



## Clinical trial results:

**Randomized, open label, multicenter phase III study of efficacy and safety in polycythemia vera subjects who are resistant to or intolerant of hydroxyurea: JAK inhibitor INC424 tablets versus best available care (The RESPONSE Trial)**

**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**

## Summary

EudraCT number	2010-020807-57
Trial protocol	BE DE ES GB IT NL HU
Global end of trial date	09 February 2018

## Results information

Result version number	v1 (current)
This version publication date	24 February 2019
First version publication date	24 February 2019

## Trial information

### Trial identification

Sponsor protocol code	CINC424B2301 (INC424, INCB018424)
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### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01243944
WHO universal trial number (UTN)	-

Notes:

## Sponsors

Sponsor organisation name	Novartis PharmaMA, AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis PharmaMA, AG, +41 613241111, <a href="mailto:novartis.email@novartis.com">novartis.email@novartis.com</a>
Scientific contact	Clinical Disclosure Office, Novartis PharmaMA, AG, +41 613241111, <a href="mailto:novartis.email@novartis.com">novartis.email@novartis.com</a>

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	09 February 2018
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	09 February 2018
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The primary objective was to compare the efficacy of ruxolitinib to Best Available Therapy (BAT) as assessed by both the absence of phlebotomy eligibility and reduction in spleen volume.

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	27 October 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 4
Country: Number of subjects enrolled	Australia: 11
Country: Number of subjects enrolled	Belgium: 11
Country: Number of subjects enrolled	Canada: 5
Country: Number of subjects enrolled	China: 3
Country: Number of subjects enrolled	France: 11
Country: Number of subjects enrolled	Germany: 25
Country: Number of subjects enrolled	Hungary: 15
Country: Number of subjects enrolled	Italy: 43
Country: Number of subjects enrolled	Japan: 18
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 4
Country: Number of subjects enrolled	Netherlands: 3
Country: Number of subjects enrolled	Russian Federation: 7
Country: Number of subjects enrolled	Spain: 13
Country: Number of subjects enrolled	Thailand: 1
Country: Number of subjects enrolled	Turkey: 6
Country: Number of subjects enrolled	United Kingdom: 7

Country: Number of subjects enrolled	United States: 35
Worldwide total number of subjects	222
EEA total number of subjects	128

Notes:

<b>Subjects enrolled per age group</b>	
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)	155
From 65 to 84 years	66
85 years and over	1

## Subject disposition

### Recruitment

Recruitment details:

Participants may be treated beyond 256 weeks due to the 14 day visit window.

### Pre-assignment

Screening details:

Although 222 were centrally randomized to ruxolitinib and BAT arms (110 patients were in the ruxolitinib arm and 112 patients were in the BAT arm 1 patient in the BAT was not treated.

### Period 1

Period 1 title	Treatment Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Ruxolitinib

Arm description:

Starting dose of 10 mg BID with individualized dose titration ranging from 5 mg once a day (QD) to 25 mg BID based on safety and efficacy

Arm type	Experimental
Investigational medicinal product name	INC424
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Starting dose of 10 mg bid on study Day 1. A standardized dosing paradigm was used to determine dose adjustments for safety and efficacy so that each patient was titrated to their most appropriate dose.

<b>Arm title</b>	Best Available Therapy (BAT)
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Arm description:

Best Available Therapy (BAT) will be selected by the Investigator for each subject. BAT may not include experimental agents (i.e. those not approved for the treatment of any indication) as well as a limited number of other selected drugs in accordance with the protocol-defined requirements.

Arm type	Active comparator
Investigational medicinal product name	Best Available Therapy (BAT)
Investigational medicinal product code	
Other name	BAT could include: Hydroxyurea, IFN/PEG-IFN, Pipobroman, Anagrelide, Lenalidomide, Pomalidomide, Observation only
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

selected by the Investigator for each subject

<b>Number of subjects in period 1</b>	<b>Ruxolitinib</b>	<b>Best Available Therapy (BAT)</b>
Started	110	112
Completed	65	61
Not completed	45	51
Adverse event, serious fatal	2	3
Physician decision	2	7
Disease progression	12	11
Adverse event, non-fatal	15	13
Subject decision	10	15
Lost to follow-up	2	1
Protocol deviation	1	1
non-compliance with study treatment	1	-

## Baseline characteristics

### Reporting groups

Reporting group title	Ruxolitinib
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Reporting group description:

Starting dose of 10 mg BID with individualized dose titration ranging from 5 mg once a day (QD) to 25 mg BID based on safety and efficacy

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

Best Available Therapy (BAT) will be selected by the Investigator for each subject. BAT may not include experimental agents (i.e. those not approved for the treatment of any indication) as well as a limited number of other selected drugs in accordance with the protocol-defined requirements.

Reporting group values	Ruxolitinib	Best Available Therapy (BAT)	Total
Number of subjects	110	112	222
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)	69	86	155
From 65-84 years	40	26	66
85 years and over	1	0	1
Age Continuous Units: years			
arithmetic mean	61.1	59.1	
standard deviation	± 10.48	± 10.25	-
Gender Categorical Units: Subjects			
Female	44	32	76
Male	66	80	146
Race/ethnicity Units: Subjects			
White/Caucasian	98	96	194
Black/African American	1	0	1
Asian	11	16	27

## End points

### End points reporting groups

Reporting group title	Ruxolitinib
Reporting group description:	
Starting dose of 10 mg BID with individualized dose titration ranging from 5 mg once a day (QD) to 25 mg BID based on safety and efficacy	
Reporting group title	Best Available Therapy (BAT)
Reporting group description:	
Best Available Therapy (BAT) will be selected by the Investigator for each subject. BAT may not include experimental agents (i.e. those not approved for the treatment of any indication) as well as a limited number of other selected drugs in accordance with the protocol-defined requirements.	

### Primary: The Percentage of Subjects Achieving a Primary Response at Week 32

End point title	The Percentage of Subjects Achieving a Primary Response at Week 32
End point description:	
Primary response was defined as having achieved hematocrit control (the absence of phlebotomy eligibility beginning at the Week 8 visit and continuing through Week 32) and Spleen Volume Reduction (a greater than or equal to 35% reduction from baseline in spleen volume at Week 32).	
End point type	Primary
End point timeframe:	
32 Weeks	

End point values	Ruxolitinib	Best Available Therapy (BAT)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	112		
Units: Percentage of subjects				
number (confidence interval 95%)	22.7 (15.3 to 31.7)	0.9 (0.0 to 4.9)		

### Statistical analyses

Statistical analysis title	Group Comparison - Primary endpoint
Comparison groups	Ruxolitinib v Best Available Therapy (BAT)
Number of subjects included in analysis	222
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Log odds ratio
Point estimate	32.67

Confidence interval	
level	95 %
sides	2-sided
lower limit	5.04
upper limit	1337

## Secondary: The Percentage of Subjects Achieving a Durable Primary Response at Week 48

End point title	The Percentage of Subjects Achieving a Durable Primary Response at Week 48
End point description: Durable Primary Response was defined as any subject who achieved the primary outcome measure and who maintained their response up to 48 weeks after randomization.	
End point type	Secondary
End point timeframe: 48 Weeks	

End point values	Ruxolitinib	Best Available Therapy (BAT)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	112		
Units: Percentage of subjects				
number (confidence interval 95%)	20.0 (13.0 to 28.7)	0.9 (0.0 to 4.9)		

## Statistical analyses

Statistical analysis title	Group Comparison - 48 weeks
Comparison groups	Ruxolitinib v Best Available Therapy (BAT)
Number of subjects included in analysis	222
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	28.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.24
upper limit	1144



## Secondary: The Percentage of Subjects Achieving Complete Hematological Remission at Week 32

End point title	The Percentage of Subjects Achieving Complete Hematological Remission at Week 32
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End point description:

Complete Hematological Remission at Week 32 was defined as any subject who achieved hematocrit control with a platelet count less than or equal to  $400 \times 10^9/L$  and a white blood cell count less than or equal to  $10 \times 10^9/L$ .

End point type	Secondary
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End point timeframe:

32 Weeks

End point values	Ruxolitinib	Best Available Therapy (BAT)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	112		
Units: Percentage of subjects				
number (confidence interval 95%)	23.6 (16.1 to 32.7)	8.0 (3.7 to 14.7)		

## Statistical analyses

Statistical analysis title	Group comparison - 32 Weeks
Comparison groups	Ruxolitinib v Best Available Therapy (BAT)
Number of subjects included in analysis	222
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0016
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	3.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.5
upper limit	9.06

## Secondary: The Percentage of Subjects Who Achieved a Durable Complete Hematological Remission at Week 48

End point title	The Percentage of Subjects Who Achieved a Durable Complete Hematological Remission at Week 48
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End point description:

Durable Complete Hematological Remission was defined as any subject who achieved Complete Hematological Remission at Week 32 and maintained their response up to 48 weeks after randomization.

End point type	Secondary
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End point timeframe:

48 Weeks

End point values	Ruxolitinib	Best Available Therapy (BAT)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	112		
Units: Percentage of subjects				
number (confidence interval 95%)	20.9 (13.7 to 29.7)	0.9 (0.0 to 4.9)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: The Percentage of Subjects Who Achieved a Durable Hematocrit Control at Week 48

End point title	The Percentage of Subjects Who Achieved a Durable Hematocrit Control at Week 48
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End point description:

Durable Hematocrit Control was defined as any subject who achieved phlebotomy eligibility independence from Week 8 to Week 32 and maintained hematocrit control up to 48 weeks after randomization.

End point type	Secondary
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End point timeframe:

48 Weeks

End point values	Ruxolitinib	Best Available Therapy (BAT)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	112		
Units: Percentage of subjects				
number (confidence interval 95%)	54.5 (44.8 to 64.1)	1.8 (0.2 to 6.3)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: The Percentage of Subjects Who Achieved Durable Spleen Volume Reduction at Week 48

End point title	The Percentage of Subjects Who Achieved Durable Spleen Volume
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## End point description:

Durable Spleen Volume Reduction was defined as a subject who achieved at least 35% reduction from baseline in spleen volume at Week 32 and maintained that response 48 weeks after randomization.

## End point type

Secondary

## End point timeframe:

48 Weeks

End point values	Ruxolitinib	Best Available Therapy (BAT)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	112		
Units: Percentage of subjects				
number (confidence interval 95%)	37.3 (28.2 to 47.0)	0.9 (0.0 to 4.9)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Estimated Duration of the Primary Response

End point title	Estimated Duration of the Primary Response <sup>[1]</sup>
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## End point description:

Duration of the primary response is defined as the time from the first occurrence when both components of the primary endpoint are met until the date of the first documented disease progression (end of response).

Kaplan-Meier estimates are provided for duration of primary response.

## End point type

Secondary

## End point timeframe:

Through study completion, analysis was conducted when all patients had completed the Week 80 visit or discontinued the study

## Notes:

[1] - 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: Duration of the Response was done only on the study drug.

End point values	Ruxolitinib			
Subject group type	Reporting group			
Number of subjects analysed	110			
Units: Probability				
number (confidence interval 95%)				
16 Weeks	1.00 (0.99 to 999)			
32 Weeks	1.00 (0.99 to 999)			
48 Weeks	0.92 (0.72 to 0.98)			
64 Weeks	0.92 (0.72 to 0.98)			

80 Weeks	0.92 (0.72 to 0.98)			
96 Weeks	0.88 (0.67 to 0.96)			
112 Weeks	0.84 (0.62 to 0.94)			
128 Weeks	0.84 (0.62 to 0.94)			
144 Weeks	0.84 (0.62 to 0.94)			
160 Weeks	0.79 (0.57 to 0.91)			
176 Weeks	0.79 (0.57 to 0.91)			
192 Weeks	0.74 (0.51 to 0.88)			
208 Weeks	0.74 (0.51 to 0.88)			
224 Weeks	0.74 (0.51 to 0.88)			
240 Weeks	999 (999 to 999)			
256 Weeks	999 (999 to 999)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: The Percentage of Subjects Who Achieved Overall Clinicohematologic Response at Week 32

End point title	The Percentage of Subjects Who Achieved Overall Clinicohematologic Response at Week 32
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End point description:

Overall Clinicohematologic Response is defined as any subject who achieved a complete or partial clinicohematologic response per the European LeukemiaNet modified criteria for response in polycythemia vera (PV). A Complete Response (CR) is defined as: hematocrit control, spleen volume reduction at least 35% from baseline, platelet count less than or equal to  $400 \times 10^9/L$ , and white blood cell count less than or equal to  $10 \times 10^9/L$ . A Partial Response (PR) is defined as hematocrit control or response in all 3 of the other criteria.

End point type	Secondary
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End point timeframe:

32 Weeks

End point values	Ruxolitinib	Best Available Therapy (BAT)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	112		
Units: Percentage of subjects				
number (not applicable)				
Complete response rate	8.2	0.9		
Partial response rate	54.5	18.8		

## Statistical analyses

No statistical analyses for this end point

### Secondary: The Percentage of Subjects Achieving a Durable Complete or Partial Clinicohematologic Response at Week 48

End point title	The Percentage of Subjects Achieving a Durable Complete or Partial Clinicohematologic Response at Week 48
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End point description:

Durable Complete or Partial Clinicohematologic Response was defined as any subject who achieved complete or partial clinicohematologic response per the European LeukemiaNet modified criteria for response in polycythemia vera at Week 32 and maintained that response 48 weeks after randomization.

End point type	Secondary
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End point timeframe:

48 Weeks

End point values	Ruxolitinib	Best Available Therapy (BAT)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	112		
Units: Percentage of subjects				
number (not applicable)				
Complete response rate	7.3	0.9		
Partial response rate	50.9	0.9		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Estimated Duration of the Complete Hematological Remission

End point title	Estimated Duration of the Complete Hematological Remission <sup>[2]</sup>
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End point description:

Duration of the complete hematological remission is defined as the time from the first occurrence of complete hematological remission until the date of the first documented progression (end of response). Kaplan-Meier estimates are provided for duration of complete hematological remission.

End point type	Secondary
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End point timeframe:

Through study completion, analysis was conducted when all patients had completed the Week 80 visit or discontinued the study

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: Estimated Duration of the Complete Hematological Remission was done only on the study drug.

End point values	Ruxolitinib			
Subject group type	Reporting group			
Number of subjects analysed	110			
Units: Probability				
number (confidence interval 95%)				
16 Weeks	1.00 (0.99 to 999)			
32 Weeks	1.00 (0.99 to 999)			
48 Weeks	0.88 (0.66 to 0.96)			
64 Weeks	0.83 (0.61 to 0.93)			
80 Weeks	0.74 (0.51 to 0.87)			
96 Weeks	0.74 (0.51 to 0.87)			
112 Weeks	0.69 (0.46 to 0.84)			
128 Weeks	0.69 (0.46 to 0.84)			
144 Weeks	0.65 (0.41 to 0.81)			
160 Weeks	0.65 (0.41 to 0.81)			
176 Weeks	0.55 (0.32 to 0.73)			
192 Weeks	0.55 (0.32 to 0.73)			
208 Weeks	0.55 (0.32 to 0.73)			
224 Weeks	0.55 (0.32 to 0.73)			
240 Weeks	999 (999 to 999)			
256 Weeks	999 (999 to 999)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Duration of Reduction in Spleen Volume

End point title	Duration of Reduction in Spleen Volume <sup>[3]</sup>
End point description: Duration of spleen volume reduction is defined as the time from the first occurrence of a $\geq 35\%$ reduction from baseline in spleen volume until the date of the first documented progression.	
End point type	Secondary

End point timeframe:

256 Weeks

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: Duration of Reduction in Spleen Volume was done only on the study drug.

End point values	Ruxolitinib			
Subject group type	Reporting group			
Number of subjects analysed	110			
Units: Probability				
number (confidence interval 95%)				
16 Weeks	1.00 (0.99 to 9.99)			
32 Weeks	1.00 (0.99 to 9.99)			
48 Weeks	1.00 (0.99 to 9.99)			
64 Weeks	1.00 (0.99 to 9.99)			
80 Weeks	1.00 (0.99 to 9.99)			
96 Weeks	0.98 (0.84 to 1.00)			
112 Weeks	0.95 (0.82 to 0.99)			
128 Weeks	0.95 (0.82 to 0.99)			
144 Weeks	0.95 (0.82 to 0.99)			
160 Weeks	0.93 (0.79 to 0.98)			
176 Weeks	0.93 (0.79 to 0.98)			
192 Weeks	0.93 (0.79 to 0.98)			
208 Weeks	0.87 (0.66 to 0.95)			
224 Weeks	0.72 (0.34 to 0.91)			
240 Weeks	999 (999 to 999)			
256 Weeks	999 (999 to 999)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Duration of The Overall Clinicohematologic Response

End point title	Duration of The Overall Clinicohematologic Response <sup>[4]</sup>
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End point description:

Duration of the overall clinicohematologic response was defined as the time from the first occurrence of complete response (CR) or partial response (PR) until the date of the first documented disease progression.

End point type	Secondary
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End point timeframe:

256 Weeks

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: Duration of The Overall Clinicohematologic Response was done only on the study drug.

End point values	Ruxolitinib			
Subject group type	Reporting group			
Number of subjects analysed	110			
Units: Probability				
number (confidence interval 95%)				
16 Weeks	1.00 (0.99 to 999)			
32 Weeks	0.99 (0.90 to 1.0)			
48 Weeks	0.96 (0.87 to 0.99)			
64 Weeks	0.91 (0.81 to 0.96)			
80 Weeks	0.88 (0.78 to 0.94)			
96 Weeks	0.88 (0.78 to 0.94)			
112 Weeks	0.85 (0.74 to 0.92)			
128 Weeks	0.82 (0.71 to 0.89)			
144 Weeks	0.82 (0.71 to 0.89)			
160 Weeks	0.80 (0.69 to 0.88)			
176 Weeks	0.75 (0.63 to 0.84)			
192 Weeks	0.70 (0.57 to 0.80)			
208 Weeks	0.67 (0.54 to 0.77)			
224 Weeks	0.67 (0.54 to 0.77)			
240 Weeks	0.67 (0.54 to 0.77)			
256 Weeks	0.67 (0.54 to 0.77)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Duration of the Absence of Phlebotomy Eligibility

End point title	Duration of the Absence of Phlebotomy Eligibility <sup>[5]</sup>
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End point description:

Duration of the absence of phlebotomy eligibility is defined as the time from the first occurrence of absence of phlebotomy eligibility until the date of the first documented progression.



End point type	Secondary
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End point timeframe:

256 Weeks

Notes:

[5] - 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: Duration of absence of Phlebotomy was done only on the study drug.

End point values	Ruxolitinib			
Subject group type	Reporting group			
Number of subjects analysed	110			
Units: Probability				
number (confidence interval 95%)				
16 Week	1.00 (0.99 to 999.99)			
32 Weeks	1.00 (0.99 to 999.99)			
48 Weeks	0.97 (0.88 to 0.99)			
64 Weeks	0.92 (0.82 to 0.97)			
80 Weeks	0.91 (0.80 to 0.96)			
96 Weeks	0.91 (0.80 to 0.96)			
112 Weeks	0.87 (0.76 to 0.93)			
128 Weeks	0.84 (0.72 to 0.91)			
144 Weeks	0.84 (0.72 to 0.91)			
160 Weeks	0.82 (0.70 to 0.90)			
176 Weeks	0.79 (0.66 to 0.87)			
192 Weeks	0.77 (0.64 to 0.86)			
208 Weeks	0.73 (0.60 to 0.83)			
224 Weeks	0.73 (0.60 to 0.83)			
240 Weeks	0.73 (0.60 to 0.83)			
256 Weeks	0.73 (0.60 to 0.83)			

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

This timeframe defines the comparative phase of the study where majority of the subjects remained on their original randomized assignment. Exposure between ruxolitinib & BAT was similar. Data, inclusive of end of study was reported up to Week 256.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

### Reporting groups

Reporting group title	Ruxolitinib (RUX)
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Reporting group description:

RUX = subjects randomized to INC424, and continued the treatment till week 256

Reporting group title	BATWEEK256
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Reporting group description:

BATWEEK256 = subjects randomized to BAT, and crossed over to INC424 after week 32, and continued the treatment till week 256

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

BAT = subjects randomized to BAT, and continued the treatment till week 32

Serious adverse events	Ruxolitinib (RUX)	BATWEEK256	Best Available Therapy (BAT)
Total subjects affected by serious adverse events			
subjects affected / exposed	44 / 110 (40.00%)	43 / 98 (43.88%)	10 / 111 (9.01%)
number of deaths (all causes)	2	4	0
number of deaths resulting from adverse events	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute leukaemia			
subjects affected / exposed	1 / 110 (0.91%)	0 / 98 (0.00%)	0 / 111 (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
Acute myeloid leukaemia			
subjects affected / exposed	0 / 110 (0.00%)	1 / 98 (1.02%)	0 / 111 (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
Adenocarcinoma gastric			

subjects affected / exposed	1 / 110 (0.91%)	0 / 98 (0.00%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Basal cell carcinoma			
subjects affected / exposed	3 / 110 (2.73%)	1 / 98 (1.02%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 3	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carcinoma in situ of skin			
subjects affected / exposed	1 / 110 (0.91%)	0 / 98 (0.00%)	0 / 111 (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
Chronic myeloid leukaemia			
subjects affected / exposed	1 / 110 (0.91%)	0 / 98 (0.00%)	0 / 111 (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
Colon neoplasm			
subjects affected / exposed	0 / 110 (0.00%)	1 / 98 (1.02%)	0 / 111 (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
Hairy cell leukaemia			
subjects affected / exposed	1 / 110 (0.91%)	0 / 98 (0.00%)	0 / 111 (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
Invasive ductal breast carcinoma			
subjects affected / exposed	1 / 110 (0.91%)	0 / 98 (0.00%)	0 / 111 (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
Keratoacanthoma			
subjects affected / exposed	1 / 110 (0.91%)	0 / 98 (0.00%)	0 / 111 (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
Malignant melanoma			

subjects affected / exposed	1 / 110 (0.91%)	0 / 98 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mediastinum neoplasm			
subjects affected / exposed	1 / 110 (0.91%)	0 / 98 (0.00%)	0 / 111 (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
Metastases to central nervous system			
subjects affected / exposed	1 / 110 (0.91%)	0 / 98 (0.00%)	0 / 111 (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
Metastasis			
subjects affected / exposed	1 / 110 (0.91%)	0 / 98 (0.00%)	0 / 111 (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
Metastatic squamous cell carcinoma			
subjects affected / exposed	2 / 110 (1.82%)	0 / 98 (0.00%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myelofibrosis			
subjects affected / exposed	1 / 110 (0.91%)	1 / 98 (1.02%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myxofibrosarcoma			
subjects affected / exposed	0 / 110 (0.00%)	1 / 98 (1.02%)	0 / 111 (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
Neoplasm malignant			
subjects affected / exposed	1 / 110 (0.91%)	0 / 98 (0.00%)	0 / 111 (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
Oropharyngeal squamous cell carcinoma			

subjects affected / exposed	0 / 110 (0.00%)	1 / 98 (1.02%)	0 / 111 (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
Polycythaemia vera			
subjects affected / exposed	0 / 110 (0.00%)	1 / 98 (1.02%)	0 / 111 (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
Prostate cancer			
subjects affected / exposed	1 / 110 (0.91%)	2 / 98 (2.04%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectosigmoid cancer			
subjects affected / exposed	1 / 110 (0.91%)	0 / 98 (0.00%)	0 / 111 (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
Squamous cell carcinoma			
subjects affected / exposed	4 / 110 (3.64%)	1 / 98 (1.02%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	3 / 9	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of lung			
subjects affected / exposed	0 / 110 (0.00%)	1 / 98 (1.02%)	0 / 111 (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
Squamous cell carcinoma of skin			
subjects affected / exposed	2 / 110 (1.82%)	0 / 98 (0.00%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 110 (0.00%)	0 / 98 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			

subjects affected / exposed	1 / 110 (0.91%)	0 / 98 (0.00%)	0 / 111 (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
Hypovolaemic shock			
subjects affected / exposed	0 / 110 (0.00%)	1 / 98 (1.02%)	0 / 111 (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
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 110 (0.00%)	1 / 98 (1.02%)	0 / 111 (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
Chest pain			
subjects affected / exposed	2 / 110 (1.82%)	1 / 98 (1.02%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	0 / 110 (0.00%)	1 / 98 (1.02%)	0 / 111 (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
Hyperthermia			
subjects affected / exposed	0 / 110 (0.00%)	1 / 98 (1.02%)	0 / 111 (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
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 110 (0.00%)	1 / 98 (1.02%)	0 / 111 (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
Pyrexia			
subjects affected / exposed	0 / 110 (0.00%)	1 / 98 (1.02%)	0 / 111 (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
Immune system disorders			

Hypersensitivity			
subjects affected / exposed	0 / 110 (0.00%)	1 / 98 (1.02%)	0 / 111 (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
Reproductive system and breast disorders			
Endometrial hyperplasia			
subjects affected / exposed	0 / 110 (0.00%)	1 / 98 (1.02%)	0 / 111 (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
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	1 / 110 (0.91%)	0 / 98 (0.00%)	0 / 111 (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
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 110 (0.91%)	0 / 98 (0.00%)	0 / 111 (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
Dyspnoea			
subjects affected / exposed	0 / 110 (0.00%)	2 / 98 (2.04%)	0 / 111 (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
Epistaxis			
subjects affected / exposed	0 / 110 (0.00%)	2 / 98 (2.04%)	0 / 111 (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
Lung disorder			
subjects affected / exposed	0 / 110 (0.00%)	1 / 98 (1.02%)	0 / 111 (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
Pulmonary arterial hypertension			

subjects affected / exposed	0 / 110 (0.00%)	1 / 98 (1.02%)	0 / 111 (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
Pulmonary embolism			
subjects affected / exposed	0 / 110 (0.00%)	0 / 98 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary hypertension			
subjects affected / exposed	0 / 110 (0.00%)	1 / 98 (1.02%)	0 / 111 (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
Respiratory failure			
subjects affected / exposed	1 / 110 (0.91%)	0 / 98 (0.00%)	0 / 111 (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
Vocal cord cyst			
subjects affected / exposed	0 / 110 (0.00%)	1 / 98 (1.02%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Attention deficit/hyperactivity disorder			
subjects affected / exposed	1 / 110 (0.91%)	0 / 98 (0.00%)	0 / 111 (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
Personality change			
subjects affected / exposed	0 / 110 (0.00%)	1 / 98 (1.02%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 110 (0.91%)	0 / 98 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0



Foot fracture			
subjects affected / exposed	0 / 110 (0.00%)	1 / 98 (1.02%)	0 / 111 (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
Forearm fracture			
subjects affected / exposed	0 / 110 (0.00%)	1 / 98 (1.02%)	0 / 111 (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
Lumbar vertebral fracture			
subjects affected / exposed	1 / 110 (0.91%)	0 / 98 (0.00%)	0 / 111 (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 haematoma			
subjects affected / exposed	1 / 110 (0.91%)	0 / 98 (0.00%)	0 / 111 (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 / 110 (0.91%)	1 / 98 (1.02%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	1 / 110 (0.91%)	0 / 98 (0.00%)	0 / 111 (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
Splenic rupture			
subjects affected / exposed	1 / 110 (0.91%)	1 / 98 (1.02%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	0 / 110 (0.00%)	0 / 98 (0.00%)	1 / 111 (0.90%)
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 / 110 (0.00%)	0 / 98 (0.00%)	1 / 111 (0.90%)
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	0 / 110 (0.00%)	1 / 98 (1.02%)	0 / 111 (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
Atrial fibrillation			
subjects affected / exposed	3 / 110 (2.73%)	1 / 98 (1.02%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block complete			
subjects affected / exposed	1 / 110 (0.91%)	0 / 98 (0.00%)	0 / 111 (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
Cardiac failure			
subjects affected / exposed	0 / 110 (0.00%)	1 / 98 (1.02%)	0 / 111 (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
Cardiac failure congestive			
subjects affected / exposed	1 / 110 (0.91%)	0 / 98 (0.00%)	0 / 111 (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
Myocardial infarction			
subjects affected / exposed	0 / 110 (0.00%)	1 / 98 (1.02%)	0 / 111 (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
Myocardial ischaemia			
subjects affected / exposed	0 / 110 (0.00%)	1 / 98 (1.02%)	0 / 111 (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
Tachycardia			

subjects affected / exposed	0 / 110 (0.00%)	0 / 98 (0.00%)	1 / 111 (0.90%)
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			
Central nervous system haemorrhage			
subjects affected / exposed	0 / 110 (0.00%)	1 / 98 (1.02%)	0 / 111 (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
Cerebral infarction			
subjects affected / exposed	1 / 110 (0.91%)	0 / 98 (0.00%)	0 / 111 (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 / 110 (0.00%)	1 / 98 (1.02%)	0 / 111 (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
Metabolic encephalopathy			
subjects affected / exposed	1 / 110 (0.91%)	0 / 98 (0.00%)	0 / 111 (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
Neurological symptom			
subjects affected / exposed	1 / 110 (0.91%)	0 / 98 (0.00%)	0 / 111 (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
Paraesthesia			
subjects affected / exposed	0 / 110 (0.00%)	1 / 98 (1.02%)	0 / 111 (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
Syncope			
subjects affected / exposed	0 / 110 (0.00%)	1 / 98 (1.02%)	0 / 111 (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
Transient ischaemic attack			

subjects affected / exposed	0 / 110 (0.00%)	2 / 98 (2.04%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Blood and lymphatic system disorders</b>			
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 110 (0.00%)	1 / 98 (1.02%)	0 / 111 (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
Leukocytosis			
subjects affected / exposed	1 / 110 (0.91%)	0 / 98 (0.00%)	0 / 111 (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
Neutropenia			
subjects affected / exposed	1 / 110 (0.91%)	0 / 98 (0.00%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Splenomegaly			
subjects affected / exposed	0 / 110 (0.00%)	1 / 98 (1.02%)	0 / 111 (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	1 / 110 (0.91%)	0 / 98 (0.00%)	0 / 111 (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
<b>Eye disorders</b>			
Blindness			
subjects affected / exposed	0 / 110 (0.00%)	1 / 98 (1.02%)	0 / 111 (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
Cataract			
subjects affected / exposed	1 / 110 (0.91%)	1 / 98 (1.02%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Glaucoma			
subjects affected / exposed	1 / 110 (0.91%)	0 / 98 (0.00%)	0 / 111 (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 detachment			
subjects affected / exposed	1 / 110 (0.91%)	0 / 98 (0.00%)	0 / 111 (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
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 110 (0.00%)	2 / 98 (2.04%)	0 / 111 (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
Anal fistula			
subjects affected / exposed	1 / 110 (0.91%)	0 / 98 (0.00%)	0 / 111 (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
Anal haemorrhage			
subjects affected / exposed	0 / 110 (0.00%)	1 / 98 (1.02%)	0 / 111 (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
Colitis			
subjects affected / exposed	0 / 110 (0.00%)	1 / 98 (1.02%)	0 / 111 (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
Dental necrosis			
subjects affected / exposed	1 / 110 (0.91%)	0 / 98 (0.00%)	0 / 111 (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
Gastric haemorrhage			
subjects affected / exposed	0 / 110 (0.00%)	1 / 98 (1.02%)	0 / 111 (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
Gastric varices haemorrhage			

subjects affected / exposed	1 / 110 (0.91%)	0 / 98 (0.00%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematochezia			
subjects affected / exposed	1 / 110 (0.91%)	0 / 98 (0.00%)	0 / 111 (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
Ileus			
subjects affected / exposed	1 / 110 (0.91%)	0 / 98 (0.00%)	0 / 111 (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
Incarcerated inguinal hernia			
subjects affected / exposed	1 / 110 (0.91%)	0 / 98 (0.00%)	0 / 111 (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
Large intestinal stenosis			
subjects affected / exposed	1 / 110 (0.91%)	0 / 98 (0.00%)	0 / 111 (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
Rectal haemorrhage			
subjects affected / exposed	2 / 110 (1.82%)	0 / 98 (0.00%)	0 / 111 (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
Varices oesophageal			
subjects affected / exposed	1 / 110 (0.91%)	0 / 98 (0.00%)	0 / 111 (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
Volvulus			
subjects affected / exposed	1 / 110 (0.91%)	0 / 98 (0.00%)	0 / 111 (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
Vomiting			

subjects affected / exposed	0 / 110 (0.00%)	1 / 98 (1.02%)	0 / 111 (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
<b>Hepatobiliary disorders</b>			
Cholecystitis acute			
subjects affected / exposed	1 / 110 (0.91%)	0 / 98 (0.00%)	0 / 111 (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
Cholelithiasis			
subjects affected / exposed	1 / 110 (0.91%)	0 / 98 (0.00%)	0 / 111 (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
<b>Renal and urinary disorders</b>			
Acute kidney injury			
subjects affected / exposed	1 / 110 (0.91%)	0 / 98 (0.00%)	0 / 111 (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
Bladder disorder			
subjects affected / exposed	0 / 110 (0.00%)	0 / 98 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrotic syndrome			
subjects affected / exposed	0 / 110 (0.00%)	1 / 98 (1.02%)	0 / 111 (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
<b>Musculoskeletal and connective tissue disorders</b>			
Intervertebral disc protrusion			
subjects affected / exposed	3 / 110 (2.73%)	1 / 98 (1.02%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar spinal stenosis			
subjects affected / exposed	1 / 110 (0.91%)	0 / 98 (0.00%)	0 / 111 (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

Muscular weakness			
subjects affected / exposed	1 / 110 (0.91%)	0 / 98 (0.00%)	0 / 111 (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
Musculoskeletal pain			
subjects affected / exposed	1 / 110 (0.91%)	0 / 98 (0.00%)	0 / 111 (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
Myalgia			
subjects affected / exposed	0 / 110 (0.00%)	1 / 98 (1.02%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	0 / 110 (0.00%)	2 / 98 (2.04%)	0 / 111 (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
Spondylolisthesis			
subjects affected / exposed	1 / 110 (0.91%)	0 / 98 (0.00%)	0 / 111 (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			
Appendicitis			
subjects affected / exposed	1 / 110 (0.91%)	1 / 98 (1.02%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 110 (0.00%)	1 / 98 (1.02%)	0 / 111 (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
Bronchitis viral			
subjects affected / exposed	1 / 110 (0.91%)	0 / 98 (0.00%)	0 / 111 (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
Cellulitis			



subjects affected / exposed	1 / 110 (0.91%)	2 / 98 (2.04%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	1 / 110 (0.91%)	1 / 98 (1.02%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	0 / 110 (0.00%)	1 / 98 (1.02%)	0 / 111 (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
Gastroenteritis			
subjects affected / exposed	0 / 110 (0.00%)	0 / 98 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis B reactivation			
subjects affected / exposed	0 / 110 (0.00%)	1 / 98 (1.02%)	0 / 111 (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
Herpes zoster			
subjects affected / exposed	1 / 110 (0.91%)	2 / 98 (2.04%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	1 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 110 (0.00%)	1 / 98 (1.02%)	0 / 111 (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
Lung infection			
subjects affected / exposed	1 / 110 (0.91%)	0 / 98 (0.00%)	0 / 111 (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
Nasal abscess			

subjects affected / exposed	0 / 110 (0.00%)	1 / 98 (1.02%)	0 / 111 (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
Osteomyelitis			
subjects affected / exposed	1 / 110 (0.91%)	0 / 98 (0.00%)	0 / 111 (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
Peritonitis			
subjects affected / exposed	1 / 110 (0.91%)	0 / 98 (0.00%)	0 / 111 (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	5 / 110 (4.55%)	6 / 98 (6.12%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	2 / 5	1 / 6	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Sepsis			
subjects affected / exposed	1 / 110 (0.91%)	0 / 98 (0.00%)	0 / 111 (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
Staphylococcal infection			
subjects affected / exposed	1 / 110 (0.91%)	0 / 98 (0.00%)	0 / 111 (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
Tooth abscess			
subjects affected / exposed	1 / 110 (0.91%)	0 / 98 (0.00%)	0 / 111 (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
Urinary tract infection			
subjects affected / exposed	1 / 110 (0.91%)	2 / 98 (2.04%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varicella zoster virus infection			

subjects affected / exposed	0 / 110 (0.00%)	2 / 98 (2.04%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vulvovaginitis trichomonal			
subjects affected / exposed	1 / 110 (0.91%)	0 / 98 (0.00%)	0 / 111 (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
Wound infection			
subjects affected / exposed	0 / 110 (0.00%)	1 / 98 (1.02%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 110 (1.82%)	0 / 98 (0.00%)	0 / 111 (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
Gout			
subjects affected / exposed	0 / 110 (0.00%)	0 / 98 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	0 / 110 (0.00%)	1 / 98 (1.02%)	0 / 111 (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

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

<b>Non-serious adverse events</b>	Ruxolitinib (RUX)	BATWEEK256	Best Available Therapy (BAT)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	108 / 110 (98.18%)	89 / 98 (90.82%)	93 / 111 (83.78%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	16 / 110 (14.55%)	5 / 98 (5.10%)	1 / 111 (0.90%)
occurrences (all)	19	7	1

Myelofibrosis subjects affected / exposed occurrences (all)	8 / 110 (7.27%) 8	5 / 98 (5.10%) 5	0 / 111 (0.00%) 0
Squamous cell carcinoma of skin subjects affected / exposed occurrences (all)	7 / 110 (6.36%) 9	4 / 98 (4.08%) 6	0 / 111 (0.00%) 0
Vascular disorders Haematoma subjects affected / exposed occurrences (all)	11 / 110 (10.00%) 13	6 / 98 (6.12%) 6	3 / 111 (2.70%) 3
Hypertension subjects affected / exposed occurrences (all)	17 / 110 (15.45%) 19	15 / 98 (15.31%) 15	4 / 111 (3.60%) 4
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all)	16 / 110 (14.55%) 22	13 / 98 (13.27%) 18	12 / 111 (10.81%) 12
Chest pain subjects affected / exposed occurrences (all)	4 / 110 (3.64%) 4	7 / 98 (7.14%) 7	1 / 111 (0.90%) 1
Fatigue subjects affected / exposed occurrences (all)	22 / 110 (20.00%) 31	13 / 98 (13.27%) 15	17 / 111 (15.32%) 17
Oedema subjects affected / exposed occurrences (all)	7 / 110 (6.36%) 7	2 / 98 (2.04%) 2	1 / 111 (0.90%) 1
Oedema peripheral subjects affected / exposed occurrences (all)	9 / 110 (8.18%) 11	5 / 98 (5.10%) 5	7 / 111 (6.31%) 7
Pyrexia subjects affected / exposed occurrences (all)	17 / 110 (15.45%) 22	10 / 98 (10.20%) 15	5 / 111 (4.50%) 7
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	20 / 110 (18.18%) 26	12 / 98 (12.24%) 17	6 / 111 (5.41%) 8

Dyspnoea subjects affected / exposed occurrences (all)	19 / 110 (17.27%) 23	10 / 98 (10.20%) 11	2 / 111 (1.80%) 3
Epistaxis subjects affected / exposed occurrences (all)	9 / 110 (8.18%) 12	7 / 98 (7.14%) 11	3 / 111 (2.70%) 6
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	11 / 110 (10.00%) 15	11 / 98 (11.22%) 13	6 / 111 (5.41%) 8
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all)	7 / 110 (6.36%) 8	6 / 98 (6.12%) 8	1 / 111 (0.90%) 1
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	7 / 110 (6.36%) 7	5 / 98 (5.10%) 10	0 / 111 (0.00%) 0
Blood cholesterol increased subjects affected / exposed occurrences (all)	6 / 110 (5.45%) 7	1 / 98 (1.02%) 1	0 / 111 (0.00%) 0
Blood lactate dehydrogenase increased subjects affected / exposed occurrences (all)	4 / 110 (3.64%) 4	8 / 98 (8.16%) 8	2 / 111 (1.80%) 2
Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all)	9 / 110 (8.18%) 12	8 / 98 (8.16%) 8	3 / 111 (2.70%) 4
Haemoglobin decreased subjects affected / exposed occurrences (all)	1 / 110 (0.91%) 1	7 / 98 (7.14%) 15	1 / 111 (0.90%) 1
Weight increased subjects affected / exposed occurrences (all)	26 / 110 (23.64%) 32	14 / 98 (14.29%) 15	1 / 111 (0.90%) 1
Injury, poisoning and procedural complications			

Contusion subjects affected / exposed occurrences (all)	6 / 110 (5.45%) 8	3 / 98 (3.06%) 3	5 / 111 (4.50%) 6
Fall subjects affected / exposed occurrences (all)	3 / 110 (2.73%) 3	6 / 98 (6.12%) 7	2 / 111 (1.80%) 2
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	17 / 110 (15.45%) 26	20 / 98 (20.41%) 22	11 / 111 (9.91%) 13
Headache subjects affected / exposed occurrences (all)	25 / 110 (22.73%) 38	17 / 98 (17.35%) 29	21 / 111 (18.92%) 26
Hypoaesthesia subjects affected / exposed occurrences (all)	6 / 110 (5.45%) 6	7 / 98 (7.14%) 9	1 / 111 (0.90%) 1
Neuralgia subjects affected / exposed occurrences (all)	6 / 110 (5.45%) 6	1 / 98 (1.02%) 1	0 / 111 (0.00%) 0
Neuropathy peripheral subjects affected / exposed occurrences (all)	6 / 110 (5.45%) 8	2 / 98 (2.04%) 3	5 / 111 (4.50%) 5
Paraesthesia subjects affected / exposed occurrences (all)	7 / 110 (6.36%) 13	7 / 98 (7.14%) 8	7 / 111 (6.31%) 9
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	38 / 110 (34.55%) 64	29 / 98 (29.59%) 42	4 / 111 (3.60%) 4
Leukocytosis subjects affected / exposed occurrences (all)	4 / 110 (3.64%) 4	7 / 98 (7.14%) 11	3 / 111 (2.70%) 3
Thrombocytopenia subjects affected / exposed occurrences (all)	19 / 110 (17.27%) 34	4 / 98 (4.08%) 6	12 / 111 (10.81%) 17
Ear and labyrinth disorders			

Tinnitus subjects affected / exposed occurrences (all)	9 / 110 (8.18%) 11	5 / 98 (5.10%) 5	3 / 111 (2.70%) 3
Vertigo subjects affected / exposed occurrences (all)	7 / 110 (6.36%) 10	4 / 98 (4.08%) 4	4 / 111 (3.60%) 4
Eye disorders Cataract subjects affected / exposed occurrences (all)	1 / 110 (0.91%) 1	6 / 98 (6.12%) 7	0 / 111 (0.00%) 0
Gastrointestinal disorders Abdominal distension subjects affected / exposed occurrences (all)	6 / 110 (5.45%) 6	1 / 98 (1.02%) 1	4 / 111 (3.60%) 4
Abdominal pain subjects affected / exposed occurrences (all)	16 / 110 (14.55%) 19	8 / 98 (8.16%) 10	13 / 111 (11.71%) 13
Abdominal pain upper subjects affected / exposed occurrences (all)	12 / 110 (10.91%) 12	6 / 98 (6.12%) 7	5 / 111 (4.50%) 6
Constipation subjects affected / exposed occurrences (all)	14 / 110 (12.73%) 15	15 / 98 (15.31%) 18	3 / 111 (2.70%) 3
Diarrhoea subjects affected / exposed occurrences (all)	30 / 110 (27.27%) 38	12 / 98 (12.24%) 12	9 / 111 (8.11%) 10
Dyspepsia subjects affected / exposed occurrences (all)	7 / 110 (6.36%) 8	3 / 98 (3.06%) 3	1 / 111 (0.90%) 1
Nausea subjects affected / exposed occurrences (all)	15 / 110 (13.64%) 19	7 / 98 (7.14%) 10	4 / 111 (3.60%) 4
Vomiting subjects affected / exposed occurrences (all)	6 / 110 (5.45%) 8	7 / 98 (7.14%) 9	4 / 111 (3.60%) 4
Skin and subcutaneous tissue disorders			

Ecchymosis			
subjects affected / exposed	2 / 110 (1.82%)	7 / 98 (7.14%)	1 / 111 (0.90%)
occurrences (all)	3	7	1
Night sweats			
subjects affected / exposed	13 / 110 (11.82%)	6 / 98 (6.12%)	9 / 111 (8.11%)
occurrences (all)	16	8	9
Pruritus			
subjects affected / exposed	30 / 110 (27.27%)	20 / 98 (20.41%)	24 / 111 (21.62%)
occurrences (all)	42	25	28
Purpura			
subjects affected / exposed	2 / 110 (1.82%)	5 / 98 (5.10%)	0 / 111 (0.00%)
occurrences (all)	2	6	0
Rash			
subjects affected / exposed	4 / 110 (3.64%)	7 / 98 (7.14%)	5 / 111 (4.50%)
occurrences (all)	4	7	6
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	24 / 110 (21.82%)	11 / 98 (11.22%)	8 / 111 (7.21%)
occurrences (all)	32	14	8
Back pain			
subjects affected / exposed	17 / 110 (15.45%)	18 / 98 (18.37%)	5 / 111 (4.50%)
occurrences (all)	21	21	5
Bone pain			
subjects affected / exposed	4 / 110 (3.64%)	4 / 98 (4.08%)	6 / 111 (5.41%)
occurrences (all)	6	4	6
Muscle spasms			
subjects affected / exposed	22 / 110 (20.00%)	11 / 98 (11.22%)	7 / 111 (6.31%)
occurrences (all)	28	12	8
Musculoskeletal pain			
subjects affected / exposed	7 / 110 (6.36%)	6 / 98 (6.12%)	4 / 111 (3.60%)
occurrences (all)	10	7	4
Myalgia			
subjects affected / exposed	7 / 110 (6.36%)	3 / 98 (3.06%)	8 / 111 (7.21%)
occurrences (all)	9	3	9
Osteoarthritis			



subjects affected / exposed occurrences (all)	6 / 110 (5.45%) 7	4 / 98 (4.08%) 4	0 / 111 (0.00%) 0
Pain in extremity subjects affected / exposed occurrences (all)	10 / 110 (9.09%) 13	11 / 98 (11.22%) 16	4 / 111 (3.60%) 5
Infections and infestations			
Bronchitis subjects affected / exposed occurrences (all)	14 / 110 (12.73%) 17	13 / 98 (13.27%) 17	5 / 111 (4.50%) 5
Gastroenteritis subjects affected / exposed occurrences (all)	2 / 110 (1.82%) 2	5 / 98 (5.10%) 5	1 / 111 (0.90%) 1
Herpes zoster subjects affected / exposed occurrences (all)	19 / 110 (17.27%) 26	12 / 98 (12.24%) 12	0 / 111 (0.00%) 0
Influenza subjects affected / exposed occurrences (all)	13 / 110 (11.82%) 14	9 / 98 (9.18%) 9	2 / 111 (1.80%) 2
Nasopharyngitis subjects affected / exposed occurrences (all)	19 / 110 (17.27%) 30	14 / 98 (14.29%) 32	9 / 111 (8.11%) 10
Pharyngitis subjects affected / exposed occurrences (all)	6 / 110 (5.45%) 7	1 / 98 (1.02%) 1	0 / 111 (0.00%) 0
Sinusitis subjects affected / exposed occurrences (all)	3 / 110 (2.73%) 7	6 / 98 (6.12%) 9	1 / 111 (0.90%) 1
Upper respiratory tract infection subjects affected / exposed occurrences (all)	10 / 110 (9.09%) 17	8 / 98 (8.16%) 14	5 / 111 (4.50%) 5
Urinary tract infection subjects affected / exposed occurrences (all)	10 / 110 (9.09%) 18	8 / 98 (8.16%) 11	0 / 111 (0.00%) 0
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	9 / 110 (8.18%)	5 / 98 (5.10%)	6 / 111 (5.41%)
occurrences (all)	9	6	6
Hypercholesterolaemia			
subjects affected / exposed	5 / 110 (4.55%)	5 / 98 (5.10%)	0 / 111 (0.00%)
occurrences (all)	6	6	0

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 August 2011	<p>Protocol amendment 1, issued after 30 patients had been randomized, introduced the following main changes:</p> <ul style="list-style-type: none"><li>• Some inclusion criteria were re-evaluated and revised:</li><li>• The inclusion criteria were revised from requiring a palpable spleen length of &gt; 5 cm to requiring palpable splenomegaly confirmed by imaging (volume <math>\geq 450</math> cm<sup>3</sup>) at Screening. Patients with palpable spleen were to be considered eligible if MRI (or CT if applicable) confirmed a spleen volume of <math>\geq 450</math> cm<sup>3</sup> (i.e. approximately twice the upper limit of a normal spleen volume).</li><li>• The inclusion criterion that required patients to have a leukocytosis &gt; <math>15 \times 10^9</math>/L and/or thrombocytosis &gt; <math>600 \times 10^9</math>/L at Screening were removed</li><li>• The definition of unacceptable non-hematological toxicities in HU intolerant patients was extended to include events reflecting severe/very severe toxicities leading to treatment discontinuation or interruption, and hospitalization</li><li>• The phlebotomy requirement prior to study entry was extended from 12 to 16 weeks between the last phlebotomy and screening, for patients with hematocrit &gt; 45% at screening for the evidence of phlebotomy dependence</li><li>• The definition of durable response for the primary endpoint and key secondary endpoints was changed to 48 weeks after randomization, however, the definition of duration of primary response was maintained as time from initial response.</li><li>• Bone marrow biopsy was mandated in the event of suspected development of MF or acute leukemia</li><li>• Sample size was reduced from 300 to 200 patients and the assumption on response rate for durable primary endpoint was modified accordingly</li></ul>
13 April 2012	<p>Protocol amendment 2, issued after 98 patients had been randomized (no patients had reached the Week 80 visit), introduced the following main changes:</p> <ul style="list-style-type: none"><li>• The treatment period of patients receiving ruxolitinib at Week 80 (end of treatment in the current protocol) was extended by 128 week from Week 80 to Week 208. This period was defined as the Extended Treatment Phase</li><li>• The PV patients benefitting from ruxolitinib at Week 80 were offered enrollment onto a 128-week Extended Treatment Phase</li></ul>
25 June 2013	<p>Protocol amendment 3, issued after all (n=222) patients had been randomized but 6 months prior to database lock for the primary analysis, introduced the following main changes:</p> <ul style="list-style-type: none"><li>• The analysis window for MRI/CT scans was extended from <math>\pm 7</math> days to <math>\pm 28</math> days.</li><li>• The analysis windows for hematocrit, WBC and platelets were specified in greater detail for individual study visits, and the use of multiple assessments available within an analysis window was defined, in order to minimize missing data, remove any ambiguity and optimize the use of available assessments.</li></ul>

13 November 2014	<p>The rationale for the amendment is as follows: • To collect long-term safety and efficacy data, treatment duration will be extended by additional 48 weeks, to a total of 256 weeks (5 years).</p> <p>• Hydroxyurea resistance/intolerance has recently been shown to be associated with significantly reduced overall survival, attributed in part to lack of effective second-line therapies (Alvarez-Larran, 2012). In the current study, ruxolitinib demonstrated superiority to BAT in hematocrit control, reduction in splenomegaly and complete hematologic remission in hydroxyurea resistant or intolerant patients. To evaluate whether these benefits translate into an improved survival, overall survival will be added as an exploratory endpoint to the study. Survival follow-up after treatment discontinuation will be conducted in all patients until Last Patient Last Visit.</p> <p>• Thromboembolic events and transformation to acute leukemia or myelofibrosis (MF) are the major causes of morbidity and mortality in PV patients (Tefferi et al, 2013). Tight hematocrit control with a target of <math>\leq 45\%</math> leads to a 4-fold reduction in the risk of thrombosis (Marchioli et al, 2013). In the current study, week 32 analysis demonstrated that hematocrit control without phlebotomy was achieved in 60% of patients in the ruxolitinib arm, compared to 20% in the BAT arm. The number of thromboembolic adverse events up to week 32 was lower in the ruxolitinib arm (N=1) compared to the BAT arm (N=6). The number of transformation events up to week 32 was too low to draw any conclusions (MF, N=2 on ruxolitinib vs N=1 on BAT; AML, N=1 on ruxolitinib vs N=0 on BAT). To assess long-term impact of ruxolitinib, the rate of thrombosis and transformation-free survival will be added as exploratory endpoints to the study.</p>
16 February 2016	<p>To remove the requirement for contraception for male participants since there were no effects of INC424 on reproductive performance or fertility in male rats. While INC424 was not measured in semen of humans or any animal species studied, the estimated dose to the woman (based on INC424 exposure in males and estimated amount expected in semen) was approximately 333'333 times smaller than the embryo-fetal NOEL. This dose would present no increased risk to the embryo-fetus. Therefore, it was not expected that INC424 would lead to any adverse reaction in women whose partner was treated by INC424. This supports the removal of the requirement for male contraception; To update the contraception requirements for female participants; To clarify that Survival Follow Up was only applicable for patients who complete/discontinue study treatment prior to Week 256 and only continues until the time when the individual Week 256 visit from randomization would have been reached; To clarify that samples for pharmacodynamic assessments must be collected at the end of study treatment in the extended treatment phase (early termination or Week 256 visit); To clarify that EORTC QLQ-C30 &amp; Pruritus Symptom Impact Scale questionnaires must be collected at the end of study treatment in the extended treatment phase (early termination or Week 256 visit); To clarify that serum pregnancy test must be performed at the end of study treatment in the extended treatment phase; To add new information on dual inhibitors of CYP2C9 &amp; CYP3A4 (e.g. , fluconazole). The concomitant use of INC424 and fluconazole doses of <math>\geq 200</math> mg daily should be avoided if clinically necessary to use doses <math>\geq 200</math> mg daily consultation with Sponsor was required; To clarify that aPTT assessment was also allowed as equivalent of PTT; To make admin. changes: clarified throughout the protocol that Survival Follow Up visits can be performed approximately every 3 months, corrected internal hyperlinks, typos, updated list of abbrevs.</p>

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: