Clinical trial results:
A Phase 2, Multicenter, Open-Label Study to Evaluate the Efficacy and Safety of Luspatercept (ACE-536) in Subjects With Myeloproliferative Neoplasm-Associated Myelofibrosis and Anemia With and Without Red Blood Cell-Transfusion Dependence

Summary

EudraCT number	2017-000322-35
Trial protocol	GB IT
Global end of trial date	18 July 2022

Results information

Result version number	v1
This version publication date	03 August 2023
First version publication date	03 August 2023

Trial information

Trial identification

Sponsor protocol code	ACE-536-MF-001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03194542
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bristol-Myers Squibb
Sponsor organisation address	Chaussée de la Hulpe 185, Brussels, Belgium, 1170
Public contact	EU Study Start-Up Unit, Bristol-Myers Squibb International Corporation, Clinical.Trials@bms.com
Scientific contact	Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, Clinical.Trials@bms.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	06 September 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 July 2022
Global end of trial reached?	Yes
Global end of trial date	18 July 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy and safety of luspatercept for the treatment of anemia in subjects with MPN-associated myelofibrosis with and without RBC-transfusion dependence.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial participants were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 November 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	Italy: 29
Country: Number of subjects enrolled	United Kingdom: 11
Country: Number of subjects enrolled	United States: 48
Worldwide total number of subjects	95
EEA total number of subjects	36

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)	19
From 65 to 84 years	74
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

The target study population included participants with myeloproliferative neoplasm (MPN)-associated myelofibrosis and anemia with and without RBC-transfusion dependence.

Pre-assignment

Screening details:

95 participants were treated in this study.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1: Anemia Only

Arm description:

Participants receive a starting dose level of luspatercept at 1.0 mg/kg subcutaneous injection every 3 weeks (administered on Day 1 of each 21-day treatment cycle). The starting dose can be titrated (increased) during the Treatment Period to 1.33 mg/kg, up to a maximum of 1.75 mg/kg, provided that the participant meets the appropriate criteria. The participant's dose may also be delayed, reduced, or discontinued, depending on the specific criteria.

Arm type	Experimental
Investigational medicinal product name	Luspatercept
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered on Day 1 of every 21-day cycle, at an initial dose level of 1.0 mg/kg. Participants may have the dose level increased in a stepwise manner beyond the starting dose level of 1.0 mg/kg to 1.33 mg/kg, and up to a maximum of 1.75 mg/kg (but no more than 168 mg) during the Treatment Period.

Arm title	Cohort 2: RBC-Transfusion Dependent

Arm description:

Participants receive a starting dose level of luspatercept at 1.0 mg/kg subcutaneous injection every 3 weeks (administered on Day 1 of each 21-day treatment cycle). The starting dose can be titrated (increased) during the Treatment Period to 1.33 mg/kg, up to a maximum of 1.75 mg/kg, provided that the participant meets the appropriate criteria. The participant's dose may also be delayed, reduced, or discontinued, depending on the specific criteria.

Arm type	Experimental
Investigational medicinal product name	Luspatercept
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered on Day 1 of every 21-day cycle, at an initial dose level of 1.0 mg/kg. Participants may have the dose level increased in a stepwise manner beyond the starting dose level of 1.0 mg/kg to 1.33 mg/kg, and up to a maximum of 1.75 mg/kg (but no more than 168 mg) during the Treatment Period.

Arm title	Cohort 3A: Anemia Only (Stable Dose-Ruxolitinib)

Arm description:

Participants receive a starting dose level of luspatercept at 1.0 mg/kg subcutaneous injection every 3 weeks (administered on Day 1 of each 21-day treatment cycle) while being on a stable dose of ruxolitinib for at least 112 days immediately prior to the enrollment date. The starting dose can be titrated (increased) during the Treatment Period to 1.33 mg/kg, up to a maximum of 1.75 mg/kg, provided that the participant meets the appropriate criteria. The participant's dose may also be delayed, reduced, or discontinued, depending on the specific criteria.

Arm type	Experimental
Investigational medicinal product name	Luspatercept
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered on Day 1 of every 21-day cycle, at an initial dose level of 1.0 mg/kg. Participants may have the dose level increased in a stepwise manner beyond the starting dose level of 1.0 mg/kg to 1.33 mg/kg, and up to a maximum of 1.75 mg/kg (but no more than 168 mg) during the Treatment Period.

Arm title	Cohort 3B: RBC-Transfusion Dependent (Stable Dose-Ruxolitinib)

Arm description:

Participants receive a starting dose level of luspatercept at 1.0 mg/kg subcutaneous injection every 3 weeks (administered on Day 1 of each 21-day treatment cycle) while being on a stable dose of ruxolitinib for at least 112 days immediately prior to the enrollment date. The starting dose can be titrated (increased) during the Treatment Period to 1.33 mg/kg, up to a maximum of 1.75 mg/kg, provided that the participant meets the appropriate criteria. The participant's dose may also be delayed, reduced, or discontinued, depending on the specific criteria.

Arm type	Experimental
Investigational medicinal product name	Luspatercept
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered on Day 1 of every 21-day cycle, at an initial dose level of 1.0 mg/kg. Participants may have the dose level increased in a stepwise manner beyond the starting dose level of 1.0 mg/kg to 1.33 mg/kg, and up to a maximum of 1.75 mg/kg (but no more than 168 mg) during the Treatment Period.

Number of subjects in period 1	Cohort 1: Anemia Only	Cohort 2: RBC-Transfusion Dependent	Cohort 3A: Anemia Only (Stable Dose-Ruxolitinib)
Started	22	21	14
Completed	0	0	0
Not completed	22	21	14
Rollover to Long-term follow-up	1	1	-
Adverse event, serious fatal	1	2	-
Consent withdrawn by subject	2	1	5
Physician decision	-	1	-
Adverse event, non-fatal	1	2	-
Progressive Disease	1	-	1
Participant to Receive Bone Marrow Transplant	1	-	-

Per Protocol Repeat Blasts of 10%	1	-	1
Did not meet clinical benefit criteria	8	10	2
Loss of Response	4	2	3
Lack of efficacy	2	2	2

Number of subjects in period 1	Cohort 3B: RBC-Transfusion Dependent (Stable Dose-Ruxolitinib)
Started	38
Completed	0
Not completed	38
Rollover to Long-term follow-up	5
Adverse event, serious fatal	5
Consent withdrawn by subject	4
Physician decision	-
Adverse event, non-fatal	5
Progressive Disease	1
Participant to Receive Bone Marrow Transplant	-
Per Protocol Repeat Blasts of 10%	-
Did not meet clinical benefit criteria	8
Loss of Response	4
Lack of efficacy	6

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1: Anemia Only
Reporting group description:	
Participants receive a starting dose level of luspatercept at 1.0 mg/kg subcutaneous injection every 3 weeks (administered on Day 1 of each 21-day treatment cycle). The starting dose can be titrated (increased) during the Treatment Period to 1.33 mg/kg, up to a maximum of 1.75 mg/kg, provided that the participant meets the appropriate criteria. The participant's dose may also be delayed, reduced, or discontinued, depending on the specific criteria.	
Reporting group title	Cohort 2: RBC-Transfusion Dependent
Reporting group description:	
Participants receive a starting dose level of luspatercept at 1.0 mg/kg subcutaneous injection every 3 weeks (administered on Day 1 of each 21-day treatment cycle). The starting dose can be titrated (increased) during the Treatment Period to 1.33 mg/kg, up to a maximum of 1.75 mg/kg, provided that the participant meets the appropriate criteria. The participant's dose may also be delayed, reduced, or discontinued, depending on the specific criteria.	
Reporting group title	Cohort 3A: Anemia Only (Stable Dose-Ruxolitinib)
Reporting group description:	
Participants receive a starting dose level of luspatercept at 1.0 mg/kg subcutaneous injection every 3 weeks (administered on Day 1 of each 21-day treatment cycle) while being on a stable dose of ruxolitinib for at least 112 days immediately prior to the enrollment date. The starting dose can be titrated (increased) during the Treatment Period to 1.33 mg/kg, up to a maximum of 1.75 mg/kg, provided that the participant meets the appropriate criteria. The participant's dose may also be delayed, reduced, or discontinued, depending on the specific criteria.	
Reporting group title	Cohort 3B: RBC-Transfusion Dependent (Stable Dose-Ruxolitinib)
Reporting group description:	
Participants receive a starting dose level of luspatercept at 1.0 mg/kg subcutaneous injection every 3 weeks (administered on Day 1 of each 21-day treatment cycle) while being on a stable dose of ruxolitinib for at least 112 days immediately prior to the enrollment date. The starting dose can be titrated (increased) during the Treatment Period to 1.33 mg/kg, up to a maximum of 1.75 mg/kg, provided that the participant meets the appropriate criteria. The participant's dose may also be delayed, reduced, or discontinued, depending on the specific criteria.	

Reporting group values	Cohort 1: Anemia Only	Cohort 2: RBC-Transfusion Dependent	Cohort 3A: Anemia Only (Stable Dose-Ruxolitinib)
Number of subjects	22	21	14
Age categorical Units: Subjects			
Adults (18-64 years)	5	2	7
From 65-84 years	16	18	7
85 years and over	1	1	0
Age Continuous Units: Years			
arithmetic mean	69	73.9	65.4
standard deviation	± 8.87	± 5.71	± 8.45
Sex: Female, Male Units: Participants			
Female	9	6	7
Male	13	15	7
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0

Asian	2	1	3
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	1
White	16	18	10
More than one race	0	0	0
Unknown or Not Reported	4	2	0
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	2	0	0
Not Hispanic or Latino	16	19	14
Unknown or Not Reported	4	2	0

Reporting group values	Cohort 3B: RBC-Transfusion Dependent (Stable Dose-Ruxolitinib)	Total	
Number of subjects	38	95	
Age categorical			
Units: Subjects			
Adults (18-64 years)	5	19	
From 65-84 years	33	74	
85 years and over	0	2	
Age Continuous			
Units: Years			
arithmetic mean	71.3		
standard deviation	± 5.80	-	
Sex: Female, Male			
Units: Participants			
Female	15	37	
Male	23	58	
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	1	7	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	2	3	
White	30	74	
More than one race	0	0	
Unknown or Not Reported	5	11	
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	1	3	
Not Hispanic or Latino	32	81	
Unknown or Not Reported	5	11	

End points

End points reporting groups

Reporting group title	Cohort 1: Anemia Only

Reporting group description:

Participants receive a starting dose level of luspatercept at 1.0 mg/kg subcutaneous injection every 3 weeks (administered on Day 1 of each 21-day treatment cycle). The starting dose can be titrated (increased) during the Treatment Period to 1.33 mg/kg, up to a maximum of 1.75 mg/kg, provided that the participant meets the appropriate criteria. The participant's dose may also be delayed, reduced, or discontinued, depending on the specific criteria.

Reporting group title	Cohort 2: RBC-Transfusion Dependent

Reporting group description:

Participants receive a starting dose level of luspatercept at 1.0 mg/kg subcutaneous injection every 3 weeks (administered on Day 1 of each 21-day treatment cycle). The starting dose can be titrated (increased) during the Treatment Period to 1.33 mg/kg, up to a maximum of 1.75 mg/kg, provided that the participant meets the appropriate criteria. The participant's dose may also be delayed, reduced, or discontinued, depending on the specific criteria.

Reporting group title	Cohort 3A: Anemia Only (Stable Dose-Ruxolitinib)

Reporting group description:

Participants receive a starting dose level of luspatercept at 1.0 mg/kg subcutaneous injection every 3 weeks (administered on Day 1 of each 21-day treatment cycle) while being on a stable dose of ruxolitinib for at least 112 days immediately prior to the enrollment date. The starting dose can be titrated (increased) during the Treatment Period to 1.33 mg/kg, up to a maximum of 1.75 mg/kg, provided that the participant meets the appropriate criteria. The participant's dose may also be delayed, reduced, or discontinued, depending on the specific criteria.

Reporting group title	Cohort 3B: RBC-Transfusion Dependent (Stable Dose-Ruxolitinib)

Reporting group description:

Participants receive a starting dose level of luspatercept at 1.0 mg/kg subcutaneous injection every 3 weeks (administered on Day 1 of each 21-day treatment cycle) while being on a stable dose of ruxolitinib for at least 112 days immediately prior to the enrollment date. The starting dose can be titrated (increased) during the Treatment Period to 1.33 mg/kg, up to a maximum of 1.75 mg/kg, provided that the participant meets the appropriate criteria. The participant's dose may also be delayed, reduced, or discontinued, depending on the specific criteria.

Primary: The Number of Participants with Anemia Reponses over Any 84-Day Period During the Primary Treatment Period

End point title	The Number of Participants with Anemia Reponses over Any 84-Day Period During the Primary Treatment Period[1]

End point description:

The number of participants that achieved anemia response as it relates to hemoglobin (Hgb) increase and red blood cell (RBC)-transfusion independence is defined below:

Cohorts 1 (anemia only) and 3A: The number of participants achieving ≥ 1.5 g/dL hemoglobin increase from baseline over any consecutive 84-day period without an RBC transfusion from Day 1 up through and including Day 168.
Cohorts 2 (RBC-transfusion dependent) and 3B: The number of participants who become RBC-transfusion free over any consecutive 84-day period from Day 1 up through and including Day 168.

Baseline value is defined as the last value (including "unscheduled") measured on or before the first dose.

End point type	Primary

End point timeframe:

Any consecutive "rolling" 84-day period from Day 1 through and including Day 168

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: Only summary statistics planned for this endpoint.

End point values	Cohort 1: Anemia Only	Cohort 2: RBC-Transfusion Dependent	Cohort 3A: Anemia Only (Stable Dose-Ruxolitinib)	Cohort 3B: RBC-Transfusion Dependent (Stable Dose-Ruxolitinib)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	22	21	14	38
Units: Participants	3	2	2	10

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Anemia Response During the Primary Treatment Period

End point title	Time to Anemia Response During the Primary Treatment Period

End point description:

Time to anemia response follows the definitions below:

Cohorts 1 (anemia only) and 3A: Time between first administration of luspatercept and the first hemoglobin increase of ≥ 1.5 g/dL from baseline that starts a consecutive 84-day period of consecutive increase ≥ 1.5 g/dL without RBC transfusions.
Cohorts 2 (RBC-transfusion dependent) and 3B: Time between first administration of luspatercept and the first day of an RBC transfusion-free period of 84 days.

Baseline value is defined as the last value (including "unscheduled") measured on or before the first dose.

End point type	Secondary

End point timeframe:

From first dose up to first onset of anemia response (calculated from Day 1 through and including Day 168)

End point values	Cohort 1: Anemia Only	Cohort 2: RBC-Transfusion Dependent	Cohort 3A: Anemia Only (Stable Dose-Ruxolitinib)	Cohort 3B: RBC-Transfusion Dependent (Stable Dose-Ruxolitinib)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	2	2	10
Units: Days				
arithmetic mean (standard deviation)	57.3 (± 14.36)	2.0 (± 0.00)	63.5 (± 30.41)	30.7 (± 27.22)

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Anemia Response

End point title	Duration of Anemia Response

End point description:

The duration of anemia response is defined as the duration of time from first day of longest response to the last day of longest response. Participants who achieved and maintained the anemia response at the time of the analysis are censored at the efficacy cutoff date. For Cohorts 1 and 3A, an anemia responder was defined as a subject with ≥ 1.5 g/dL hemoglobin increase from baseline over any consecutive 84-day period without an RBC transfusion. For Cohorts 2 and 3B, an anemia responder was defined as a subject who becomes RBC transfusion free over any consecutive 84-day period.

Baseline value is defined as the last value (including "unscheduled") measured on or before the first dose.

End point type	Secondary

End point timeframe:

From first dose through last day of longest response (calculated from Day 1 through end of treatment, up to approximately 232 weeks)

End point values	Cohort 1: Anemia Only	Cohort 2: RBC-Transfusion Dependent	Cohort 3A: Anemia Only (Stable Dose-Ruxolitinib)	Cohort 3B: RBC-Transfusion Dependent (Stable Dose-Ruxolitinib)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	2	2	10
Units: Days				
arithmetic mean (standard deviation)	457.7 (± 611.20)	623.0 (± 29.70)	88.5 (± 6.36)	534.7 (± 527.67)

Statistical analyses

No statistical analyses for this end point

Secondary: The Number of RBC Units Transfused per Participant per 28 Days (Cohorts 2 and 3B Only)

End point title	The Number of RBC Units Transfused per Participant per 28 Days (Cohorts 2 and 3B Only)[2]

End point description:

Frequency of RBC transfusion is defined as the mean number of RBC units transfused per participant every 4 weeks (28 days). The primary treatment period is from Day 1 to and including Day 168. The entire treatment period is from Day 1 through the end of treatment.

End point type	Secondary

End point timeframe:

From Day 1 through end of treatment (up to approximately 232 weeks).

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: Pre-specified for Cohorts 2 and 3B only

End point values	Cohort 2: RBC-Transfusion Dependent	Cohort 3B: RBC-Transfusion Dependent (Stable Dose-Ruxolitinib)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	38		
Units: RBC Units				
arithmetic mean (standard deviation)				
Primary Treatment Period	2.76 (± 1.967)	1.49 (± 1.345)		
Entire Treatment Period	2.70 (± 2.040)	1.52 (± 1.365)		

Statistical analyses

No statistical analyses for this end point

Secondary: The Number Participants Achieving >=50% RBC Transfusion Burden Reduction from Baseline Over Any 84-Day Period (Cohorts 2 and 3B Only)

End point title	The Number Participants Achieving >=50% RBC Transfusion Burden Reduction from Baseline Over Any 84-Day Period (Cohorts 2 and 3B Only)[3]

End point description:

The number of participants who reduce their transfusion burden by ≥ 50% from baseline over any consecutive 84-day period. Baseline is defined as average number of RBC units per 28 days over the 84 days period on or prior to the C1D1 date. The primary treatment period is from Day 1 to and including Day 168. The entire treatment period is from Day 1 through the end of treatment.

End point type	Secondary

End point timeframe:

Baseline and from Day 1 through end of treatment (up to approximately 232 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: Pre-specified for Cohorts 2 and 3B only

End point values	Cohort 2: RBC-Transfusion Dependent	Cohort 3B: RBC-Transfusion Dependent (Stable Dose-Ruxolitinib)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	38		
Units: Participants				
Primary Treatment Period	10	19		
Entire Treatment Period	10	20		

Statistical analyses

No statistical analyses for this end point

Secondary: The Number of Participants who Achieve ≥ 50% Reduction in Fatigue Symptom as Measured by the Myeloproliferative Neoplasms Symptom Assessment Form Total Symptom Score (MPN-SAF TSS)

End point title	The Number of Participants who Achieve ≥ 50% Reduction in Fatigue Symptom as Measured by the Myeloproliferative Neoplasms Symptom Assessment Form Total Symptom Score (MPN-SAF TSS)

End point description:

Symptoms response improvement will be assessed using the number of participants who achieve ≥ 50% reduction in fatigue symptoms. Fatigue is 1 out of 10 total symptoms scored on a 0 (absent/as good as it can be) to 10 (worst imaginable/as bad as it can be).

The primary treatment period is from Day 1 to and including Day 168. The entire treatment period is from Day 1 through the end of treatment. Baseline is defined as the last value on or before the first dose of study drug.

Last Available = Last available assessment on or before the end of the treatment period.
Mean = Mean value of the weekly assessments over the treatment period.

End point type	Secondary

End point timeframe:

Baseline and from Day 1 through end of treatment (up to approximately 232 weeks)

End point values	Cohort 1: Anemia Only	Cohort 2: RBC-Transfusion Dependent	Cohort 3A: Anemia Only (Stable Dose-Ruxolitinib)	Cohort 3B: RBC-Transfusion Dependent (Stable Dose-Ruxolitinib)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	22	21	14	38
Units: Participants				
Primary Treatment Period (Last Available)	4	2	4	10
Entire Treatment Period (Last Available)	4	1	4	7
Primary Treatment Period (Mean)	5	1	3	5
Entire Treatment Period (Mean)	4	0	3	5

Statistical analyses

No statistical analyses for this end point

Secondary: Mean changes in the Functional Assessment of Cancer Therapy – Anemia (FACT-An) Total Scores Over the Study Compared to Baseline

End point title	Mean changes in the Functional Assessment of Cancer Therapy – Anemia (FACT-An) Total Scores Over the Study Compared to Baseline

End point description:

The FACT-An questionnaire includes 40 items rating from 0 (not at all) to 4 (very much) on five primary subscales:
- Physical well-being (PWB; 7 items),
- Social/Family well-being (SWB; 7 items),
- Emotional well-being (EWB; 6 items),
- Functional well-being (FWB; 7 items).
- Anemia-related symptoms (AS; 20 items)

The Functional Assessment of Cancer Therapy-Fatigue (FACT-F) fatigue subscale (FS) is a 13-item questionnaire that is part of the AS as well and focuses only on fatigue-related symptoms of anemia. The subscale score is calculated by summing item responses within each subscale. The scoring of negatively worded items will be reversed by subtracting from 4 (e.g. 4 – item response) so that a higher score always indicates a favorable response. Missing values will be imputed by using average value of items for a subscale as long as > 50% of the questions in the subscale were answered. Baseline is defined as the last value on or before the first dose of study drug.

End point type	Secondary

End point timeframe:

Day 169 and End of treatment (up to approximately 232 weeks)

End point values	Cohort 1: Anemia Only	Cohort 2: RBC-Transfusion Dependent	Cohort 3A: Anemia Only (Stable Dose-Ruxolitinib)	Cohort 3B: RBC-Transfusion Dependent (Stable Dose-Ruxolitinib)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9[4]	9[5]	8[6]	14[7]
Units: Score on a scale				
arithmetic mean (standard deviation)				
Day 169	-10.4 (± 13.23)	-15.7 (± 14.24)	-9.4 (± 9.24)	5.0 (± 21.77)
End of Treatment	-15.9 (± 18.35)	-16.6 (± 16.80)	-12.6 (± 10.03)	-14.2 (± 21.98)

Notes:

[4] - Day 169 (n= 9)
End of Treatment (n=9)
[5] - Day 169 (n= 9)
End of Treatment (n=8)
[6] - Day 169 (n= 5)
End of Treatment (n=8)
[7] - Day 169 (n= 14)
End of Treatment (n=14)

Statistical analyses

No statistical analyses for this end point

Secondary: The Number of Participants who Achieve ≥ 50% Reduction in Total Symptom Score (TSS) as Measured by the Myeloproliferative Neoplasms Symptom Assessment Form Total Symptom Score (MPN-SAF TSS)

End point title	The Number of Participants who Achieve ≥ 50% Reduction in Total Symptom Score (TSS) as Measured by the Myeloproliferative Neoplasms Symptom Assessment Form Total Symptom Score (MPN-SAF TSS)

End point description:

TSS includes 10 items - worst fatigue, concentration, early satiety, inactivity, night sweats, itching, bone pain, abdominal discomfort, weight loss, and fevers, scored on a 0 (absent/as good as it can be) to 10 (worst imaginable/as bad as it can be). For participants who completed at least six of these 10 items, the MPN-SAF TSS was computed as the average of the observed items multiplied by 10 to achieve a 0-to-100 scale. The MPN-SAF TSS thus had a possible range of 0 to 100.

The primary treatment period is from Day 1 to and including Day 168. The entire treatment period is from Day 1 through the end of treatment. Baseline is defined as the last value on or before the first dose of study drug.

Last Available = Last available assessment on or before the end of the treatment period.
Mean = Mean value of the weekly assessments over the treatment period.

End point type	Secondary

End point timeframe:

Baseline and from Day 1 through end of treatment (up to approximately 232 weeks)

End point values	Cohort 1: Anemia Only	Cohort 2: RBC-Transfusion Dependent	Cohort 3A: Anemia Only (Stable Dose-Ruxolitinib)	Cohort 3B: RBC-Transfusion Dependent (Stable Dose-Ruxolitinib)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	22	21	14	38
Units: Participants				
Primary Treatment Period (Last Available)	2	2	2	9
Entire Treatment Period (Last Available)	2	1	2	7
Primary Treatment Period (Mean)	2	2	3	6
Entire Treatment Period (Mean)	2	2	3	6

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in EQ-5D-5L Utility Score Compared to Baseline

End point title	Mean change in EQ-5D-5L Utility Score Compared to Baseline

End point description:

The European Quality of Life 5D-5L Scale (EQ-5D-5L) assesses general health-related quality of life. Health is defined in 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. Responses are coded so that a '1' indicates no problem, and '5' indicates the most serious problem. The responses for the 5 dimensions are combined in a 5-digit number. The EQ-5D-5L health utility index for this analysis will be derived using the United Kingdom (UK) value sets based on UK time trade-off (TTO) valuation techniques and will use the Decision Support Unit (DSU) model to cross-walk to the EQ-5D-3L value set from the UK to derive a single index value. The EQ-5D-3L health utility index based on the UK population weights range from -0.594 to 1.0 with higher scores indicating higher health utility.

End point type	Secondary

End point timeframe:

Day 169 and End of treatment (up to approximately 232 weeks)

End point values	Cohort 1: Anemia Only	Cohort 2: RBC-Transfusion Dependent	Cohort 3A: Anemia Only (Stable Dose-Ruxolitinib)	Cohort 3B: RBC-Transfusion Dependent (Stable Dose-Ruxolitinib)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11[8]	9[9]	8[10]	14[11]
Units: Score on a scale				

arithmetic mean (standard deviation)				
Day 169	-0.043 (± 0.1466)	-0.063 (± 0.1152)	-0.126 (± 0.1246)	0.005 (± 0.1084)
End of Treatment	-0.029 (± 0.1029)	-0.120 (± 0.1740)	-0.129 (± 0.1812)	-0.103 (± 0.2055)

Notes:

[8] - Day 169 (n= 11)
End of Treatment (n=10)
[9] - Day 169 (n= 9)
End of Treatment (n=9)
[10] - Day 169 (n= 6)
End of Treatment (n=8)
[11] - Day 169 (n= 14)
End of Treatment (n=12)

Statistical analyses

No statistical analyses for this end point

Secondary: The Number of Participants Treatment-Emergent Adverse Events (TEAE)

End point title	The Number of Participants Treatment-Emergent Adverse Events (TEAE)

End point description:

TEAE is defined as any AEs that begin or worsen on or after the day of the first dose. An AE is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. An SAE is any AE occurring at any dose that: results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, or constitutes an important medical event. The severity/intensity of AEs will be graded based on the Common Terminology Criteria for Adverse Events (CTCAE,
version 4.03) where Grade 3 = Severe, Grade 4 = Life-threatening, and Grade 5 = Death.

End point type	Secondary

End point timeframe:

From first dose through 42 days after the last dose (up to approximately 238 weeks)

End point values	Cohort 1: Anemia Only	Cohort 2: RBC-Transfusion Dependent	Cohort 3A: Anemia Only (Stable Dose-Ruxolitinib)	Cohort 3B: RBC-Transfusion Dependent (Stable Dose-Ruxolitinib)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	22	21	14	38
Units: Participants				
TEAE	21	19	13	36
Treatment-Related TEAE	14	5	7	19
Serious TEAE	8	8	4	17
Treatment-Related Serious TEAE	1	0	0	2
TEAE Grade >=3	9	11	4	24
Treatment-Related TEAE Grade >=3	0	1	2	7
TEAE Leading to Dose Interruption	2	2	3	12
Treatment-Related TEAE to Dose Interruption	1	1	1	4
TEAE Leading to Dose Reduction	1	0	2	2
Treatment-Related TEAE Leading to Dose Reduction	1	0	2	2

TEAE Leading to Study Drug Withdrawn	1	2	1	5
Treatment-Related TEAE to Study Drug Withdrawn	0	0	0	1
TEAE Leading to Death	1	2	0	5
Treatment-Related TEAE Leading to Death	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: V1/F (L)

End point title	V1/F (L)

End point description:

Apparent volume of distribution of the central compartment

End point type	Secondary

End point timeframe:

C1D1 (pre-dose), C1D8, C1D15, C2D1, C4D1, C5D1, C5D8, C6D1, and C8D1, day 169, Day 1 of every 4th Extension Phase treatment cycle for up to 1 year post the date of first dose of luspatercept, and end of treatment.

End point values	Cohort 1: Anemia Only	Cohort 2: RBC-Transfusion Dependent	Cohort 3A: Anemia Only (Stable Dose-Ruxolitinib)	Cohort 3B: RBC-Transfusion Dependent (Stable Dose-Ruxolitinib)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	22	21	14	38
Units: Liter				
geometric mean (geometric coefficient of variation)	11.65 (± 53)	10.15 (± 31)	11.36 (± 34)	10.84 (± 39)

Statistical analyses

No statistical analyses for this end point

Secondary: CL/F (L/day)

End point title	CL/F (L/day)

End point description:

Apparent clearance

End point type	Secondary

End point timeframe:

C1D1 (pre-dose), C1D8, C1D15, C2D1, C4D1, C5D1, C5D8, C6D1, and C8D1, day 169, Day 1 of every 4th Extension Phase treatment cycle for up to 1 year post the date of first dose of luspatercept, and end of treatment.

End point values	Cohort 1: Anemia Only	Cohort 2: RBC-Transfusion Dependent	Cohort 3A: Anemia Only (Stable Dose-Ruxolitinib)	Cohort 3B: RBC-Transfusion Dependent (Stable Dose-Ruxolitinib)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	22	21	14	38
Units: L/day				
geometric mean (geometric coefficient of variation)	0.61 (± 51)	0.53 (± 31)	0.46 (± 34)	0.44 (± 38)

Statistical analyses

No statistical analyses for this end point

Secondary: T1/2 (day)

End point title	T1/2 (day)

End point description:

Elimination half-life

End point type	Secondary

End point timeframe:

C1D1 (pre-dose), C1D8, C1D15, C2D1, C4D1, C5D1, C5D8, C6D1, and C8D1, day 169, Day 1 of every 4th Extension Phase treatment cycle for up to 1 year post the date of first dose of luspatercept, and end of treatment.

End point values	Cohort 1: Anemia Only	Cohort 2: RBC-Transfusion Dependent	Cohort 3A: Anemia Only (Stable Dose-Ruxolitinib)	Cohort 3B: RBC-Transfusion Dependent (Stable Dose-Ruxolitinib)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	22	21	14	38
Units: Day				
geometric mean (geometric coefficient of variation)	13.28 (± 2.4)	13.3 (± 1.4)	16.96 (± 2.1)	16.98 (± 2.2)

Statistical analyses

No statistical analyses for this end point

Secondary: Tmax (day)

End point title	Tmax (day)

End point description:

Time to reach the maximum concentration for the first dose (Cmax)

End point type	Secondary

End point timeframe:

C1D1 (pre-dose), C1D8, C1D15, C2D1, C4D1, C5D1, C5D8, C6D1, and C8D1, day 169, Day 1 of every 4th Extension Phase treatment cycle for up to 1 year post the date of first dose of luspatercept, and end of treatment.

End point values	Cohort 1: Anemia Only	Cohort 2: RBC-Transfusion Dependent	Cohort 3A: Anemia Only (Stable Dose-Ruxolitinib)	Cohort 3B: RBC-Transfusion Dependent (Stable Dose-Ruxolitinib)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	22	21	14	38
Units: Day				
median (full range (min-max))	6.72 (4.84 to 10.01)	7.38 (5.75 to 9.14)	7.85 (6.17 to 9.54)	7.96 (5.24 to 11.34)

Statistical analyses

No statistical analyses for this end point

Secondary: Ka (day-1)

End point title	Ka (day-1)

End point description:

First-order rate constant of absorption

End point type	Secondary

End point timeframe:

C1D1 (pre-dose), C1D8, C1D15, C2D1, C4D1, C5D1, C5D8, C6D1, and C8D1, day 169, Day 1 of every 4th Extension Phase treatment cycle for up to 1 year post the date of first dose of luspatercept, and end of treatment.

End point values	Cohort 1: Anemia Only	Cohort 2: RBC-Transfusion Dependent	Cohort 3A: Anemia Only (Stable Dose-Ruxolitinib)	Cohort 3B: RBC-Transfusion Dependent (Stable Dose-Ruxolitinib)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	22	21	14	38
Units: Day-1				
geometric mean (geometric coefficient of variation)	0.3 (± 37)	0.28 (± 19)	0.29 (± 21)	0.28 (± 28)

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax.ss (µg/mL)

End point title	Cmax.ss (µg/mL)

End point description:

Maximum concentration for the first dose (Cmax) at steady state for the starting dose

End point type	Secondary

End point timeframe:

C1D1 (pre-dose), C1D8, C1D15, C2D1, C4D1, C5D1, C5D8, C6D1, and C8D1, day 169, Day 1 of every 4th Extension Phase treatment cycle for up to 1 year post the date of first dose of luspatercept, and end of treatment.

End point values	Cohort 1: Anemia Only	Cohort 2: RBC-Transfusion Dependent	Cohort 3A: Anemia Only (Stable Dose-Ruxolitinib)	Cohort 3B: RBC-Transfusion Dependent (Stable Dose-Ruxolitinib)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	22	21	14	38
Units: µg/mL				
geometric mean (geometric coefficient of variation)	7.28 (± 42)	7.72 (± 21)	9.45 (± 24)	9.6 (± 32)

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax (µg/mL)

End point title	Cmax (µg/mL)

End point description:

Maximum concentration for the first dose

End point type	Secondary

End point timeframe:

C1D1 (pre-dose), C1D8, C1D15, C2D1, C4D1, C5D1, C5D8, C6D1, and C8D1, day 169, Day 1 of every 4th Extension Phase treatment cycle for up to 1 year post the date of first dose of luspatercept, and end of treatment.

End point values	Cohort 1: Anemia Only	Cohort 2: RBC-Transfusion Dependent	Cohort 3A: Anemia Only (Stable Dose-Ruxolitinib)	Cohort 3B: RBC-Transfusion Dependent (Stable Dose-Ruxolitinib)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	22	21	14	38
Units: µg/mL				
geometric mean (geometric coefficient of variation)	4.41 (± 39)	4.68 (± 20)	4.96 (± 23)	5.01 (± 30)

Statistical analyses

No statistical analyses for this end point

Secondary: AUCss (day* µg/mL)

End point title	AUCss (day* µg/mL)

End point description:

Area under the concentration-time curve at the steady state for the starting dose

End point type	Secondary

End point timeframe:

C1D1 (pre-dose), C1D8, C1D15, C2D1, C4D1, C5D1, C5D8, C6D1, and C8D1, day 169, Day 1 of every 4th Extension Phase treatment cycle for up to 1 year post the date of first dose of luspatercept, and end of treatment.

End point values	Cohort 1: Anemia Only	Cohort 2: RBC-Transfusion Dependent	Cohort 3A: Anemia Only (Stable Dose-Ruxolitinib)	Cohort 3B: RBC-Transfusion Dependent (Stable Dose-Ruxolitinib)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	22	21	14	38
Units: day* µg/mL				
geometric mean (geometric coefficient of variation)	123 (± 47)	132 (± 24)	168 (± 26)	171 (± 35)

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Changes in Hemoglobin over the study compared to baseline in the absence of RBC transfusions (Cohorts 1 and 3A)

End point title	Mean Changes in Hemoglobin over the study compared to baseline in the absence of RBC transfusions (Cohorts 1 and 3A)[12]

End point description:

Calculated based on average hemoglobin measurements collected during the treatment period.The

primary treatment period is from Day 1 to and including Day 168. The entire treatment period is from Day 1 through the end of treatment. The baseline RBC transfusion is defined as average number of RBC units/28 days over the 84 days period immediately prior to the C1D1 date.

End point type	Secondary

End point timeframe:

Baseline and Day 1 through end of treatment (up to approximately 232 weeks)

Notes:

[12] - 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: Pre-specified for Cohorts 2 and 3B only

End point values	Cohort 1: Anemia Only	Cohort 3A: Anemia Only (Stable Dose-Ruxolitinib)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	14		
Units: Change in hemoglobin (Hgb)				
arithmetic mean (standard deviation)				
Primary Treatment Period	0.795 (± 0.7697)	1.157 (± 0.5178)		
Entire Treatment Period	0.824 (± 0.8613)	1.172 (± 0.5992)		

Statistical analyses

No statistical analyses for this end point

Secondary: The Number of Participants with Antidrug Antibody (ADA) Measurements

End point title	The Number of Participants with Antidrug Antibody (ADA) Measurements

End point description:

The ADA status of a participant during treatment is determined based on the longitudinal ADA results as follows:

Negative: All samples (baseline and post-baseline) are negative.
Positive to treatment-emergent ADA: At least one post-baseline sample is positive if the baseline sample is negative, or at least one post-baseline sample is positive with a titer ≥ 4-fold of the baseline titer if the baseline sample is positive

End point type	Secondary

End point timeframe:

C1D1 (pre- dose), C2D1, C4D1, C6D1, C8D1, Day 1 of every 4th Extension Phase treatment cycle for up to 1 year post the date of first dose of luspatercept, and end of treatment.

End point values	Cohort 1: Anemia Only	Cohort 2: RBC-Transfusion Dependent	Cohort 3A: Anemia Only (Stable Dose-Ruxolitinib)	Cohort 3B: RBC-Transfusion Dependent (Stable Dose-Ruxolitinib)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	22	21	14	38
Units: Participants				
Positive	1	2	2	2
Negative	21	19	12	36

Statistical analyses

No statistical analyses for this end point

Secondary: The Number of Participants with a Mean Hemoglobin Increase >= 1.5 g/dL from Baseline Over any Consecutive 84-day Period (Cohorts 1 and 3A)

End point title	The Number of Participants with a Mean Hemoglobin Increase >= 1.5 g/dL from Baseline Over any Consecutive 84-day Period (Cohorts 1 and 3A)[13]

End point description:

The number of participants with a Mean hemoglobin increase of ≥ 1.5 g/dL from baseline over any consecutive 84-day period without an RBC transfusion. The primary treatment period is from Day 1 to and including Day 168. The entire treatment period is from Day 1 through the end of treatment. Baseline is defined as all non-missing Hgb records within 28 days on or prior to date of first dose (or date of enrollment if not treated).

End point type	Secondary

End point timeframe:

Baseline and Day 1 through end of treatment (up to approximately 232 weeks)

Notes:

[13] - 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: Pre-specified for Cohorts 2 and 3B only

End point values	Cohort 1: Anemia Only	Cohort 3A: Anemia Only (Stable Dose-Ruxolitinib)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	14		
Units: Participants				
Primary Treatment Period	5	6		
Entire Treatment Period	6	7		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

SAEs and NSAEs were assessed from first dose through 42 days after the last dose (up to approximately 238 weeks)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	Cohort 1: Anemia Only

Reporting group description:

Participants receive a starting dose level of luspatercept at 1.0 mg/kg subcutaneous injection every 3 weeks (administered on Day 1 of each 21-day treatment cycle). The starting dose can be titrated (increased) during the Treatment Period to 1.33 mg/kg, up to a maximum of 1.75 mg/kg, provided that the participant meets the appropriate criteria. The participant's dose may also be delayed, reduced, or discontinued, depending on the specific criteria.

Reporting group title	Cohort 3B: RBC-Transfusion Dependent (Stable Dose-Ruxolitinib)

Reporting group description:

Participants receive a starting dose level of luspatercept at 1.0 mg/kg subcutaneous injection every 3 weeks (administered on Day 1 of each 21-day treatment cycle) while being on a stable dose of ruxolitinib for at least 112 days immediately prior to the enrollment date. The starting dose can be titrated (increased) during the Treatment Period to 1.33 mg/kg, up to a maximum of 1.75 mg/kg, provided that the participant meets the appropriate criteria. The participant's dose may also be delayed, reduced, or discontinued, depending on the specific criteria.

Reporting group title	Cohort 2: RBC-Transfusion Dependent

Reporting group description:

Participants receive a starting dose level of luspatercept at 1.0 mg/kg subcutaneous injection every 3 weeks (administered on Day 1 of each 21-day treatment cycle). The starting dose can be titrated (increased) during the Treatment Period to 1.33 mg/kg, up to a maximum of 1.75 mg/kg, provided that the participant meets the appropriate criteria. The participant's dose may also be delayed, reduced, or discontinued, depending on the specific criteria.

Reporting group title	Cohort 3A: Anemia Only (Stable Dose-Ruxolitinib)

Reporting group description:

Participants receive a starting dose level of luspatercept at 1.0 mg/kg subcutaneous injection every 3 weeks (administered on Day 1 of each 21-day treatment cycle) while being on a stable dose of ruxolitinib for at least 112 days immediately prior to the enrollment date. The starting dose can be titrated (increased) during the Treatment Period to 1.33 mg/kg, up to a maximum of 1.75 mg/kg, provided that the participant meets the appropriate criteria. The participant's dose may also be delayed, reduced, or discontinued, depending on the specific criteria.

Serious adverse events	Cohort 1: Anemia Only	Cohort 3B: RBC-Transfusion Dependent (Stable Dose-Ruxolitinib)	Cohort 2: RBC-Transfusion Dependent
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 22 (36.36%)	17 / 38 (44.74%)	8 / 21 (38.10%)
number of deaths (all causes)	6	13	12
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Acute leukaemia			
subjects affected / exposed	0 / 22 (0.00%)	0 / 38 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal cell carcinoma			
subjects affected / exposed	0 / 22 (0.00%)	2 / 38 (5.26%)	0 / 21 (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
Bowen's disease			
subjects affected / exposed	0 / 22 (0.00%)	1 / 38 (2.63%)	0 / 21 (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	0 / 22 (0.00%)	1 / 38 (2.63%)	0 / 21 (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			
subjects affected / exposed	0 / 22 (0.00%)	1 / 38 (2.63%)	0 / 21 (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
Skin squamous cell carcinoma recurrent			
subjects affected / exposed	0 / 22 (0.00%)	1 / 38 (2.63%)	0 / 21 (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
Chloroma			
subjects affected / exposed	0 / 22 (0.00%)	0 / 38 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic embolus			
subjects affected / exposed	1 / 22 (4.55%)	0 / 38 (0.00%)	0 / 21 (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			
Systemic inflammatory response syndrome			
subjects affected / exposed	1 / 22 (4.55%)	0 / 38 (0.00%)	0 / 21 (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
Non-cardiac chest pain			
subjects affected / exposed	0 / 22 (0.00%)	0 / 38 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 22 (0.00%)	1 / 38 (2.63%)	0 / 21 (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
Gait disturbance			
subjects affected / exposed	1 / 22 (4.55%)	0 / 38 (0.00%)	0 / 21 (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
Fatigue			
subjects affected / exposed	0 / 22 (0.00%)	0 / 38 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthenia			
subjects affected / exposed	0 / 22 (0.00%)	0 / 38 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	1 / 22 (4.55%)	1 / 38 (2.63%)	0 / 21 (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
Pulmonary embolism			

subjects affected / exposed	0 / 22 (0.00%)	0 / 38 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 38 (2.63%)	0 / 21 (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
Epistaxis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 38 (2.63%)	0 / 21 (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
Acute respiratory failure			
subjects affected / exposed	0 / 22 (0.00%)	1 / 38 (2.63%)	0 / 21 (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
Dyspnoea			
subjects affected / exposed	1 / 22 (4.55%)	1 / 38 (2.63%)	0 / 21 (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
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 22 (0.00%)	1 / 38 (2.63%)	0 / 21 (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			
Troponin T increased			
subjects affected / exposed	0 / 22 (0.00%)	1 / 38 (2.63%)	0 / 21 (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
Ejection fraction decreased			
subjects affected / exposed	0 / 22 (0.00%)	1 / 38 (2.63%)	0 / 21 (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
Injury, poisoning and procedural			

complications			
Subdural haematoma			
subjects affected / exposed	1 / 22 (4.55%)	0 / 38 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Post procedural haemorrhage			
subjects affected / exposed	1 / 22 (4.55%)	0 / 38 (0.00%)	0 / 21 (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
Humerus fracture			
subjects affected / exposed	0 / 22 (0.00%)	0 / 38 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ankle fracture			
subjects affected / exposed	0 / 22 (0.00%)	1 / 38 (2.63%)	0 / 21 (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 disorders			
Cardiac failure			
subjects affected / exposed	0 / 22 (0.00%)	1 / 38 (2.63%)	0 / 21 (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	0 / 22 (0.00%)	1 / 38 (2.63%)	0 / 21 (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
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 22 (0.00%)	1 / 38 (2.63%)	0 / 21 (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
Disturbance in attention			

subjects affected / exposed	0 / 22 (0.00%)	1 / 38 (2.63%)	0 / 21 (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 / 22 (0.00%)	1 / 38 (2.63%)	2 / 21 (9.52%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 22 (0.00%)	1 / 38 (2.63%)	0 / 21 (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
Somnolence			
subjects affected / exposed	0 / 22 (0.00%)	0 / 38 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	0 / 22 (0.00%)	1 / 38 (2.63%)	0 / 21 (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
Haemorrhage intracranial			
subjects affected / exposed	0 / 22 (0.00%)	0 / 38 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 38 (2.63%)	0 / 21 (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
Anaemia			
subjects affected / exposed	0 / 22 (0.00%)	0 / 38 (0.00%)	2 / 21 (9.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			

Diarrhoea			
subjects affected / exposed	0 / 22 (0.00%)	1 / 38 (2.63%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	1 / 22 (4.55%)	0 / 38 (0.00%)	0 / 21 (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
Diverticular perforation			
subjects affected / exposed	1 / 22 (4.55%)	1 / 38 (2.63%)	0 / 21 (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
Small intestinal haemorrhage			
subjects affected / exposed	0 / 22 (0.00%)	1 / 38 (2.63%)	0 / 21 (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
Enteritis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 38 (2.63%)	0 / 21 (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
Stomatitis			
subjects affected / exposed	1 / 22 (4.55%)	0 / 38 (0.00%)	0 / 21 (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			
Hepatic failure			
subjects affected / exposed	0 / 22 (0.00%)	1 / 38 (2.63%)	0 / 21 (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
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 22 (4.55%)	1 / 38 (2.63%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0

Haematuria			
subjects affected / exposed	0 / 22 (0.00%)	0 / 38 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute kidney injury			
subjects affected / exposed	0 / 22 (0.00%)	1 / 38 (2.63%)	0 / 21 (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
Musculoskeletal and connective tissue disorders			
Chest wall haematoma			
subjects affected / exposed	0 / 22 (0.00%)	1 / 38 (2.63%)	0 / 21 (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
Infections and infestations			
Biliary tract infection			
subjects affected / exposed	0 / 22 (0.00%)	1 / 38 (2.63%)	0 / 21 (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
Pneumonia			
subjects affected / exposed	1 / 22 (4.55%)	1 / 38 (2.63%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Kidney infection			
subjects affected / exposed	0 / 22 (0.00%)	1 / 38 (2.63%)	0 / 21 (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
Influenza			
subjects affected / exposed	1 / 22 (4.55%)	0 / 38 (0.00%)	0 / 21 (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
Gastroenteritis			
subjects affected / exposed	0 / 22 (0.00%)	0 / 38 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Escherichia bacteraemia			
subjects affected / exposed	1 / 22 (4.55%)	0 / 38 (0.00%)	0 / 21 (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
Pyelonephritis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 38 (2.63%)	0 / 21 (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
Cerebral toxoplasmosis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 38 (2.63%)	0 / 21 (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
Pulmonary sepsis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 38 (2.63%)	0 / 21 (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
Sepsis			
subjects affected / exposed	1 / 22 (4.55%)	1 / 38 (2.63%)	0 / 21 (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
Septic shock			
subjects affected / exposed	0 / 22 (0.00%)	1 / 38 (2.63%)	0 / 21 (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
Diverticulitis			
subjects affected / exposed	1 / 22 (4.55%)	0 / 38 (0.00%)	0 / 21 (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
Urosepsis			
subjects affected / exposed	0 / 22 (0.00%)	0 / 38 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			

subjects affected / exposed	2 / 22 (9.09%)	0 / 38 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Cohort 3A: Anemia Only (Stable Dose-Ruxolitinib)		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 14 (28.57%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute leukaemia			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Basal cell carcinoma			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Bowen's disease			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Squamous cell carcinoma			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin squamous cell carcinoma recurrent			

subjects affected / exposed	0 / 14 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Chloroma				
subjects affected / exposed	0 / 14 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Aortic embolus				
subjects affected / exposed	0 / 14 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Systemic inflammatory response syndrome				
subjects affected / exposed	0 / 14 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Non-cardiac chest pain				
subjects affected / exposed	0 / 14 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Multiple organ dysfunction syndrome				
subjects affected / exposed	0 / 14 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gait disturbance				
subjects affected / exposed	0 / 14 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Fatigue				
subjects affected / exposed	0 / 14 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Asthenia				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Respiratory failure				
subjects affected / exposed	0 / 14 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonitis				
subjects affected / exposed	0 / 14 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Epistaxis				
subjects affected / exposed	0 / 14 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Acute respiratory failure				
subjects affected / exposed	0 / 14 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	0 / 14 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Confusional state				
subjects affected / exposed	0 / 14 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Investigations			
Troponin T increased			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ejection fraction decreased			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Subdural haematoma			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Post procedural haemorrhage			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Humerus fracture			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ankle fracture			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac failure congestive			

subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Disturbance in attention			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Somnolence			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ischaemic stroke			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haemorrhage intracranial			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			

Leukopenia				
subjects affected / exposed	0 / 14 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Anaemia				
subjects affected / exposed	0 / 14 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Diarrhoea				
subjects affected / exposed	0 / 14 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Abdominal pain				
subjects affected / exposed	0 / 14 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diverticular perforation				
subjects affected / exposed	0 / 14 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Small intestinal haemorrhage				
subjects affected / exposed	0 / 14 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Enteritis				
subjects affected / exposed	0 / 14 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Stomatitis				
subjects affected / exposed	0 / 14 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				

Hepatic failure			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haematuria			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Acute kidney injury			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Chest wall haematoma			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Biliary tract infection			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Kidney infection			

subjects affected / exposed	0 / 14 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Influenza				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	0 / 14 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Escherichia bacteraemia				
subjects affected / exposed	0 / 14 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis				
subjects affected / exposed	0 / 14 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cerebral toxoplasmosis				
subjects affected / exposed	0 / 14 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary sepsis				
subjects affected / exposed	0 / 14 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	0 / 14 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Septic shock				

subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diverticulitis			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urosepsis			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Cohort 1: Anemia Only	Cohort 3B: RBC-Transfusion Dependent (Stable Dose-Ruxolitinib)	Cohort 2: RBC-Transfusion Dependent
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 22 (95.45%)	33 / 38 (86.84%)	19 / 21 (90.48%)
Vascular disorders			
Hypertension			
subjects affected / exposed	5 / 22 (22.73%)	9 / 38 (23.68%)	3 / 21 (14.29%)
occurrences (all)	6	16	3
Hypotension			
subjects affected / exposed	0 / 22 (0.00%)	4 / 38 (10.53%)	0 / 21 (0.00%)
occurrences (all)	0	6	0
General disorders and administration site conditions			
Early satiety			
subjects affected / exposed	0 / 22 (0.00%)	2 / 38 (5.26%)	0 / 21 (0.00%)
occurrences (all)	0	3	0
Asthenia			

subjects affected / exposed	1 / 22 (4.55%)	5 / 38 (13.16%)	3 / 21 (14.29%)
occurrences (all)	1	7	3
Influenza like illness			
subjects affected / exposed	1 / 22 (4.55%)	1 / 38 (2.63%)	1 / 21 (4.76%)
occurrences (all)	1	1	1
Injection site pain			
subjects affected / exposed	0 / 22 (0.00%)	0 / 38 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Non-cardiac chest pain			
subjects affected / exposed	2 / 22 (9.09%)	1 / 38 (2.63%)	0 / 21 (0.00%)
occurrences (all)	2	1	0
Oedema peripheral			
subjects affected / exposed	3 / 22 (13.64%)	5 / 38 (13.16%)	0 / 21 (0.00%)
occurrences (all)	3	5	0
Pain			
subjects affected / exposed	0 / 22 (0.00%)	0 / 38 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Peripheral swelling			
subjects affected / exposed	0 / 22 (0.00%)	0 / 38 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Pyrexia			
subjects affected / exposed	5 / 22 (22.73%)	7 / 38 (18.42%)	1 / 21 (4.76%)
occurrences (all)	7	10	1
Chills			
subjects affected / exposed	0 / 22 (0.00%)	1 / 38 (2.63%)	1 / 21 (4.76%)
occurrences (all)	0	1	1
Fatigue			
subjects affected / exposed	4 / 22 (18.18%)	6 / 38 (15.79%)	5 / 21 (23.81%)
occurrences (all)	4	12	5
Respiratory, thoracic and mediastinal disorders			
Nasal congestion			
subjects affected / exposed	0 / 22 (0.00%)	1 / 38 (2.63%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Oropharyngeal pain			

subjects affected / exposed	0 / 22 (0.00%)	1 / 38 (2.63%)	1 / 21 (4.76%)
occurrences (all)	0	1	1
Sleep apnoea syndrome			
subjects affected / exposed	2 / 22 (9.09%)	0 / 38 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Epistaxis			
subjects affected / exposed	1 / 22 (4.55%)	4 / 38 (10.53%)	2 / 21 (9.52%)
occurrences (all)	1	4	2
Dyspnoea			
subjects affected / exposed	4 / 22 (18.18%)	9 / 38 (23.68%)	5 / 21 (23.81%)
occurrences (all)	4	10	5
Cough			
subjects affected / exposed	3 / 22 (13.64%)	4 / 38 (10.53%)	5 / 21 (23.81%)
occurrences (all)	5	7	6
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 22 (0.00%)	2 / 38 (5.26%)	0 / 21 (0.00%)
occurrences (all)	0	3	0
Depression			
subjects affected / exposed	2 / 22 (9.09%)	0 / 38 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Insomnia			
subjects affected / exposed	1 / 22 (4.55%)	1 / 38 (2.63%)	2 / 21 (9.52%)
occurrences (all)	1	1	2
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 22 (0.00%)	7 / 38 (18.42%)	2 / 21 (9.52%)
occurrences (all)	0	10	2
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 22 (0.00%)	2 / 38 (5.26%)	1 / 21 (4.76%)
occurrences (all)	0	2	1
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 22 (4.55%)	1 / 38 (2.63%)	1 / 21 (4.76%)
occurrences (all)	1	1	1
Blood bilirubin increased			

subjects affected / exposed	0 / 22 (0.00%)	2 / 38 (5.26%)	1 / 21 (4.76%)
occurrences (all)	0	3	1
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 22 (0.00%)	0 / 38 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Blood creatinine increased			
subjects affected / exposed	1 / 22 (4.55%)	0 / 38 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Blood glucose increased			
subjects affected / exposed	0 / 22 (0.00%)	0 / 38 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Weight decreased			
subjects affected / exposed	1 / 22 (4.55%)	1 / 38 (2.63%)	2 / 21 (9.52%)
occurrences (all)	1	1	2
White blood cell count increased			
subjects affected / exposed	0 / 22 (0.00%)	2 / 38 (5.26%)	0 / 21 (0.00%)
occurrences (all)	0	2	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 22 (0.00%)	4 / 38 (10.53%)	2 / 21 (9.52%)
occurrences (all)	0	4	2
Fall			
subjects affected / exposed	1 / 22 (4.55%)	3 / 38 (7.89%)	2 / 21 (9.52%)
occurrences (all)	2	10	4
Lower limb fracture			
subjects affected / exposed	0 / 22 (0.00%)	0 / 38 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Disturbance in attention			
subjects affected / exposed	0 / 22 (0.00%)	2 / 38 (5.26%)	0 / 21 (0.00%)
occurrences (all)	0	2	0
Dizziness			
subjects affected / exposed	2 / 22 (9.09%)	7 / 38 (18.42%)	2 / 21 (9.52%)
occurrences (all)	2	11	2
Headache			

subjects affected / exposed	3 / 22 (13.64%)	3 / 38 (7.89%)	1 / 21 (4.76%)
occurrences (all)	3	3	1
Memory impairment			
subjects affected / exposed	0 / 22 (0.00%)	0 / 38 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 22 (13.64%)	1 / 38 (2.63%)	1 / 21 (4.76%)
occurrences (all)	3	1	1
Splenomegaly			
subjects affected / exposed	0 / 22 (0.00%)	0 / 38 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Thrombocytopenia			
subjects affected / exposed	3 / 22 (13.64%)	11 / 38 (28.95%)	3 / 21 (14.29%)
occurrences (all)	3	17	3
Neutropenia			
subjects affected / exposed	0 / 22 (0.00%)	2 / 38 (5.26%)	1 / 21 (4.76%)
occurrences (all)	0	2	1
Eye disorders			
Glaucoma			
subjects affected / exposed	0 / 22 (0.00%)	0 / 38 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	2 / 22 (9.09%)	2 / 38 (5.26%)	0 / 21 (0.00%)
occurrences (all)	2	2	0
Abdominal discomfort			
subjects affected / exposed	1 / 22 (4.55%)	1 / 38 (2.63%)	1 / 21 (4.76%)
occurrences (all)	1	1	1
Abdominal distension			
subjects affected / exposed	1 / 22 (4.55%)	2 / 38 (5.26%)	0 / 21 (0.00%)
occurrences (all)	1	2	0
Abdominal pain			
subjects affected / exposed	5 / 22 (22.73%)	4 / 38 (10.53%)	2 / 21 (9.52%)
occurrences (all)	6	5	2
Constipation			

subjects affected / exposed	2 / 22 (9.09%)	1 / 38 (2.63%)	2 / 21 (9.52%)
occurrences (all)	2	1	2
Diarrhoea			
subjects affected / exposed	3 / 22 (13.64%)	11 / 38 (28.95%)	4 / 21 (19.05%)
occurrences (all)	4	17	10
Dyspepsia			
subjects affected / exposed	1 / 22 (4.55%)	0 / 38 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Dysphagia			
subjects affected / exposed	0 / 22 (0.00%)	0 / 38 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	2
Mouth haemorrhage			
subjects affected / exposed	2 / 22 (9.09%)	0 / 38 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Nausea			
subjects affected / exposed	2 / 22 (9.09%)	6 / 38 (15.79%)	3 / 21 (14.29%)
occurrences (all)	4	8	3
Skin and subcutaneous tissue disorders			
Ecchymosis			
subjects affected / exposed	0 / 22 (0.00%)	0 / 38 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Erythema			
subjects affected / exposed	2 / 22 (9.09%)	1 / 38 (2.63%)	0 / 21 (0.00%)
occurrences (all)	2	1	0
Night sweats			
subjects affected / exposed	2 / 22 (9.09%)	2 / 38 (5.26%)	2 / 21 (9.52%)
occurrences (all)	3	3	2
Pruritus			
subjects affected / exposed	3 / 22 (13.64%)	3 / 38 (7.89%)	2 / 21 (9.52%)
occurrences (all)	3	3	3
Seborrhoeic dermatitis			
subjects affected / exposed	0 / 22 (0.00%)	0 / 38 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Pollakiuria			

subjects affected / exposed	1 / 22 (4.55%)	2 / 38 (5.26%)	0 / 21 (0.00%)
occurrences (all)	1	3	0
Chronic kidney disease			
subjects affected / exposed	0 / 22 (0.00%)	3 / 38 (7.89%)	0 / 21 (0.00%)
occurrences (all)	0	3	0
Acute kidney injury			
subjects affected / exposed	2 / 22 (9.09%)	0 / 38 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	2 / 22 (9.09%)	2 / 38 (5.26%)	0 / 21 (0.00%)
occurrences (all)	2	2	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	3 / 22 (13.64%)	2 / 38 (5.26%)	1 / 21 (4.76%)
occurrences (all)	4	2	1
Neck pain			
subjects affected / exposed	1 / 22 (4.55%)	2 / 38 (5.26%)	1 / 21 (4.76%)
occurrences (all)	1	2	1
Neck mass			
subjects affected / exposed	0 / 22 (0.00%)	0 / 38 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Myalgia			
subjects affected / exposed	3 / 22 (13.64%)	4 / 38 (10.53%)	0 / 21 (0.00%)
occurrences (all)	3	4	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 22 (0.00%)	2 / 38 (5.26%)	0 / 21 (0.00%)
occurrences (all)	0	2	0
Muscle spasms			
subjects affected / exposed	0 / 22 (0.00%)	1 / 38 (2.63%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Bursitis			
subjects affected / exposed	0 / 22 (0.00%)	0 / 38 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Bone pain			

subjects affected / exposed	4 / 22 (18.18%)	4 / 38 (10.53%)	2 / 21 (9.52%)
occurrences (all)	5	5	2
Arthralgia			
subjects affected / exposed	2 / 22 (9.09%)	6 / 38 (15.79%)	0 / 21 (0.00%)
occurrences (all)	2	6	0
Pain in extremity			
subjects affected / exposed	1 / 22 (4.55%)	3 / 38 (7.89%)	1 / 21 (4.76%)
occurrences (all)	1	4	1
Spinal pain			
subjects affected / exposed	0 / 22 (0.00%)	2 / 38 (5.26%)	0 / 21 (0.00%)
occurrences (all)	0	2	0
Infections and infestations			
Abscess limb			
subjects affected / exposed	0 / 22 (0.00%)	1 / 38 (2.63%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Cellulitis			
subjects affected / exposed	0 / 22 (0.00%)	2 / 38 (5.26%)	0 / 21 (0.00%)
occurrences (all)	0	2	0
Cystitis			
subjects affected / exposed	1 / 22 (4.55%)	1 / 38 (2.63%)	0 / 21 (0.00%)
occurrences (all)	5	2	0
Nasopharyngitis			
subjects affected / exposed	1 / 22 (4.55%)	2 / 38 (5.26%)	0 / 21 (0.00%)
occurrences (all)	1	2	0
Pyelonephritis			
subjects affected / exposed	0 / 22 (0.00%)	0 / 38 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Sinusitis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 38 (2.63%)	1 / 21 (4.76%)
occurrences (all)	0	1	1
Tooth infection			
subjects affected / exposed	0 / 22 (0.00%)	0 / 38 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	2 / 22 (9.09%)	2 / 38 (5.26%)	2 / 21 (9.52%)
occurrences (all)	2	2	2

Urinary tract infection			
subjects affected / exposed	2 / 22 (9.09%)	3 / 38 (7.89%)	4 / 21 (19.05%)
occurrences (all)	2	3	6
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 22 (4.55%)	2 / 38 (5.26%)	1 / 21 (4.76%)
occurrences (all)	1	2	1
Dehydration			
subjects affected / exposed	2 / 22 (9.09%)	2 / 38 (5.26%)	0 / 21 (0.00%)
occurrences (all)	2	3	0
Hyponatraemia			
subjects affected / exposed	0 / 22 (0.00%)	0 / 38 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Gout			
subjects affected / exposed	0 / 22 (0.00%)	0 / 38 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	2
Hyperglycaemia			
subjects affected / exposed	1 / 22 (4.55%)	1 / 38 (2.63%)	0 / 21 (0.00%)
occurrences (all)	1	2	0
Hyperkalaemia			
subjects affected / exposed	2 / 22 (9.09%)	3 / 38 (7.89%)	1 / 21 (4.76%)
occurrences (all)	3	4	1
Hypernatraemia			
subjects affected / exposed	0 / 22 (0.00%)	0 / 38 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Hyperuricaemia			
subjects affected / exposed	2 / 22 (9.09%)	3 / 38 (7.89%)	2 / 21 (9.52%)
occurrences (all)	2	4	2
Hypocalcaemia			
subjects affected / exposed	0 / 22 (0.00%)	3 / 38 (7.89%)	0 / 21 (0.00%)
occurrences (all)	0	3	0
Hypokalaemia			
subjects affected / exposed	1 / 22 (4.55%)	2 / 38 (5.26%)	0 / 21 (0.00%)
occurrences (all)	1	5	0
Hypomagnesaemia			

subjects affected / exposed	2 / 22 (9.09%)	1 / 38 (2.63%)	1 / 21 (4.76%)
occurrences (all)	2	2	2

Non-serious adverse events	Cohort 3A: Anemia Only (Stable Dose-Ruxolitinib)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 14 (92.86%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	6 / 14 (42.86%)		
occurrences (all)	6		
Hypotension			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
General disorders and administration site conditions			
Early satiety			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
Asthenia			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Influenza like illness			
subjects affected / exposed	3 / 14 (21.43%)		
occurrences (all)	3		
Injection site pain			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Non-cardiac chest pain			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Oedema peripheral			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Pain			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Peripheral swelling			

subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Chills			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Nasal congestion			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Sleep apnoea syndrome			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Epistaxis			
subjects affected / exposed	3 / 14 (21.43%)		
occurrences (all)	3		
Dyspnoea			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	3		
Cough			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Depression			

subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Insomnia			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	2		
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Blood bilirubin increased			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Blood creatinine increased			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
Blood glucose increased			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Weight decreased			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
White blood cell count increased			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			

Contusion subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Fall subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 3		
Lower limb fracture subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Nervous system disorders			
Disturbance in attention subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Dizziness subjects affected / exposed occurrences (all)	3 / 14 (21.43%) 4		
Headache subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 2		
Memory impairment subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Splenomegaly subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 2		
Thrombocytopenia subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Neutropenia subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Eye disorders			

Glaucoma			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	3		
Abdominal discomfort			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Abdominal distension			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Abdominal pain			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
Constipation			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	4 / 14 (28.57%)		
occurrences (all)	5		
Dyspepsia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Dysphagia			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Mouth haemorrhage			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Nausea			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			

Ecchymosis			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Erythema			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Night sweats			
subjects affected / exposed	3 / 14 (21.43%)		
occurrences (all)	3		
Pruritus			
subjects affected / exposed	3 / 14 (21.43%)		
occurrences (all)	3		
Seborrhoeic dermatitis			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Chronic kidney disease			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Acute kidney injury			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
Neck pain			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		

Neck mass			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Musculoskeletal chest pain			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Muscle spasms			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Bursitis			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Bone pain			
subjects affected / exposed	3 / 14 (21.43%)		
occurrences (all)	4		
Arthralgia			
subjects affected / exposed	3 / 14 (21.43%)		
occurrences (all)	3		
Pain in extremity			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Spinal pain			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Abscess limb			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Cellulitis			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Cystitis			

subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Pyelonephritis			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Sinusitis			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	2		
Tooth infection			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
Urinary tract infection			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Dehydration			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Hyponatraemia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Gout			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Hyperglycaemia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		

Hyperkalaemia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Hypernatraemia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Hyperuricaemia			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Hypocalcaemia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Hypokalaemia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Hypomagnesaemia			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 March 2018	Addition of exclusion criterion for a white blood count threshold. Addition of exclusion criterion for a platelet count threshold. Addition of exclusion criterion for subjects on anticoagulant therapy who are not under appropriate control or not on a stable dose of anticoagulant therapy for ≥ 8 weeks up to the enrollment date. Addition of exclusion criterion for subjects on anagrelide within 28 days immediately up to the enrollment date. Addition of exclusion criterion for subjects with a major bleeding event in the last 6 months prior to enrollment. Addition of secondary endpoint to capture changes in hemoglobin over the study compared to baseline in the absence of red blood cell (RBC) transfusions. Addition of minimum number of days between hemoglobin assessments as outlined within Inclusion Criterion 3A. Modified protocol criteria related to dose modification (dose delay, dose reductions, and discontinuation) measures to account for elevated white blood counts at the day of dosing.
18 December 2018	Clarification to collection of exploratory biomarkers in Section 1.4.4, Section 2 (Table 2) and Section 5 (Table 3)
01 August 2019	Expansion of Cohort 3 enrollment. Modifying Cohorts 2 and 3B inclusion criterion. Statistical considerations supporting Cohort 3 expansion. Addition of secondary endpoint to assess mean hemoglobin increase. Modifying dose titration criteria. Adapting clinical benefit criteria to allow subjects to continue in the Extension Phase. Addition of language supporting the ACE-536-LTFU-001 roll-over study. New starting dose level of 1.33 mg/kg. Amended Exclusion Criterion #3 for ruxolitinib dosing in Cohort 3. Added Section 10.9 Monitoring of Toxicity and Study Stopping Rules.
19 February 2020	Prolongation of Extension Phase of the Treatment Period.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported