



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 |
|-----------------------|----------|

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 |
|------------------|-------------------|

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 >= 400 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 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 |
|-----------------------|-------------------|

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.

| 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] |
|-----------------|---|

End point description:

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

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 \geq 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] |
|-----------------|---|

End point description:

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

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 \geq 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 |
|-----------------|--|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

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 |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

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 |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

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 |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

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 |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

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 |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

End of Cycles 1, 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 |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

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 |
|-----------------|--|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

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 |
|-----------------|--|

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 |
|----------------|-----------|

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 |
|-----------------|------------|

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 17.0 |

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 >= 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 |
|-----------------------|-------------------|

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 | <ol style="list-style-type: none">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 | <ol style="list-style-type: none">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 | <ol style="list-style-type: none">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 | <p>The primary reason for issuance of Protocol Amendment was to halt further enrollment subjects with essential thrombocythemia (ET).</p> <p>Other changes included following points:</p> <ol style="list-style-type: none">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 | <p>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.</p> |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported