



Clinical trial results:

Randomized, open-label, multi-center Phase IIIb study evaluating the efficacy and safety of ruxolitinib versus best available therapy in patients with polycythemia vera who are hydroxyurea resistant or intolerant (RESPONSE-2)

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2013-003583-31 |
| Trial protocol | DE ES IT HU BE FR |
| Global end of trial date | 07 April 2020 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 |
| This version publication date | 22 April 2021 |
| First version publication date | 22 April 2021 |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | CINC424B2401 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02038036 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Novartis Pharma AG |
| Sponsor organisation address | CH-4002, Basel, Switzerland, |
| Public contact | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com |
| Scientific contact | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.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 | 07 April 2020 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 07 April 2020 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to compare the efficacy of ruxolitinib to best available therapy (BAT) as assessed by hematocrit (Hct) control at Week 28.

Due to EudraCT system limitations, which EMA is aware of, results of crossover studies and data using 999 as data points are not accurately represented in this record. Please go to <https://www.novctrd.com/CtrdWeb/home.nov> for complete trial results

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 25 March 2014 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-----------------------|
| Country: Number of subjects enrolled | Australia: 4 |
| Country: Number of subjects enrolled | Belgium: 9 |
| Country: Number of subjects enrolled | Canada: 5 |
| Country: Number of subjects enrolled | France: 15 |
| Country: Number of subjects enrolled | Germany: 27 |
| Country: Number of subjects enrolled | Hungary: 12 |
| Country: Number of subjects enrolled | India: 3 |
| Country: Number of subjects enrolled | Israel: 6 |
| Country: Number of subjects enrolled | Italy: 31 |
| Country: Number of subjects enrolled | Korea, Republic of: 6 |
| Country: Number of subjects enrolled | Spain: 25 |
| Country: Number of subjects enrolled | Turkey: 6 |
| Worldwide total number of subjects | 149 |
| EEA total number of subjects | 119 |

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) | 69 |
| From 65 to 84 years | 77 |
| 85 years and over | 3 |

Subject disposition

Recruitment

Recruitment details:

Participants were randomized in 48 centers across 12 countries: Australia (1), Belgium (2), Canada (1), France (7), Germany (9), Hungary (3), India (2), Israel (3), Italy (7), South Korea (2), Spain (9) and Turkey (2)

Pre-assignment

Screening details:

Participants were randomized in a 1:1 ratio either to Ruxolitinib or Best available Therapy (BAT). Randomization was stratified by patients who were resistant to or intolerant of Hydroxyurea (HU).

Period 1

| | |
|------------------------------|-------------------------|
| Period 1 title | Core Study |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Blinding implementation details:
open-label

Arms

| | |
|------------------------------|-------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Ruxolitinib |

Arm description:

Ruxolitinib at a starting dose of 10 mg twice a day (bid). Dose was adjusted based on efficacy and safety parameters up to a maximum dose of 25 mg bid

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Ruxolitinib |
| Investigational medicinal product code | INC424 |
| Other name | Jakafi® |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Ruxolitinib at a starting dose of 10 mg twice a day (bid). Dose was adjusted based on efficacy and safety parameters up to a maximum dose of 25 mg bid

| | |
|------------------|------------------------------|
| Arm title | Best Available Therapy (BAT) |
|------------------|------------------------------|

Arm description:

Best Available Therapy as selected by the investigator from: Hydroxyurea, Pegylated-Interferon (IFN/PEG-IFN), pipobroman, anagrelide, IMiDs, or observation. Participants randomized to BAT who did not respond by Week 28 were eligible to crossover and start treatment with ruxolitinib

| | |
|--|--|
| Arm type | Active comparator |
| Investigational medicinal product name | Hydroxyurea, IFN/PEG-IFN, pipobroman, anagrelide, IMiDs, or observation. |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Hydroxyurea, Pegylated-Interferon (IFN/PEG-IFN), pipobroman, anagrelide, IMiDs, or observation as prescribed by the Investigator

| Number of subjects in period 1 | Ruxolitinib | Best Available Therapy (BAT) |
|--------------------------------|------------------|------------------------------|
| Started | 74 | 75 |
| Full analysis set | 74 | 75 |
| Crossover set | 0 ^[1] | 58 ^[2] |
| Completed | 59 | 61 |
| Not completed | 15 | 14 |
| Adverse event, serious fatal | 1 | 1 |
| Physician decision | 2 | 1 |
| Consent withdrawn by subject | 3 | 1 |
| Disease progression | 2 | 2 |
| Adverse event, non-fatal | 7 | 7 |
| Lost to follow-up | - | 1 |
| Subject/guardian decision | - | 1 |

Notes:

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

Justification: Participants randomized to BAT who did not respond by Week 28 were eligible to crossover and start treatment with ruxolitinib.

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

Justification: Participants randomized to BAT who did not respond by Week 28 were eligible to crossover and start treatment with ruxolitinib.

Period 2

| | |
|------------------------------|------------------|
| Period 2 title | Crossover Period |
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Blinding implementation details:

Open-label

Arms

| | |
|-----------|------------------------------|
| Arm title | Best Available Therapy (BAT) |
|-----------|------------------------------|

Arm description:

Best Available Therapy as selected by the investigator from: Hydroxyurea, Pegylated-Interferon (IFN/PEG-IFN), pipobroman, anagrelide, IMiDs, or observation. Participants randomized to BAT who did not respond by Week 28 were eligible to crossover and start treatment with ruxolitinib

| | |
|--|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Hydroxyurea, IFN/PEG-IFN, pipobroman, anagrelide, IMiDs, or observation |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Hydroxyurea, Pegylated-Interferon (IFN/PEG-IFN), pipobroman, anagrelide, IMiDs, or observation as prescribed by the investigator

| Number of subjects in period 2^[3] | Best Available Therapy (BAT) |
|---|-------------------------------------|
| Started | 58 |
| Completed | 38 |
| Not completed | 20 |
| Adverse event, serious fatal | 2 |
| Consent withdrawn by subject | 3 |
| Physician decision | 2 |
| Disease progression | 3 |
| Adverse event, non-fatal | 9 |
| Lost to follow-up | 1 |

Notes:

[3] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Participants randomized to BAT who did not respond by Week 28 were eligible to crossover and start treatment with ruxolitinib.

Baseline characteristics

Reporting groups

| | |
|--|------------------------------|
| Reporting group title | Ruxolitinib |
| Reporting group description: Ruxolitinib at a starting dose of 10 mg twice a day (bid). Dose was adjusted based on efficacy and safety parameters up to a maximum dose of 25 mg bid | |
| Reporting group title | Best Available Therapy (BAT) |
| Reporting group description: Best Available Therapy as selected by the investigator from: Hydroxyurea, Pegylated-Interferon (IFN/PEG-IFN), pipobroman, anagrelide, IMiDs, or observation. Participants randomized to BAT who did not respond by Week 28 were eligible to crossover and start treatment with ruxolitinib | |

| Reporting group values | Ruxolitinib | Best Available Therapy (BAT) | Total |
|--|-------------|------------------------------|-------|
| Number of subjects | 74 | 75 | 149 |
| Age categorical Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 40 | 29 | 69 |
| From 65-84 years | 34 | 43 | 77 |
| 85 years and over | 0 | 3 | 3 |
| Age Continuous Units: years | | | |
| arithmetic mean | 62.8 | 66.0 | |
| standard deviation | ± 11.31 | ± 11.12 | - |
| Sex: Female, Male Units: Participants | | | |
| Female | 35 | 28 | 63 |
| Male | 39 | 47 | 86 |
| Race/Ethnicity, Customized Units: Subjects | | | |
| Caucasian | 67 | 66 | 133 |
| Asian | 4 | 5 | 9 |
| Other | 3 | 4 | 7 |

Subject analysis sets

| | |
|---|------------------------|
| Subject analysis set title | All crossover patients |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: All participants randomized to the BAT arm, who crossed over and received at least one dose of ruxolitinib | |

| | | | |
|--|------------------------|--|--|
| Reporting group values | All crossover patients | | |
| Number of subjects | 58 | | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | | |
| Preterm newborn infants (gestational age < 37 wks) | 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) | 22 | | |
| From 65-84 years | 33 | | |
| 85 years and over | 3 | | |
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | | | |
| standard deviation | ± | | |
| Sex: Female, Male | | | |
| Units: Participants | | | |
| Female | | | |
| Male | | | |
| Race/Ethnicity, Customized | | | |
| Units: Subjects | | | |
| Caucasian | | | |
| Asian | | | |
| Other | | | |

End points

End points reporting groups

| | |
|--|------------------------------|
| Reporting group title | Ruxolitinib |
| Reporting group description: Ruxolitinib at a starting dose of 10 mg twice a day (bid). Dose was adjusted based on efficacy and safety parameters up to a maximum dose of 25 mg bid | |
| Reporting group title | Best Available Therapy (BAT) |
| Reporting group description: Best Available Therapy as selected by the investigator from: Hydroxyurea, Pegylated-Interferon (IFN/PEG-IFN), pipobroman, anagrelide, IMiDs, or observation. Participants randomized to BAT who did not respond by Week 28 were eligible to crossover and start treatment with ruxolitinib | |
| Reporting group title | Best Available Therapy (BAT) |
| Reporting group description: Best Available Therapy as selected by the investigator from: Hydroxyurea, Pegylated-Interferon (IFN/PEG-IFN), pipobroman, anagrelide, IMiDs, or observation. Participants randomized to BAT who did not respond by Week 28 were eligible to crossover and start treatment with ruxolitinib | |
| Subject analysis set title | All crossover patients |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: All participants randomized to the BAT arm, who crossed over and received at least one dose of ruxolitinib | |

Primary: Number of participants achieving hematocrit (Hct) control at Week 28

| | |
|---|---|
| End point title | Number of participants achieving hematocrit (Hct) control at Week 28 ^[1] |
| End point description: Proportion of patients achieving Hct control at Week 28 was defined by the absence of phlebotomy eligibility starting at Week 8 and continuing through Week 28, with no more than one phlebotomy eligibility occurring post randomization and prior to Week 8. Phlebotomy eligibility was defined by: - Confirmed Hct > 45% that is at least 3 percentage points higher than the Hct obtained at Baseline Or - Confirmed Hct > 48% The confirmation occurred 2 to 14 days subsequent to the initial observation. No statistical analysis was planned for this primary outcome. | |
| End point type | Primary |
| End point timeframe: Week 28 | |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned for this outcome measure.

| End point values | Ruxolitinib | Best Available Therapy (BAT) | | |
|-----------------------------|-----------------|------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 74 | 75 | | |
| Units: Participants | 46 | 14 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants achieving a complete hematological remission at Week 28

| | |
|--|--|
| End point title | Number of participants achieving a complete hematological remission at Week 28 |
| End point description: Proportion of patients achieving a complete hematological remission at Week 28 was defined by: - Hct control at Week 28 defined by the absence of phlebotomy eligibility starting at Week 8 and continuing through Week 28, with no more than one phlebotomy eligibility occurring post randomization and prior to Week 8, and - WBC < 10 x10 ⁹ /L at Week 28, and - Platelets ≤ 400 x 10 ⁹ /L at Week 28 | |
| End point type | Secondary |
| End point timeframe: Week 28 | |

| End point values | Ruxolitinib | Best Available Therapy (BAT) | | |
|-----------------------------|-----------------|------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 74 | 75 | | |
| Units: Participants | 17 | 4 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants achieving a hematocrit (Hct) control at Week 52 and Week 80

| | |
|--|--|
| End point title | Number of participants achieving a hematocrit (Hct) control at Week 52 and Week 80 |
| End point description: Proportion of patients achieving a Hct control at Week 52 was defined by the absence of phlebotomy eligibility starting at Week 8 and continuing through Week 52, and no more than one phlebotomy eligibility occurring post randomization and prior to Week 8 - Endpoint for Week 80 was defined, similarly. | |
| End point type | Secondary |
| End point timeframe: Week 52 and 80 | |

| End point values | Ruxolitinib | Best Available Therapy (BAT) | | |
|-----------------------------|-----------------|------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 74 | 75 | | |
| Units: Participants | | | | |
| Week 52 | 44 | 5 | | |
| Week 80 | 35 | 2 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants achieving a complete hematological remission at Week 52 and Week 80

| | |
|-----------------|--|
| End point title | Number of participants achieving a complete hematological remission at Week 52 and Week 80 |
|-----------------|--|

End point description:

Proportion of patients achieving a complete hematological remission at Week 52, was defined by:

- Hct control at Week 52, as defined by the absence of phlebotomy eligibility starting at Week 8 and continuing through Week 52 with no more than one phlebotomy eligibility occurring post randomization and prior to Week 8, and
- White Blood Count (WBC) $< 10 \times 10^9/L$ at Week 52, and
- Platelets $\leq 400 \times 10^9/L$ at Week 52
- Endpoint for Week 80 was defined, similarly.

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

End point timeframe:

Week 52 and 80

| End point values | Ruxolitinib | Best Available Therapy (BAT) | | |
|-----------------------------|-----------------|------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 74 | 75 | | |
| Units: Participants | | | | |
| Week 52 | 17 | 3 | | |
| Week 80 | 18 | 2 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of phlebotomies over time

| | |
|-----------------|----------------------------------|
| End point title | Number of phlebotomies over time |
|-----------------|----------------------------------|

End point description:

Phlebotomy eligibility was defined by Confirmed Hct $> 45\%$ that is at least 3 percentage points higher than the Hct obtained at Baseline Or Confirmed Hct $> 48\%$. The confirmation occurred 2 to 14 days subsequent to the initial observation.

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

End point timeframe:

Baseline to Week 260

| End point values | Ruxolitinib | Best Available Therapy (BAT) | | |
|--------------------------------|-----------------|------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 74 | 75 | | |
| Units: Participants | | | | |
| Phlebotomy frequency: >0 - <=2 | 12 | 29 | | |
| Phlebotomy frequency: >2 - <=4 | 7 | 17 | | |
| Phlebotomy frequency: >4 - <=6 | 4 | 2 | | |
| Phlebotomy frequency: >6 - <=8 | 0 | 1 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Hematocrit (Hct) at each visit

| | |
|---|--|
| End point title | Change from baseline in Hematocrit (Hct) at each visit |
| End point description: Hematocrit is volume the percentage of red blood cells (RBC) in the blood. | |
| End point type | Secondary |
| End point timeframe: Baseline, Week 4, 8, 12, 16, 20, 24, 28, 40, 52, 66, 80, 92, 104, 117, 130, 143, 156, 169, 182, 195, 208, 221, 234, 247 and 260 | |

| End point values | Ruxolitinib | Best Available Therapy (BAT) | | |
|--|-----------------|------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 74 | 75 | | |
| Units: volume percentage of RBC in blood | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4 | -0.65 (± 2.943) | 1.25 (± 2.994) | | |
| Week 8 | -1.22 (± 3.634) | 1.63 (± 3.344) | | |
| Week 12 | -2.33 (± 4.581) | 1.70 (± 3.485) | | |
| Week 16 | -3.25 (± 4.179) | 1.83 (± 3.439) | | |
| Week 20 | -3.05 (± 4.307) | 1.45 (± 3.984) | | |
| Week 24 | -2.85 (± 4.094) | 1.52 (± 2.934) | | |
| Week 28 | -2.60 (± 4.101) | 2.09 (± 3.852) | | |
| Week 40 | -2.77 (± 4.538) | 2.05 (± 4.587) | | |

| | | | | |
|----------|-----------------|----------------|--|--|
| Week 52 | -2.49 (± 4.445) | 1.68 (± 4.854) | | |
| Week 66 | -3.06 (± 4.573) | 2.73 (± 2.922) | | |
| Week 80 | -3.20 (± 3.886) | 0.62 (± 4.436) | | |
| Week 92 | -2.91 (± 4.203) | 999 (± 999) | | |
| Week 104 | -3.19 (± 4.314) | 999 (± 999) | | |
| Week 117 | -2.86 (± 4.540) | 999 (± 999) | | |
| Week 130 | -3.13 (± 4.263) | 999 (± 999) | | |
| Week 143 | -3.50 (± 3.463) | 999 (± 999) | | |
| Week 156 | -3.54 (± 4.005) | 999 (± 999) | | |
| Week 169 | -3.57 (± 4.477) | 999 (± 999) | | |
| Week 182 | -2.94 (± 4.428) | 999 (± 999) | | |
| Week 195 | -3.36 (± 4.515) | 999 (± 999) | | |
| Week 208 | -3.23 (± 4.150) | 999 (± 999) | | |
| Week 221 | -3.55 (± 4.413) | 999 (± 999) | | |
| Week 234 | -3.31 (± 4.621) | 999 (± 999) | | |
| Week 247 | -3.45 (± 4.053) | 999 (± 999) | | |
| Week 260 | -2.93 (± 3.799) | 999 (± 999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Spleen length by visit

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|-----------------|------------------------|
| End point title | Spleen length by visit |
|-----------------|------------------------|

End point description:

Spleen length was assessed by manual palpation at every study visit.

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

End point timeframe:

Week 4, 8, 12, 16, 20, 24, 28, 40, 52, 66, 80, 92, 104, 117, 130, 143, 156, 169, 182, 195, 208, 221, 234, 247 and 260

| End point values | Ruxolitinib | Best Available Therapy (BAT) | | |
|--------------------------------------|-----------------|------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 74 | 75 | | |
| Units: cm | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4 | 0.00 (± 0.000) | 0.04 (± 0.351) | | |
| Week 8 | 0.00 (± 0.000) | 0.01 (± 0.119) | | |
| Week 12 | 0.00 (± 0.000) | 0.01 (± 0.120) | | |
| Week 16 | 0.00 (± 0.000) | 0.23 (± 1.010) | | |
| Week 20 | 0.00 (± 0.000) | 0.13 (± 0.716) | | |
| Week 24 | 0.00 (± 0.000) | 0.09 (± 0.555) | | |
| Week 28 | 0.00 (± 0.000) | 0.20 (± 0.909) | | |
| Week 40 | 0.01 (± 0.120) | 0.52 (± 1.473) | | |
| Week 52 | 0.06 (± 0.482) | 0.07 (± 0.258) | | |
| Week 66 | 0.00 (± 0.000) | 0.00 (± 0.000) | | |
| Week 80 | 0.03 (± 0.246) | 0.00 (± 0.000) | | |
| Week 92 | 0.00 (± 0.000) | 999 (± 999) | | |
| Week 104 | 0.05 (± 0.378) | 999 (± 999) | | |
| Week 117 | 0.12 (± 0.985) | 999 (± 999) | | |
| Week 130 | 0.18 (± 1.162) | 999 (± 999) | | |
| Week 143 | 0.08 (± 0.458) | 999 (± 999) | | |
| Week 156 | 0.05 (± 0.372) | 999 (± 999) | | |
| Week 169 | 0.05 (± 0.378) | 999 (± 999) | | |
| Week 182 | 0.05 (± 0.381) | 999 (± 999) | | |
| Week 195 | 0.00 (± 0.000) | 999 (± 999) | | |
| Week 208 | 0.00 (± 0.000) | 999 (± 999) | | |
| Week 221 | 0.02 (± 0.129) | 999 (± 999) | | |
| Week 234 | 0.00 (± 0.000) | 999 (± 999) | | |
| Week 247 | 0.02 (± 0.136) | 999 (± 999) | | |
| Week 260 | 0.10 (± 0.617) | 999 (± 999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Eastern Cooperative Oncology Group (ECOG) performance status up to Week 28

| | |
|-----------------|--|
| End point title | Change from baseline in Eastern Cooperative Oncology Group (ECOG) performance status up to Week 28 |
|-----------------|--|

End point description:

The ECOG scale of performance status described the level of functioning of participants in terms of their ability to care for themselves, daily activity, and physical ability. The ECOG performance was recorded as per ECOG performance status grades ranging from 0 (fully active, able to carry on all pre-disease performance without restriction) to 5 (dead).

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

End point timeframe:

Baseline and Week 28

| End point values | Ruxolitinib | Best Available Therapy (BAT) | | |
|--|-----------------|------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 74 | 75 | | |
| Units: Participants | | | | |
| Grade 0 at baseline 0: Fully active | 49 | 17 | | |
| Grade 1 at baseline 0: Fully active | 9 | 1 | | |
| Grade 0 at baseline 1: Restricted | 2 | 1 | | |
| Grade 1 at baseline 1: Restricted | 10 | 5 | | |
| Grade 0 at baseline 2: Ambulatory | 0 | 0 | | |
| Grade 1 at baseline 2: Ambulatory | 1 | 0 | | |
| Grade 0 at baseline 3: limited self-care | 0 | 0 | | |
| Grade 1 at baseline 3: limited self-care | 0 | 0 | | |
| Grade 0 at baseline 4: Completely disabled | 0 | 0 | | |
| Grade 1 at baseline 4: Completely disabled | 0 | 0 | | |
| Grade 0 at baseline Missing | 2 | 38 | | |
| Grade 1 at baseline Missing | 1 | 13 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants achieving a partial remission based on the European Leukemia Net (ELN) and International Working Group for Myelofibrosis Research and Treatment (IWG-MRT) criteria at Week 28

| | |
|-----------------|--|
| End point title | Number of participants achieving a partial remission based on the European Leukemia Net (ELN) and International Working Group for Myelofibrosis Research and Treatment (IWG-MRT) criteria at Week 28 |
|-----------------|--|

End point description:

Proportion of patients achieving a partial remission at Week 28, based on the ELN and IWG-MRT criteria, as defined by:

- Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPN-SAF TSS) score reduction of greater than or equal to 10 points from baseline to Week 28,
- Hct control defined by the absence of phlebotomy eligibility starting at Week 8 and continuing through Week 28, with no more than one phlebotomy eligibility occurring post randomization and prior to Week 8,
- WBC < 10 x10⁹/L at Week 28,
- Platelets ≤ 400 x 10⁹/L at Week 28,
- No palpable spleen at Week 28,
- No hemorrhagic or thrombotic events,
- No transformation into post-PV myelofibrosis, myelodysplastic syndrome (IWG-MRT criteria) or acute leukemia (WHO criteria).

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

End point timeframe:

Week 28

| End point values | Ruxolitinib | Best Available Therapy (BAT) | | |
|-----------------------------|-----------------|------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 74 | 75 | | |
| Units: Participants | 7 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants who achieved partial remission based on the European Leukemia Net (ELN) and International Working Group for Myelofibrosis Research and Treatment (IWG-MRT) criteria at Week 52 and Week 80

| | |
|-----------------|---|
| End point title | Number of participants who achieved partial remission based on the European Leukemia Net (ELN) and International Working Group for Myelofibrosis Research and Treatment (IWG-MRT) criteria at Week 52 and Week 80 |
|-----------------|---|

End point description:

Proportion of patients who achieved partial remission at Week 52 based on the ELN and IWG-MRT criteria, as defined by:

- MPN-SAF TSS score reduction of greater than or equal to 10 points from baseline to Week 52
- Hct control defined by the absence of phlebotomy eligibility starting at Week 8 and continuing through Week 52 with no more than one phlebotomy eligibility occurring post randomization and prior to Week 8,
- WBC < 10 x10⁹/L at Week 52
- Platelets ≤ 400 x 10⁹/L at Week 52
- No palpable spleen at Week 52
- No hemorrhagic or thrombotic events,
- No transformation into post-PV myelofibrosis, myelodysplastic syndrome (IWG-MRT criteria) or acute leukemia (WHO criteria)
- Endpoint for Week 80 was defined, similarly.

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

End point timeframe:

Week 52 and 80

| End point values | Ruxolitinib | Best Available Therapy (BAT) | | |
|-----------------------------|-----------------|------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 74 | 75 | | |
| Units: Participants | | | | |
| Week 52 | 5 | 0 | | |
| Week 80 | 4 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants achieving a Hematocrit (Hct) control at Week 104, Week 156, Week 208 and Week 260.

| | |
|-----------------|--|
| End point title | Number of participants achieving a Hematocrit (Hct) control at Week 104, Week 156, Week 208 and Week 260. ^[2] |
|-----------------|--|

End point description:

Proportion of patients achieving a Hct control at Week 104 as defined by the absence of phlebotomy eligibility starting at Week 8 and continuing through Week 104 and with no more than one phlebotomy eligibility occurring post randomization and prior to Week 8

Endpoint for Week 156, Week 208 and Week 260 were defined, similarly.

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

End point timeframe:

From Week 8 to Week 104, 156, 208 and 260

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned for this outcome measure.

| End point values | Ruxolitinib | | | |
|-----------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 74 | | | |
| Units: Participants | | | | |
| Week 104 HU Resistant | 9 | | | |
| Week 156 HU Resistant | 9 | | | |
| Week 208 HU Resistant | 7 | | | |
| Week 260 HU Resistant | 4 | | | |
| Week 104 HU Intolerant | 25 | | | |
| Week 156 HU Intolerant | 21 | | | |
| Week 208 HU Intolerant | 18 | | | |
| Week 260 HU Intolerant | 12 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants achieving a complete hematological remission at Week 104, Week 156, Week 208 and Week 260

| | |
|-----------------|---|
| End point title | Number of participants achieving a complete hematological remission at Week 104, Week 156, Week 208 and Week 260 ^[3] |
|-----------------|---|

End point description:

Proportion of patients achieving a complete hematological remission at Week 104 as defined by Hct control defined by the absence of phlebotomy eligibility starting at Week 8 and continuing through Week 104, with no more than one phlebotomy eligibility occurring post randomization and prior to Week 8, and

- WBC < 10 x10⁹/L at Week 104, and

- Platelets ≤ 400 x 10⁹/L at Week 104

Endpoint for Week 156, Week 208 and Week 260 were defined, similarly.

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

End point timeframe:

From Week 8 to Week 104, 156, 208 and 260

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis was planned for this outcome measure.

| End point values | Ruxolitinib | | | |
|-----------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 74 | | | |
| Units: Participants | | | | |
| Week 104 | 15 | | | |
| Week 156 | 19 | | | |
| Week 208 | 11 | | | |
| Week 260 | 9 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants who achieved partial remission based on the European Leukemia Net (ELN) and International Working Group for Myelofibrosis Research and Treatment (IWG-MRT) criteria at Week 104, Week 156, Week 208 and Week 260.

| | |
|-----------------|---|
| End point title | Number of participants who achieved partial remission based on the European Leukemia Net (ELN) and International Working Group for Myelofibrosis Research and Treatment (IWG-MRT) criteria at Week 104, Week 156, Week 208 and Week 260. ^[4] |
|-----------------|---|

End point description:

Proportion of patients who achieved partial remission at Week 104, based on the ELN and IWG-MRT criteria, as defined by:

- MPN-SAF TSS score reduction of greater than or equal to 10 points from baseline to Week 104,
- Hct control defined by the absence of phlebotomy eligibility starting at Week 8 and continuing through Week 104, with no more than one phlebotomy eligibility occurring post-randomization and prior to Week 8,
- WBC < 10 x10⁹/L at Week 104,
- Platelets ≤ 400 x 10⁹/L at Week 104,
- No palpable spleen at Week 104,
- No hemorrhagic or thrombotic events,
- No transformation into post-PV myelofibrosis, myelodysplastic syndrome (IWG-MRT criteria) or acute leukemia (WHO criteria)

Endpoint for Week 156, Week 208 and Week 260 are defined, similarly.

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

End point timeframe:

From Week 8 to Week 104, 156, 208 and 260

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis was planned for this outcome measure.

| End point values | Ruxolitinib | | | |
|-----------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 74 | | | |
| Units: Participants | | | | |
| Week 104 | 4 | | | |
| Week 156 | 9 | | | |
| Week 208 | 4 | | | |
| Week 260 | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with Transformation free survival events

| | |
|-----------------|---|
| End point title | Number of participants with Transformation free survival events |
|-----------------|---|

End point description:

Transformation-free survival is defined as one of the following:

1. Myelofibrosis (MF) as evidenced by bone marrow biopsy, or
2. Acute leukemia as evidenced by bone marrow blast counts of at least 20%, or peripheral blast counts of at least 20% lasting at least 2 weeks.
3. Death due to any cause during treatment period

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

End point timeframe:

Week 260 (ruxolitinib arm) and Week 80 (BAT arm)

| End point values | Ruxolitinib | Best Available Therapy (BAT) | | |
|-----------------------------|-----------------|------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 74 | 75 | | |
| Units: Participants | 4 | 3 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with Overall survival (OS) events

| | |
|-----------------|--|
| End point title | Number of participants with Overall survival (OS) events |
|-----------------|--|

End point description:

Overall survival (OS) is defined as the proportion of participants from the date of randomization to the date of death due to any cause. For BAT patients not censored at the time of cross over – survival time were censored at the date of last contact irrespective of whether patients randomized to BAT arm crossed over to receive ruxolitinib (i.e. survival time was not censored at the date of last assessment prior to the start date of ruxolitinib for the cross over patients).

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

End point timeframe:
up to Week 260

| End point values | Ruxolitinib | Best Available Therapy (BAT) | | |
|-----------------------------|-----------------|------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 74 | 75 | | |
| Units: Participants | 3 | 6 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPN-SAF TSS)

| | |
|-----------------|---|
| End point title | Change from baseline in Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPN-SAF TSS) |
|-----------------|---|

End point description:

The MPN-SAF TSS is a disease specific questionnaire comprised of 10 items that measures fatigue related to MPN disease and the severity of nine of the most prevalent associated symptoms. Each item is scored on a scale ranging from 0 (no fatigue/absent) to 10 (As bad as you can imagine/worst imaginable). The MPN-SAF TSS is computed as the average of the observed items multiplied by 10 to achieve a 0-to-100 scale. The MPN-SAF TSS thus has a possible score range of 0 to 100 where a decrease indicates improvement.

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

End point timeframe:

Baseline, Week 4, 8, 16, 28, 40, 52, 80, 92, 104, 117, 130, 143, 156, 169, 182, 195, 208, 221, 234 and 247

| End point values | Ruxolitinib | Best Available Therapy (BAT) | | |
|--------------------------------------|-------------------|------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 74 | 75 | | |
| Units: Score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4 | -8.43 (± 12.341) | 0.40 (± 12.586) | | |
| Week 8 | -9.86 (± 12.210) | 1.37 (± 12.046) | | |
| Week 16 | -9.14 (± 13.980) | 1.41 (± 10.760) | | |
| Week 28 | -10.29 (± 14.204) | 2.34 (± 13.047) | | |
| Week 40 | -9.35 (± 14.027) | 0.10 (± 9.586) | | |
| Week 52 | -8.63 (± 13.403) | 0.63 (± 9.334) | | |
| Week 80 | -9.04 (± 13.520) | 999 (± 999) | | |

| | | | | |
|----------|------------------|-------------|--|--|
| Week 92 | -7.69 (± 11.971) | 999 (± 999) | | |
| Week 104 | -6.82 (± 13.297) | 999 (± 999) | | |
| Week 117 | -6.76 (± 13.702) | 999 (± 999) | | |
| Week 130 | -8.26 (± 16.234) | 999 (± 999) | | |
| Week 143 | -8.56 (± 15.653) | 999 (± 999) | | |
| Week 156 | -8.48 (± 15.081) | 999 (± 999) | | |
| Week 169 | -7.65 (± 14.392) | 999 (± 999) | | |
| Week 182 | -9.34 (± 14.675) | 999 (± 999) | | |
| Week 195 | -7.57 (± 14.922) | 999 (± 999) | | |
| Week 208 | -9.26 (± 16.347) | 999 (± 999) | | |
| Week 221 | -7.20 (± 16.054) | 999 (± 999) | | |
| Week 234 | -7.50 (± 15.922) | 999 (± 999) | | |
| Week 247 | -7.82 (± 16.905) | 999 (± 999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in score as per European Quality of Life 5-Dimension 5-level (EQ-5D-5L) questionnaire

| | |
|-----------------|--|
| End point title | Change from baseline in score as per European Quality of Life 5-Dimension 5-level (EQ-5D-5L) questionnaire |
|-----------------|--|

End point description:

EQ-5D-5L is a standardized instrument for measuring health outcomes in a wide range of health conditions and treatments. It consists of visual analogue scale (EQ VAS) which records the respondent's self-rated health on a vertical, visual analogue scale where the endpoints are labeled 'Best imaginable health state' and 'worst imaginable health state'. The EQ VAS scores were anchored on 100 = the best health you can imagine and 0 = worst health you can imagine.

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

End point timeframe:

Baseline, Week 4, 8, 16, 28, 52, 80, 92, 104, 117, 130, 143, 156, 169, 182, 195, 208, 221, 234 and 247

| End point values | Ruxolitinib | Best Available Therapy (BAT) | | |
|--------------------------------------|-----------------|------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 74 | 75 | | |
| Units: Score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |

| | | | | |
|----------|-----------------|------------------|--|--|
| Week 4 | 4.24 (± 11.661) | 0.04 (± 18.323) | | |
| Week 8 | 7.62 (± 14.846) | -2.73 (± 16.097) | | |
| Week 16 | 6.35 (± 17.946) | -3.12 (± 14.435) | | |
| Week 28 | 7.56 (± 14.309) | 0.16 (± 15.201) | | |
| Week 52 | 7.36 (± 13.996) | 2.50 (± 10.697) | | |
| Week 80 | 4.50 (± 18.273) | 999 (± 999) | | |
| Week 92 | 6.77 (± 18.948) | 999 (± 999) | | |
| Week 104 | 6.25 (± 18.143) | 999 (± 999) | | |
| Week 117 | 6.42 (± 15.130) | 999 (± 999) | | |
| Week 130 | 7.70 (± 16.488) | 999 (± 999) | | |
| Week 143 | 5.68 (± 17.332) | 999 (± 999) | | |
| Week 156 | 4.74 (± 19.032) | 999 (± 999) | | |
| Week 169 | 6.08 (± 18.717) | 999 (± 999) | | |
| Week 182 | 7.68 (± 17.992) | 999 (± 999) | | |
| Week 195 | 6.41 (± 18.239) | 999 (± 999) | | |
| Week 208 | 7.94 (± 18.614) | 999 (± 999) | | |
| Week 221 | 3.64 (± 19.866) | 999 (± 999) | | |
| Week 234 | 5.48 (± 18.625) | 999 (± 999) | | |
| Week 247 | 6.28 (± 17.854) | 999 (± 999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in work productivity and activity impairment (WPAI) questionnaire

| | |
|-----------------|--|
| End point title | Change from baseline in work productivity and activity impairment (WPAI) questionnaire |
|-----------------|--|

End point description:

The Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP) is a six item questionnaire which intended to measure work and activity impairment associated with polycythemia vera. WPAI consisted of 6 questions (Q1=Employment status; Q2=Hours absent from work due to the polycythemia vera; Q3=Hours absent from work due to other reasons; Q4=Hours actually worked; Q5=Impact of the polycythemia vera on productivity while working; Q6=Impact of the polycythemia vera on productivity while doing regular daily activities other than work). Higher WPAI scores indicated greater activity impairment. Scores were multiplied by 100 to express in percentages.
Percent work time missed due to problem (past 7 days) = $Q2/(Q2+Q4)$
Percent impairment while working due to problem (past 7 days): $Q5/10$
Percent overall work impairment due to problem (past 7 says): $Q2/(Q2+Q4)+[(1Q2/(Q2+Q4)) \times (Q5/10)]$

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 4, 8, 16, 28, 52 and 80 | |

| End point values | Ruxolitinib | Best Available Therapy (BAT) | | |
|--|-------------------|------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 74 | 75 | | |
| Units: Percent | | | | |
| arithmetic mean (standard deviation) | | | | |
| Percent work time missed Week 4 | -5.50 (± 18.425) | -0.40 (± 13.928) | | |
| Percent work time missed Week 8 | -4.88 (± 13.381) | -4.35 (± 20.820) | | |
| Percent work time missed Week 16 | 4.50 (± 35.948) | 4.79 (± 25.917) | | |
| Percent work time missed Week 28 | -5.85 (± 17.119) | -2.19 (± 9.852) | | |
| Percent work time missed Week 52 | -2.82 (± 30.770) | -8.33 (± 11.785) | | |
| Percent work time missed Week 80 | 1.87 (± 34.151) | 999 (± 999) | | |
| Percent impairment while working Week 4 | -6.67 (± 23.310) | 0.00 (± 14.951) | | |
| Percent impairment while working Week 8 | -13.16 (± 19.164) | -0.59 (± 13.449) | | |
| Percent impairment while working Week 16 | -14.00 (± 21.374) | 4.12 (± 16.977) | | |
| Percent impairment while working Week 28 | -14.29 (± 23.994) | -10.00 (± 14.142) | | |
| Percent impairment while working Week 52 | -10.00 (± 23.170) | -20.00 (± 42.426) | | |
| Percent impairment while working Week 80 | -14.76 (± 26.385) | 999 (± 999) | | |
| Percent overall work impairment Week 4 | -9.63 (± 22.495) | -2.34 (± 14.807) | | |
| Percent overall work impairment Week 8 | -11.32 (± 18.505) | -4.38 (± 17.568) | | |
| Percent overall work impairment Week 16 | -10.26 (± 33.296) | 5.34 (± 22.063) | | |
| Percent overall work impairment Week 28 | -15.98 (± 23.077) | -8.85 (± 11.722) | | |
| Percent overall work impairment Week 52 | -12.61 (± 27.576) | -22.50 (± 45.962) | | |
| Percent overall work impairment Week 80 | -14.36 (± 30.691) | 999 (± 999) | | |
| Percent activity impairment Week 4 | -11.97 (± 22.122) | 2.42 (± 24.310) | | |
| Percent activity impairment Week 8 | -11.58 (± 24.985) | 1.97 (± 16.413) | | |
| Percent activity impairment Week 16 | -14.36 (± 25.222) | 0.65 (± 18.980) | | |
| Percent activity impairment Week 28 | -11.67 (± 25.826) | 2.73 (± 23.941) | | |
| Percent activity impairment Week 52 | -11.23 (± 25.360) | 0.00 (± 15.374) | | |

| | | | | |
|-------------------------------------|------------------------|------------------|--|--|
| Percent activity impairment Week 80 | -11.09 (\pm 24.166) | 999 (\pm 999) | | |
|-------------------------------------|------------------------|------------------|--|--|

Statistical analyses

No statistical analyses for this end point

Secondary: Patient global impression of change (PGIC)

| | |
|-----------------|--|
| End point title | Patient global impression of change (PGIC) |
|-----------------|--|

End point description:

The Patient Global Impression of Change (PGIC) is comprised of a single question intended to measure a patient's perspective of improvement or deterioration over time relative to treatment. The PGIC uses a seven-point scale where one (1) equals very much improved and seven (7) equals very much worse.

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

End point timeframe:

Week 4, 8, 16, 28, 40, 52 and 80

| End point values | Ruxolitinib | Best Available Therapy (BAT) | | |
|-----------------------------|-----------------|------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 74 | 75 | | |
| Units: Participants | | | | |
| Week 4 Very much improved | 10 | 0 | | |
| Week 8 Very much improved | 11 | 1 | | |
| Week 16 Very much improved | 18 | 2 | | |
| Week 28 Very much improved | 19 | 0 | | |
| Week 40 Very much improved | 23 | 0 | | |
| Week 52 Very much improved | 27 | 2 | | |
| Week 66 Very much improved | 23 | 1 | | |
| Week 80 Very much improved | 22 | 0 | | |
| Week 4 Much improved | 22 | 8 | | |
| Week 8 Much improved | 27 | 14 | | |
| Week 16 Much improved | 25 | 13 | | |
| Week 28 Much improved | 25 | 4 | | |
| Week 40 Much improved | 30 | 7 | | |
| Week 52 Much improved | 28 | 5 | | |
| Week 66 Much improved | 31 | 1 | | |
| Week 80 Much improved | 24 | 0 | | |
| Week 4 Minimally improved | 21 | 7 | | |
| Week 8 Minimally improved | 15 | 9 | | |
| Week 16 Minimally improved | 13 | 12 | | |
| Week 28 Minimally improved | 12 | 5 | | |
| Week 40 Minimally improved | 5 | 2 | | |
| Week 52 Minimally improved | 8 | 1 | | |
| Week 66 Minimally improved | 6 | 3 | | |
| Week 80 Minimally improved | 9 | 0 | | |

| | | | | |
|-------------------------|----|----|--|--|
| Week 4 No change | 14 | 50 | | |
| Week 8 No change | 15 | 35 | | |
| Week 16 No change | 8 | 33 | | |
| Week 28 No change | 9 | 15 | | |
| Week 40 No change | 6 | 10 | | |
| Week 52 No change | 5 | 5 | | |
| Week 66 No change | 6 | 0 | | |
| Week 80 No change | 10 | 0 | | |
| Week 4 Minimally worse | 1 | 6 | | |
| Week 8 Minimally worse | 0 | 10 | | |
| Week 16 Minimally worse | 2 | 4 | | |
| Week 28 Minimally worse | 1 | 3 | | |
| Week 40 Minimally worse | 2 | 0 | | |
| Week 52 Minimally worse | 2 | 1 | | |
| Week 66 Minimally worse | 1 | 0 | | |
| Week 80 Minimally worse | 2 | 0 | | |
| Week 4 Much worse | 0 | 0 | | |
| Week 8 Much worse | 1 | 0 | | |
| Week 16 Much worse | 0 | 5 | | |
| Week 28 Much worse | 0 | 0 | | |
| Week 40 Much worse | 0 | 0 | | |
| Week 52 Much worse | 0 | 0 | | |
| Week 66 Much worse | 0 | 0 | | |
| Week 80 Much worse | 0 | 0 | | |
| Week 4 Very much worse | 0 | 1 | | |
| Week 8 Very much worse | 0 | 1 | | |
| Week 16 Very much worse | 0 | 0 | | |
| Week 28 Very much worse | 0 | 0 | | |
| Week 40 Very much worse | 0 | 0 | | |
| Week 52 Very much worse | 0 | 0 | | |
| Week 66 Very much worse | 0 | 0 | | |
| Week 80 Very much worse | 1 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants developing thrombosis

| | |
|-----------------|--|
| End point title | Number of participants developing thrombosis |
|-----------------|--|

End point description:

Proportion of participants developing any arterial or venous thromboembolic event

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

End point timeframe:

From randomization to Week 80 for BAT and Week 260 for Ruxolitinib

| End point values | Ruxolitinib | Best Available Therapy (BAT) | | |
|-----------------------------|-----------------|------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 74 | 75 | | |
| Units: Participants | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in hematocrit (Hct) at each scheduled visit after crossover in participants randomized to BAT who cross over to ruxolitinib

| | |
|-----------------|--|
| End point title | Change from Baseline in hematocrit (Hct) at each scheduled visit after crossover in participants randomized to BAT who cross over to ruxolitinib |
|-----------------|--|

End point description:

Hematocrit is the percentage of red blood cells (RBC) in the blood.

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

End point timeframe:

Baseline (last assessment before cross over), Week 4, 8, 12, 16, 20, 24, 28, 40, 52, 64, 76, 89, 102, 115, 128, 141, 154, 167, 180, 193, 206, 219 and 232 after cross-over

| End point values | All crossover patients | | | |
|--|------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 58 | | | |
| Units: Volume percentage of RBC in blood | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week +4 | -2.44 (± 3.394) | | | |
| Week +8 | -4.24 (± 5.322) | | | |
| Week +12 | -5.73 (± 6.597) | | | |
| Week +16 | -6.27 (± 7.101) | | | |
| Week +20 | -5.76 (± 6.563) | | | |
| Week +24 | -5.29 (± 6.518) | | | |
| Week +28 | -6.04 (± 5.825) | | | |
| Week +40 | -6.06 (± 6.301) | | | |
| Week +52 | -5.91 (± 6.399) | | | |
| Week +64 | -7.06 (± 6.051) | | | |
| Week +76 | -6.16 (± 6.247) | | | |

| | | | | |
|-----------|-----------------|--|--|--|
| Week +89 | -6.79 (± 6.046) | | | |
| Week +102 | -6.21 (± 6.599) | | | |
| Week +115 | -7.04 (± 6.103) | | | |
| Week +128 | -7.41 (± 6.812) | | | |
| Week +141 | -7.00 (± 6.310) | | | |
| Week +154 | -7.06 (± 7.000) | | | |
| Week +167 | -7.44 (± 7.426) | | | |
| Week +180 | -7.51 (± 7.298) | | | |
| Week +193 | -7.16 (± 5.331) | | | |
| Week +206 | -7.09 (± 5.742) | | | |
| Week +219 | -6.95 (± 5.936) | | | |
| Week +232 | -7.51 (± 5.880) | | | |

Statistical analyses

No statistical analyses for this end point

Post-hoc: Total number of deaths

| | |
|-----------------|------------------------|
| End point title | Total number of deaths |
|-----------------|------------------------|

End point description:

On-treatment deaths were reported from the day of first dose of study medication to the End of study (End of Treatment +30 days) visit which was Week 260 or prior (+30 days for Rux + crossover) and Week 80 or prior (+30 days for BAT only). Post-treatment deaths were reported following completion study treatment (Week 80 for patients receiving BAT, or Week 260 for patients receiving ruxolitinib) or from the time of premature discontinuation. Patients were followed for survival every three months up to end of study.

| | |
|----------------|----------|
| End point type | Post-hoc |
|----------------|----------|

End point timeframe:

Up to Week 260

| End point values | Ruxolitinib | Best Available Therapy (BAT) | | |
|---------------------------------------|-----------------|------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 74 | 75 | | |
| Units: Participants | | | | |
| Death up to 30 days after EOT | 1 | 1 | | |
| Death after cross over (BAT arm only) | 0 | 3 | | |
| Death more than 30 days after EOT | 2 | 2 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from the day of first dose of study medication to the End of study (End of Treatment +30 days) visit which was Week 260 or prior (+30 days for Rux + crossover) and Week 80 or prior (+30 days for BAT only).

Adverse event reporting additional description:

Any signs or symptoms that occurred from the day of first dose of study medication to the End of study (End of Treatment +30 days) visit which was Week 260 or prior (+30 days for Rux + crossover) and Week 80 or prior (+30 days for BAT only).

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| Assessment type | Systematic |
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Dictionary used

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| Dictionary name | MedDRA |
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| Dictionary version | 22.1 |
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Reporting groups

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| Reporting group title | Ruxolitinib |
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Reporting group description:

Ruxolitinib at a starting dose of 10 mg twice a day (bid). Dose was adjusted based on efficacy and safety parameters up to a maximum dose of 25 mg bid

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| Reporting group title | Best Available Therapy (BAT) |
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Reporting group description:

Best Available Therapy as selected by the investigator from: Hydroxyurea, Pegylated-Interferon (IFN/PEG-IFN), pipobroman, anagrelide, IMiDs, or observation. Participants randomized to BAT who did not respond by Week 28 were eligible to crossover and start treatment with ruxolitinib

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|-----------------------|------------------------|
| Reporting group title | All crossover patients |
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Reporting group description:

All participants randomized to the BAT arm, who crossed over and received at least one dose of ruxolitinib.

| Serious adverse events | Ruxolitinib | Best Available Therapy (BAT) | All crossover patients |
|---|------------------|------------------------------|------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 34 / 74 (45.95%) | 9 / 75 (12.00%) | 23 / 58 (39.66%) |
| number of deaths (all causes) | 1 | 1 | 3 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Acute myeloid leukaemia | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | 1 / 75 (1.33%) | 0 / 58 (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 |
| Basal cell carcinoma | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 5 / 74 (6.76%) | 0 / 75 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 7 / 10 | 0 / 0 | 3 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Basosquamous carcinoma of skin | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 75 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bladder transitional cell carcinoma | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | 1 / 75 (1.33%) | 0 / 58 (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 |
| Blast cell crisis | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | 0 / 75 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bone marrow tumour cell infiltration | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | 0 / 75 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bowen's disease | | | |
| subjects affected / exposed | 2 / 74 (2.70%) | 0 / 75 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 6 / 7 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Breast cancer | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | 1 / 75 (1.33%) | 0 / 58 (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 |
| Carcinoma in situ | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 75 (0.00%) | 0 / 58 (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 |
| Juvenile melanoma benign | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 75 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung adenocarcinoma | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | 0 / 75 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metastases to spine | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | 0 / 75 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metastatic malignant melanoma | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 75 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Myelofibrosis | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | 1 / 75 (1.33%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Non-small cell lung cancer metastatic | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 75 (0.00%) | 0 / 58 (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 |
| Parathyroid tumour benign | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 75 (0.00%) | 0 / 58 (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 |
| Prostate cancer | | | |
| subjects affected / exposed | 2 / 74 (2.70%) | 0 / 75 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Prostatic adenoma | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 74 (0.00%) | 0 / 75 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal cancer | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 75 (0.00%) | 0 / 58 (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 |
| Skin cancer | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 75 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Squamous cell carcinoma of skin | | | |
| subjects affected / exposed | 3 / 74 (4.05%) | 0 / 75 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 6 / 8 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Uterine neoplasm | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 75 (0.00%) | 0 / 58 (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 |
| Vaginal cancer | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 75 (0.00%) | 0 / 58 (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 | | | |
| Blue toe syndrome | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 75 (0.00%) | 0 / 58 (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 |
| Extremity necrosis | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | 1 / 75 (1.33%) | 0 / 58 (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 |
| Peripheral arterial occlusive disease | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 75 (0.00%) | 0 / 58 (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 |
| Peripheral artery occlusion | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 75 (0.00%) | 0 / 58 (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 |
| Peripheral artery thrombosis | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | 0 / 75 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Venous haemorrhage | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 75 (0.00%) | 0 / 58 (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 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | 0 / 75 (0.00%) | 2 / 58 (3.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fatigue | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | 0 / 75 (0.00%) | 1 / 58 (1.72%) |
| 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 physical health deterioration | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 75 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 75 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyrexia | | | |

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|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 75 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute pulmonary oedema | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | 0 / 75 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 75 (0.00%) | 0 / 58 (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 |
| Hypoxia | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 75 (0.00%) | 0 / 58 (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 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 75 (0.00%) | 2 / 58 (3.45%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | 1 / 75 (1.33%) | 0 / 58 (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 |
| Investigations | | | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 75 (0.00%) | 0 / 58 (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 |
| Blood lactate dehydrogenase increased | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 75 (0.00%) | 0 / 58 (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 |

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| Blood uric acid increased | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 75 (0.00%) | 0 / 58 (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 |
| Weight decreased | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | 0 / 75 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Hip fracture | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 75 (0.00%) | 0 / 58 (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 |
| Lumbar vertebral fracture | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 75 (0.00%) | 0 / 58 (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 |
| Muscle rupture | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 75 (0.00%) | 0 / 58 (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 |
| Post procedural haemorrhage | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 75 (0.00%) | 0 / 58 (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 |
| Radius fracture | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 75 (0.00%) | 0 / 58 (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 |
| Spinal fracture | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 75 (0.00%) | 0 / 58 (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 |

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|---|----------------|----------------|----------------|
| Tendon rupture | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | 0 / 75 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ulna fracture | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | 0 / 75 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | 0 / 75 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Angina pectoris | | | |
| subjects affected / exposed | 2 / 74 (2.70%) | 0 / 75 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aortic valve incompetence | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 75 (0.00%) | 0 / 58 (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 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 2 / 74 (2.70%) | 1 / 75 (1.33%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorder | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | 0 / 75 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Cardiac failure | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | 1 / 75 (1.33%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coronary artery disease | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 75 (0.00%) | 0 / 58 (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 |
| Mitral valve incompetence | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | 0 / 75 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial infarction | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 75 (0.00%) | 0 / 58 (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 |
| Pericardial effusion | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | 0 / 75 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 75 (0.00%) | 0 / 58 (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 |
| Cognitive disorder | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 75 (0.00%) | 0 / 58 (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 |
| Dizziness | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 75 (0.00%) | 0 / 58 (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 |
| Epilepsy | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 75 (0.00%) | 0 / 58 (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 |
| Facial neuralgia | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 75 (0.00%) | 0 / 58 (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 | 1 / 74 (1.35%) | 0 / 75 (0.00%) | 0 / 58 (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 |
| Ischaemic stroke | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | 0 / 75 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | 1 / 75 (1.33%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | 1 / 75 (1.33%) | 0 / 58 (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 |
| Hyperleukocytosis | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 75 (0.00%) | 0 / 58 (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 |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | 1 / 75 (1.33%) | 0 / 58 (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 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | 2 / 75 (2.67%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombocytosis | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 74 (0.00%) | 1 / 75 (1.33%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ear and labyrinth disorders | | | |
| Vertigo positional | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | 0 / 75 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Glaucoma | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 75 (0.00%) | 0 / 58 (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 |
| Retinal artery occlusion | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | 0 / 75 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vision blurred | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 75 (0.00%) | 0 / 58 (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 |
| Visual acuity reduced | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | 0 / 75 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal discomfort | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | 0 / 75 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 75 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Constipation | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | 0 / 75 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | 1 / 75 (1.33%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal inflammation | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 75 (0.00%) | 0 / 58 (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 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | 0 / 75 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Inguinal hernia | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 75 (0.00%) | 0 / 58 (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 |
| Nausea | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | 0 / 75 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oesophageal varices haemorrhage | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | 0 / 75 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | 1 / 75 (1.33%) | 0 / 58 (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 |
| Small intestinal obstruction | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 75 (0.00%) | 0 / 58 (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 |
| Hepatobiliary disorders | | | |
| Cholelithiasis | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 75 (0.00%) | 0 / 58 (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 |
| Skin and subcutaneous tissue disorders | | | |
| Actinic keratosis | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 75 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Haematuria | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 75 (0.00%) | 0 / 58 (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 |
| Nephrolithiasis | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 75 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal failure | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | 1 / 75 (1.33%) | 0 / 58 (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 |
| Ureterolithiasis | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | 0 / 75 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urethral stenosis | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | 0 / 75 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Musculoskeletal and connective tissue disorders | | | |
| Foot deformity | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 75 (0.00%) | 0 / 58 (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 |
| Haemarthrosis | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 75 (0.00%) | 0 / 58 (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 |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | 0 / 75 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 75 (0.00%) | 0 / 58 (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 |
| Osteoarthritis | | | |
| subjects affected / exposed | 2 / 74 (2.70%) | 0 / 75 (0.00%) | 3 / 58 (5.17%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pain in extremity | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 75 (0.00%) | 0 / 58 (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 |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 3 / 74 (4.05%) | 0 / 75 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | 1 / 75 (1.33%) | 0 / 58 (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 |

| | | | |
|---|----------------|----------------|----------------|
| Cystitis | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | 0 / 75 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | 1 / 75 (1.33%) | 0 / 58 (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 |
| Localised infection | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | 0 / 75 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | 0 / 75 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Meningitis | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | 1 / 75 (1.33%) | 0 / 58 (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 |
| Ophthalmic herpes zoster | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 75 (0.00%) | 0 / 58 (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 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | 1 / 75 (1.33%) | 2 / 58 (3.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | 0 / 75 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyonephrosis | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 75 (0.00%) | 0 / 58 (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 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | 0 / 75 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | 0 / 75 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Septic shock | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | 1 / 75 (1.33%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Sinusitis | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | 0 / 75 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 74 (2.70%) | 0 / 75 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urosepsis | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 75 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | 0 / 75 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dehydration | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 75 (0.00%) | 0 / 58 (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 |
| Diabetes mellitus | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | 0 / 75 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperuricaemia | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | 0 / 75 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | 1 / 75 (1.33%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| 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 | Ruxolitinib | Best Available Therapy (BAT) | All crossover patients |
|---|------------------|------------------------------|------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 73 / 74 (98.65%) | 56 / 75 (74.67%) | 56 / 58 (96.55%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 2 / 74 (2.70%) | 0 / 75 (0.00%) | 3 / 58 (5.17%) |
| occurrences (all) | 2 | 0 | 4 |
| Vascular disorders | | | |
| Haematoma | | | |
| subjects affected / exposed | 10 / 74 (13.51%) | 1 / 75 (1.33%) | 4 / 58 (6.90%) |
| occurrences (all) | 12 | 1 | 6 |
| Hypertension | | | |
| subjects affected / exposed | 15 / 74 (20.27%) | 3 / 75 (4.00%) | 11 / 58 (18.97%) |
| occurrences (all) | 18 | 4 | 15 |
| General disorders and administration site conditions | | | |

| | | | |
|--|------------------------|---------------------|-----------------------|
| Asthenia subjects affected / exposed occurrences (all) | 8 / 74 (10.81%) 11 | 6 / 75 (8.00%) 7 | 6 / 58 (10.34%) 12 |
| Fatigue subjects affected / exposed occurrences (all) | 13 / 74 (17.57%) 15 | 6 / 75 (8.00%) 7 | 6 / 58 (10.34%) 7 |
| Oedema peripheral subjects affected / exposed occurrences (all) | 10 / 74 (13.51%) 13 | 2 / 75 (2.67%) 2 | 6 / 58 (10.34%) 6 |
| Pyrexia subjects affected / exposed occurrences (all) | 13 / 74 (17.57%) 23 | 1 / 75 (1.33%) 1 | 7 / 58 (12.07%) 8 |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 7 / 74 (9.46%) 11 | 2 / 75 (2.67%) 2 | 6 / 58 (10.34%) 7 |
| Dyspnoea subjects affected / exposed occurrences (all) | 11 / 74 (14.86%) 11 | 2 / 75 (2.67%) 2 | 4 / 58 (6.90%) 4 |
| Epistaxis subjects affected / exposed occurrences (all) | 4 / 74 (5.41%) 7 | 2 / 75 (2.67%) 2 | 7 / 58 (12.07%) 7 |
| Psychiatric disorders Depression subjects affected / exposed occurrences (all) | 5 / 74 (6.76%) 5 | 1 / 75 (1.33%) 1 | 2 / 58 (3.45%) 2 |
| Investigations Blood creatine phosphokinase increased subjects affected / exposed occurrences (all) | 9 / 74 (12.16%) 11 | 0 / 75 (0.00%) 0 | 2 / 58 (3.45%) 3 |
| Blood lactate dehydrogenase increased subjects affected / exposed occurrences (all) | 2 / 74 (2.70%) 2 | 1 / 75 (1.33%) 1 | 4 / 58 (6.90%) 4 |
| Gamma-glutamyltransferase increased | | | |

| | | | |
|--------------------------------------|------------------|-----------------|------------------|
| subjects affected / exposed | 5 / 74 (6.76%) | 1 / 75 (1.33%) | 1 / 58 (1.72%) |
| occurrences (all) | 5 | 2 | 2 |
| Haematocrit increased | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | 5 / 75 (6.67%) | 1 / 58 (1.72%) |
| occurrences (all) | 0 | 5 | 1 |
| Weight decreased | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | 4 / 75 (5.33%) | 0 / 58 (0.00%) |
| occurrences (all) | 1 | 4 | 0 |
| Weight increased | | | |
| subjects affected / exposed | 19 / 74 (25.68%) | 1 / 75 (1.33%) | 9 / 58 (15.52%) |
| occurrences (all) | 22 | 1 | 10 |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 8 / 74 (10.81%) | 5 / 75 (6.67%) | 7 / 58 (12.07%) |
| occurrences (all) | 10 | 5 | 11 |
| Headache | | | |
| subjects affected / exposed | 13 / 74 (17.57%) | 9 / 75 (12.00%) | 8 / 58 (13.79%) |
| occurrences (all) | 19 | 10 | 9 |
| Memory impairment | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | 0 / 75 (0.00%) | 4 / 58 (6.90%) |
| occurrences (all) | 0 | 0 | 4 |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | 0 / 75 (0.00%) | 3 / 58 (5.17%) |
| occurrences (all) | 0 | 0 | 3 |
| Paraesthesia | | | |
| subjects affected / exposed | 7 / 74 (9.46%) | 0 / 75 (0.00%) | 2 / 58 (3.45%) |
| occurrences (all) | 7 | 0 | 3 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 27 / 74 (36.49%) | 1 / 75 (1.33%) | 19 / 58 (32.76%) |
| occurrences (all) | 48 | 1 | 29 |
| Leukocytosis | | | |
| subjects affected / exposed | 5 / 74 (6.76%) | 4 / 75 (5.33%) | 3 / 58 (5.17%) |
| occurrences (all) | 6 | 5 | 6 |
| Thrombocytopenia | | | |

| | | | |
|--|------------------------|----------------------|-----------------------|
| subjects affected / exposed occurrences (all) | 5 / 74 (6.76%) 7 | 6 / 75 (8.00%) 12 | 3 / 58 (5.17%) 3 |
| Thrombocytosis subjects affected / exposed occurrences (all) | 8 / 74 (10.81%) 10 | 3 / 75 (4.00%) 3 | 5 / 58 (8.62%) 9 |
| Ear and labyrinth disorders | | | |
| Tinnitus subjects affected / exposed occurrences (all) | 3 / 74 (4.05%) 3 | 2 / 75 (2.67%) 2 | 3 / 58 (5.17%) 3 |
| Vertigo subjects affected / exposed occurrences (all) | 4 / 74 (5.41%) 7 | 1 / 75 (1.33%) 1 | 1 / 58 (1.72%) 1 |
| Gastrointestinal disorders | | | |
| Abdominal discomfort subjects affected / exposed occurrences (all) | 1 / 74 (1.35%) 1 | 2 / 75 (2.67%) 3 | 4 / 58 (6.90%) 5 |
| Abdominal distension subjects affected / exposed occurrences (all) | 5 / 74 (6.76%) 8 | 1 / 75 (1.33%) 1 | 0 / 58 (0.00%) 0 |
| Abdominal pain subjects affected / exposed occurrences (all) | 10 / 74 (13.51%) 12 | 1 / 75 (1.33%) 1 | 8 / 58 (13.79%) 9 |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 5 / 74 (6.76%) 5 | 3 / 75 (4.00%) 3 | 2 / 58 (3.45%) 2 |
| Constipation subjects affected / exposed occurrences (all) | 13 / 74 (17.57%) 14 | 4 / 75 (5.33%) 4 | 8 / 58 (13.79%) 11 |
| Diarrhoea subjects affected / exposed occurrences (all) | 7 / 74 (9.46%) 7 | 7 / 75 (9.33%) 9 | 4 / 58 (6.90%) 4 |
| Dyspepsia subjects affected / exposed occurrences (all) | 5 / 74 (6.76%) 5 | 2 / 75 (2.67%) 3 | 4 / 58 (6.90%) 4 |
| Flatulence | | | |

| | | | |
|--|------------------------|------------------------|----------------------|
| subjects affected / exposed occurrences (all) | 1 / 74 (1.35%) 1 | 1 / 75 (1.33%) 1 | 3 / 58 (5.17%) 4 |
| Nausea subjects affected / exposed occurrences (all) | 4 / 74 (5.41%) 4 | 5 / 75 (6.67%) 5 | 3 / 58 (5.17%) 3 |
| Vomiting subjects affected / exposed occurrences (all) | 2 / 74 (2.70%) 3 | 1 / 75 (1.33%) 1 | 4 / 58 (6.90%) 5 |
| Skin and subcutaneous tissue disorders | | | |
| Erythema subjects affected / exposed occurrences (all) | 2 / 74 (2.70%) 2 | 4 / 75 (5.33%) 7 | 0 / 58 (0.00%) 0 |
| Night sweats subjects affected / exposed occurrences (all) | 6 / 74 (8.11%) 8 | 5 / 75 (6.67%) 6 | 1 / 58 (1.72%) 1 |
| Pruritus subjects affected / exposed occurrences (all) | 12 / 74 (16.22%) 16 | 17 / 75 (22.67%) 18 | 7 / 58 (12.07%) 7 |
| Skin ulcer subjects affected / exposed occurrences (all) | 4 / 74 (5.41%) 4 | 0 / 75 (0.00%) 0 | 2 / 58 (3.45%) 3 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia subjects affected / exposed occurrences (all) | 20 / 74 (27.03%) 23 | 3 / 75 (4.00%) 3 | 6 / 58 (10.34%) 7 |
| Back pain subjects affected / exposed occurrences (all) | 12 / 74 (16.22%) 12 | 0 / 75 (0.00%) 0 | 7 / 58 (12.07%) 8 |
| Bone pain subjects affected / exposed occurrences (all) | 4 / 74 (5.41%) 4 | 0 / 75 (0.00%) 0 | 0 / 58 (0.00%) 0 |
| Intervertebral disc protrusion subjects affected / exposed occurrences (all) | 4 / 74 (5.41%) 4 | 0 / 75 (0.00%) 0 | 1 / 58 (1.72%) 1 |
| Muscle spasms | | | |

| | | | |
|-----------------------------|------------------|----------------|------------------|
| subjects affected / exposed | 5 / 74 (6.76%) | 1 / 75 (1.33%) | 0 / 58 (0.00%) |
| occurrences (all) | 6 | 1 | 0 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 4 / 74 (5.41%) | 1 / 75 (1.33%) | 1 / 58 (1.72%) |
| occurrences (all) | 4 | 1 | 1 |
| Myalgia | | | |
| subjects affected / exposed | 5 / 74 (6.76%) | 2 / 75 (2.67%) | 2 / 58 (3.45%) |
| occurrences (all) | 7 | 2 | 3 |
| Osteoarthritis | | | |
| subjects affected / exposed | 5 / 74 (6.76%) | 1 / 75 (1.33%) | 2 / 58 (3.45%) |
| occurrences (all) | 6 | 1 | 2 |
| Osteoporosis | | | |
| subjects affected / exposed | 4 / 74 (5.41%) | 0 / 75 (0.00%) | 0 / 58 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| Pain in extremity | | | |
| subjects affected / exposed | 11 / 74 (14.86%) | 2 / 75 (2.67%) | 4 / 58 (6.90%) |
| occurrences (all) | 15 | 2 | 6 |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 12 / 74 (16.22%) | 2 / 75 (2.67%) | 2 / 58 (3.45%) |
| occurrences (all) | 12 | 2 | 2 |
| Cystitis | | | |
| subjects affected / exposed | 10 / 74 (13.51%) | 0 / 75 (0.00%) | 2 / 58 (3.45%) |
| occurrences (all) | 13 | 0 | 2 |
| Herpes zoster | | | |
| subjects affected / exposed | 11 / 74 (14.86%) | 0 / 75 (0.00%) | 8 / 58 (13.79%) |
| occurrences (all) | 13 | 0 | 8 |
| Influenza | | | |
| subjects affected / exposed | 10 / 74 (13.51%) | 4 / 75 (5.33%) | 2 / 58 (3.45%) |
| occurrences (all) | 12 | 4 | 2 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 8 / 74 (10.81%) | 2 / 75 (2.67%) | 10 / 58 (17.24%) |
| occurrences (all) | 12 | 2 | 16 |
| Sinusitis | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 75 (0.00%) | 3 / 58 (5.17%) |
| occurrences (all) | 1 | 0 | 3 |

| | | | |
|---|----------------------|----------------------|---------------------|
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 5 / 74 (6.76%) 6 | 7 / 75 (9.33%) 10 | 5 / 58 (8.62%) 9 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 6 / 74 (8.11%) 13 | 0 / 75 (0.00%) 0 | 2 / 58 (3.45%) 2 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite subjects affected / exposed occurrences (all) | 5 / 74 (6.76%) 5 | 4 / 75 (5.33%) 4 | 0 / 58 (0.00%) 0 |
| Dyslipidaemia subjects affected / exposed occurrences (all) | 0 / 74 (0.00%) 0 | 0 / 75 (0.00%) 0 | 4 / 58 (6.90%) 4 |
| Hypercholesterolaemia subjects affected / exposed occurrences (all) | 5 / 74 (6.76%) 5 | 0 / 75 (0.00%) 0 | 5 / 58 (8.62%) 5 |
| Hypertriglyceridaemia subjects affected / exposed occurrences (all) | 4 / 74 (5.41%) 4 | 0 / 75 (0.00%) 0 | 0 / 58 (0.00%) 0 |
| Hyperuricaemia subjects affected / exposed occurrences (all) | 3 / 74 (4.05%) 3 | 1 / 75 (1.33%) 1 | 3 / 58 (5.17%) 3 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 20 November 2014 | -At most one phlebotomy was allowed between randomization and Week 4, which was changed from randomization to Week 8. -Study treatment period was extended up to 5 years from the last patient randomized and Survival follow-up after treatment discontinuation to be conducted in all patients until last patient last visit. -Addition of secondary endpoints. -Change to local labs for the hematology assessments. -Sample size increased from 104 to 130 patients. |
| 24 March 2016 | -Removal of data cut, 52 weeks after last patient first visit (LPFV). -End of Study definition changed: The study was extended to a total of 5 years and 30 days from the date when the last patient was randomized. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to EudraCT system limitations, which EMA is aware of, results of crossover studies and data using 999 as data points are not accurately represented in this record. Please go to <https://www.novctrd.com/CtrdWeb/home.nov> for complete trial results

Notes: