 (11.76%)	5 / 24 (20.83%)
occurrences (all)	0	5	5
Dyspnoea			
subjects affected / exposed	2 / 22 (9.09%)	4 / 34 (11.76%)	0 / 24 (0.00%)
occurrences (all)	2	5	0
Epistaxis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 34 (2.94%)	2 / 24 (8.33%)
occurrences (all)	0	1	2
Oropharyngeal Pain			
subjects affected / exposed	0 / 22 (0.00%)	3 / 34 (8.82%)	1 / 24 (4.17%)
occurrences (all)	0	3	1
Rhinorrhoea			
subjects affected / exposed	2 / 22 (9.09%)	0 / 34 (0.00%)	0 / 24 (0.00%)
occurrences (all)	3	0	0
Sleep Apnoea Syndrome			

subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2	0 / 34 (0.00%) 0	0 / 24 (0.00%) 0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 22 (4.55%)	2 / 34 (5.88%)	0 / 24 (0.00%)
occurrences (all)	1	3	0
Confusional State			
subjects affected / exposed	2 / 22 (9.09%)	1 / 34 (2.94%)	0 / 24 (0.00%)
occurrences (all)	2	2	0
Depression			
subjects affected / exposed	1 / 22 (4.55%)	2 / 34 (5.88%)	0 / 24 (0.00%)
occurrences (all)	1	2	0
Insomnia			
subjects affected / exposed	3 / 22 (13.64%)	1 / 34 (2.94%)	1 / 24 (4.17%)
occurrences (all)	3	1	1
Investigations			
Amylase Increased			
subjects affected / exposed	1 / 22 (4.55%)	4 / 34 (11.76%)	0 / 24 (0.00%)
occurrences (all)	1	5	0
Alanine Aminotransferase Increased			
subjects affected / exposed	3 / 22 (13.64%)	5 / 34 (14.71%)	0 / 24 (0.00%)
occurrences (all)	3	5	0
Aspartate Aminotransferase Increased			
subjects affected / exposed	1 / 22 (4.55%)	2 / 34 (5.88%)	0 / 24 (0.00%)
occurrences (all)	1	2	0
Blood Alkaline Phosphatase Increased			
subjects affected / exposed	0 / 22 (0.00%)	3 / 34 (8.82%)	0 / 24 (0.00%)
occurrences (all)	0	3	0
Blood Creatinine Increased			
subjects affected / exposed	0 / 22 (0.00%)	5 / 34 (14.71%)	0 / 24 (0.00%)
occurrences (all)	0	7	0
Lipase Increased			
subjects affected / exposed	1 / 22 (4.55%)	6 / 34 (17.65%)	1 / 24 (4.17%)
occurrences (all)	1	9	2
Weight Decreased			

subjects affected / exposed	0 / 22 (0.00%)	3 / 34 (8.82%)	2 / 24 (8.33%)
occurrences (all)	0	3	2
Weight Increased			
subjects affected / exposed	2 / 22 (9.09%)	1 / 34 (2.94%)	0 / 24 (0.00%)
occurrences (all)	2	1	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	2 / 22 (9.09%)	1 / 34 (2.94%)	2 / 24 (8.33%)
occurrences (all)	2	1	4
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 22 (4.55%)	3 / 34 (8.82%)	0 / 24 (0.00%)
occurrences (all)	2	3	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	4 / 22 (18.18%)	4 / 34 (11.76%)	2 / 24 (8.33%)
occurrences (all)	6	4	5
Headache			
subjects affected / exposed	8 / 22 (36.36%)	4 / 34 (11.76%)	7 / 24 (29.17%)
occurrences (all)	10	4	10
Memory Impairment			
subjects affected / exposed	0 / 22 (0.00%)	2 / 34 (5.88%)	0 / 24 (0.00%)
occurrences (all)	0	2	0
Peripheral Sensory Neuropathy			
subjects affected / exposed	3 / 22 (13.64%)	3 / 34 (8.82%)	1 / 24 (4.17%)
occurrences (all)	3	4	1
Sciatica			
subjects affected / exposed	0 / 22 (0.00%)	0 / 34 (0.00%)	2 / 24 (8.33%)
occurrences (all)	0	0	2
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 22 (4.55%)	5 / 34 (14.71%)	0 / 24 (0.00%)
occurrences (all)	3	6	0
Neutropenia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 34 (2.94%)	0 / 24 (0.00%)
occurrences (all)	0	1	0

Eye disorders			
Eye Pain			
subjects affected / exposed	0 / 22 (0.00%)	2 / 34 (5.88%)	0 / 24 (0.00%)
occurrences (all)	0	2	0
Periorbital Oedema			
subjects affected / exposed	0 / 22 (0.00%)	2 / 34 (5.88%)	0 / 24 (0.00%)
occurrences (all)	0	2	0
Vision Blurred			
subjects affected / exposed	0 / 22 (0.00%)	1 / 34 (2.94%)	2 / 24 (8.33%)
occurrences (all)	0	1	2
Gastrointestinal disorders			
Abdominal Discomfort			
subjects affected / exposed	2 / 22 (9.09%)	0 / 34 (0.00%)	1 / 24 (4.17%)
occurrences (all)	3	0	1
Abdominal Pain			
subjects affected / exposed	2 / 22 (9.09%)	6 / 34 (17.65%)	2 / 24 (8.33%)
occurrences (all)	2	14	4
Abdominal Pain Upper			
subjects affected / exposed	1 / 22 (4.55%)	4 / 34 (11.76%)	0 / 24 (0.00%)
occurrences (all)	1	4	0
Diarrhoea			
subjects affected / exposed	9 / 22 (40.91%)	21 / 34 (61.76%)	10 / 24 (41.67%)
occurrences (all)	11	31	22
Constipation			
subjects affected / exposed	1 / 22 (4.55%)	8 / 34 (23.53%)	4 / 24 (16.67%)
occurrences (all)	1	8	5
Dyspepsia			
subjects affected / exposed	2 / 22 (9.09%)	1 / 34 (2.94%)	1 / 24 (4.17%)
occurrences (all)	2	1	1
Dry Mouth			
subjects affected / exposed	2 / 22 (9.09%)	3 / 34 (8.82%)	1 / 24 (4.17%)
occurrences (all)	2	3	1
Flatulence			
subjects affected / exposed	0 / 22 (0.00%)	3 / 34 (8.82%)	0 / 24 (0.00%)
occurrences (all)	0	3	0
Gastrointestinal Disorder			

subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	2 / 34 (5.88%) 2	1 / 24 (4.17%) 1
Nausea subjects affected / exposed occurrences (all)	9 / 22 (40.91%) 10	22 / 34 (64.71%) 32	12 / 24 (50.00%) 18
Oesophageal Pain subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	1 / 34 (2.94%) 1	0 / 24 (0.00%) 0
Vomiting subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 4	16 / 34 (47.06%) 31	8 / 24 (33.33%) 13
Skin and subcutaneous tissue disorders			
Actinic Keratosis subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	2 / 34 (5.88%) 3	0 / 24 (0.00%) 0
Ecchymosis subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 34 (0.00%) 0	3 / 24 (12.50%) 5
Erythema subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 34 (0.00%) 0	3 / 24 (12.50%) 4
Night Sweats subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	2 / 34 (5.88%) 2	2 / 24 (8.33%) 2
Pain Of Skin subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	2 / 34 (5.88%) 2	0 / 24 (0.00%) 0
Pruritus subjects affected / exposed occurrences (all)	4 / 22 (18.18%) 4	4 / 34 (11.76%) 4	2 / 24 (8.33%) 3
Pruritus Generalised subjects affected / exposed occurrences (all)	3 / 22 (13.64%) 3	1 / 34 (2.94%) 1	2 / 24 (8.33%) 2
Skin Lesion subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	2 / 34 (5.88%) 2	1 / 24 (4.17%) 1

Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 22 (9.09%)	5 / 34 (14.71%)	2 / 24 (8.33%)
occurrences (all)	2	5	2
Bone Pain			
subjects affected / exposed	2 / 22 (9.09%)	3 / 34 (8.82%)	1 / 24 (4.17%)
occurrences (all)	2	3	1
Back Pain			
subjects affected / exposed	4 / 22 (18.18%)	5 / 34 (14.71%)	0 / 24 (0.00%)
occurrences (all)	4	6	0
Haemarthrosis			
subjects affected / exposed	0 / 22 (0.00%)	2 / 34 (5.88%)	0 / 24 (0.00%)
occurrences (all)	0	3	0
Muscle Spasms			
subjects affected / exposed	4 / 22 (18.18%)	7 / 34 (20.59%)	2 / 24 (8.33%)
occurrences (all)	5	13	2
Musculoskeletal Chest Pain			
subjects affected / exposed	2 / 22 (9.09%)	1 / 34 (2.94%)	0 / 24 (0.00%)
occurrences (all)	3	1	0
Myalgia			
subjects affected / exposed	0 / 22 (0.00%)	2 / 34 (5.88%)	1 / 24 (4.17%)
occurrences (all)	0	2	1
Pain In Extremity			
subjects affected / exposed	0 / 22 (0.00%)	6 / 34 (17.65%)	2 / 24 (8.33%)
occurrences (all)	0	8	4
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	2 / 22 (9.09%)	1 / 34 (2.94%)	0 / 24 (0.00%)
occurrences (all)	2	1	0
Influenza			
subjects affected / exposed	0 / 22 (0.00%)	1 / 34 (2.94%)	2 / 24 (8.33%)
occurrences (all)	0	1	2
Nasopharyngitis			
subjects affected / exposed	1 / 22 (4.55%)	0 / 34 (0.00%)	2 / 24 (8.33%)
occurrences (all)	1	0	2
Upper Respiratory Tract Infection			

subjects affected / exposed	3 / 22 (13.64%)	3 / 34 (8.82%)	2 / 24 (8.33%)
occurrences (all)	4	3	2
Urinary Tract Infection			
subjects affected / exposed	2 / 22 (9.09%)	4 / 34 (11.76%)	1 / 24 (4.17%)
occurrences (all)	2	4	1
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	0 / 22 (0.00%)	2 / 34 (5.88%)	2 / 24 (8.33%)
occurrences (all)	0	3	2
Hyperlipasaemia			
subjects affected / exposed	1 / 22 (4.55%)	3 / 34 (8.82%)	0 / 24 (0.00%)
occurrences (all)	1	4	0
Hyperamylasaemia			
subjects affected / exposed	0 / 22 (0.00%)	3 / 34 (8.82%)	0 / 24 (0.00%)
occurrences (all)	0	8	0
Hyperuricaemia			
subjects affected / exposed	0 / 22 (0.00%)	2 / 34 (5.88%)	3 / 24 (12.50%)
occurrences (all)	0	2	5
Hypocalcaemia			
subjects affected / exposed	0 / 22 (0.00%)	2 / 34 (5.88%)	0 / 24 (0.00%)
occurrences (all)	0	2	0
Hypokalaemia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 34 (2.94%)	0 / 24 (0.00%)
occurrences (all)	0	2	0
Type 2 Diabetes Mellitus			
subjects affected / exposed	0 / 22 (0.00%)	1 / 34 (2.94%)	0 / 24 (0.00%)
occurrences (all)	0	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 May 2011	Addition of electrocardiograms (ECG) to safety monitoring.
09 December 2011	1.Exclusion Criteria E 20 was changed to harmonize the exclusion of CYP3A4 concomitant medications across protocols studying SAR302503, the discretion for subjects's use such of medications with the sponsor's approval as allowed in E 20 was removed. 2. Added language that drugs which are strong inhibitors of CYP2C19 should be used with caution. 3. sites were increased form 8 to approximately 45 globally.
17 February 2012	1. Updated exclusion criteria of subjects who may be at risk for liver function test (LFT) abnormalities : added more frequent monitoring of LFTs (alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin [total and direct]) during the first 3 cycles of treatment in case severe liver enzyme elevations occur at any time during study treatment. 2. To give explicit instructions for dose modifications in case LFT abnormalities are detected. 3. Clarification in 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.
07 November 2012	1. Clarification on 'Dose modification for toxicity' of the interval allowed for dose interruption in case of transfusion dependency. 2. 'Adverse events of special interest' list was updated. 3. Statistical section was updated. 4. Initially a singular center was selected to evaluate changes in endogenous erythroid colony formation and replenishment of iron in iron-deficient subjects in subjects with PV, however the test was not set up contractually and therefore was deleted from the protocol and will be revisited at future studies.
12 July 2013	The primary reason for issuance of Protocol Amendment was to halt further enrollment subjects with essential thrombocythemia (ET). Other changes included following points: 1. Statistical considerations had revised to account for the closure of enrollment to ET subjects. 2. Clarification was added to specify that granulocyte tumor samples may be analyzed for additional MPN related gene mutations in addition to JAK2V617F. 3. Administrative corrections/revisions throughout the document was made.
27 November 2013	Based on an internal assessment of the potential benefits and risks of the treatment, Sanofi has decided to terminate all SAR302503 clinical trials including those in myelofibrosis, polycythemia vera, essential thrombocythemia, and solid tumors, and would not ask the FDA to remove the clinical hold that was imposed. Thus going forward, all subjects permanently discontinued from further SAR302503 treatment. Sanofi, therefore, urges investigators to seek alternative therapies for the subjects on their studies. All subjects will continue to be followed for safety.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported