



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
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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)
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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)
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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
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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
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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
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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
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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

End point title	Spleen length by visit
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End point description:

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

End point type	Secondary
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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
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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
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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
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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
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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
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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]
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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
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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]
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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
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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]
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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
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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
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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
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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
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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
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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)
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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
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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
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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
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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
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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 (± 24.166)	999 (± 999)		
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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)
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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
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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
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End point description:

Proportion of participants developing any arterial or venous thromboembolic event

End point type	Secondary
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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
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End point description:

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

End point type	Secondary
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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
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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
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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).

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	22.1
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Reporting groups

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

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

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			

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

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

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	8 / 74 (10.81%)	6 / 75 (8.00%)	6 / 58 (10.34%)
occurrences (all)	11	7	12
Fatigue			
subjects affected / exposed	13 / 74 (17.57%)	6 / 75 (8.00%)	6 / 58 (10.34%)
occurrences (all)	15	7	7
Oedema peripheral			
subjects affected / exposed	10 / 74 (13.51%)	2 / 75 (2.67%)	6 / 58 (10.34%)
occurrences (all)	13	2	6
Pyrexia			
subjects affected / exposed	13 / 74 (17.57%)	1 / 75 (1.33%)	7 / 58 (12.07%)
occurrences (all)	23	1	8
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	7 / 74 (9.46%)	2 / 75 (2.67%)	6 / 58 (10.34%)
occurrences (all)	11	2	7
Dyspnoea			
subjects affected / exposed	11 / 74 (14.86%)	2 / 75 (2.67%)	4 / 58 (6.90%)
occurrences (all)	11	2	4
Epistaxis			
subjects affected / exposed	4 / 74 (5.41%)	2 / 75 (2.67%)	7 / 58 (12.07%)
occurrences (all)	7	2	7
Psychiatric disorders			
Depression			
subjects affected / exposed	5 / 74 (6.76%)	1 / 75 (1.33%)	2 / 58 (3.45%)
occurrences (all)	5	1	2
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	9 / 74 (12.16%)	0 / 75 (0.00%)	2 / 58 (3.45%)
occurrences (all)	11	0	3
Blood lactate dehydrogenase increased			
subjects affected / exposed	2 / 74 (2.70%)	1 / 75 (1.33%)	4 / 58 (6.90%)
occurrences (all)	2	1	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	5 / 74 (6.76%)	6 / 75 (8.00%)	3 / 58 (5.17%)
occurrences (all)	7	12	3
Thrombocytosis			
subjects affected / exposed	8 / 74 (10.81%)	3 / 75 (4.00%)	5 / 58 (8.62%)
occurrences (all)	10	3	9
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	3 / 74 (4.05%)	2 / 75 (2.67%)	3 / 58 (5.17%)
occurrences (all)	3	2	3
Vertigo			
subjects affected / exposed	4 / 74 (5.41%)	1 / 75 (1.33%)	1 / 58 (1.72%)
occurrences (all)	7	1	1
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 74 (1.35%)	2 / 75 (2.67%)	4 / 58 (6.90%)
occurrences (all)	1	3	5
Abdominal distension			
subjects affected / exposed	5 / 74 (6.76%)	1 / 75 (1.33%)	0 / 58 (0.00%)
occurrences (all)	8	1	0
Abdominal pain			
subjects affected / exposed	10 / 74 (13.51%)	1 / 75 (1.33%)	8 / 58 (13.79%)
occurrences (all)	12	1	9
Abdominal pain upper			
subjects affected / exposed	5 / 74 (6.76%)	3 / 75 (4.00%)	2 / 58 (3.45%)
occurrences (all)	5	3	2
Constipation			
subjects affected / exposed	13 / 74 (17.57%)	4 / 75 (5.33%)	8 / 58 (13.79%)
occurrences (all)	14	4	11
Diarrhoea			
subjects affected / exposed	7 / 74 (9.46%)	7 / 75 (9.33%)	4 / 58 (6.90%)
occurrences (all)	7	9	4
Dyspepsia			
subjects affected / exposed	5 / 74 (6.76%)	2 / 75 (2.67%)	4 / 58 (6.90%)
occurrences (all)	5	3	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: