Clinical trial results:
An Open-Label Phase 2 Study of Itacitinib (INCB039110) in Combination With Low-Dose Ruxolitinib or Itacitinib Alone Following Ruxolitinib in Subjects With Myelofibrosis

Summary

EudraCT number	2017-005109-11
Trial protocol	NL AT
Global end of trial date	01 June 2021

Results information

Result version number	v1 (current)
This version publication date	02 June 2022
First version publication date	02 June 2022

Trial information

Trial identification

Sponsor protocol code	INCB 39110-209

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03144687
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Incyte Corporation
Sponsor organisation address	1801 Augustine Cutoff, Wilmington, United States, 19803
Public contact	Study Director, Incyte Corporation, 1 8554633463, medinfo@incyte.com
Scientific contact	Study Director, Incyte Corporation, 1 8554633463, medinfo@incyte.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	01 June 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 June 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study was to evaluate the efficacy and safety of itacitinib combined with low-dose ruxolitinib or itacitinib alone in participants with myelofibrosis (MF).

Protection of trial subjects:

This study was to be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and conducted in adherence to the study Protocol, Good Clinical Practices as defined in Title 21 of the United States Code of Federal Regulations Parts 11, 50, 54, 56, and 312, as well as International Conference on Harmonization Good Clinical Practice consolidated guidelines (E6) and applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 January 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	United States: 21
Worldwide total number of subjects	23
EEA total number of subjects	2

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)	4

From 65 to 84 years	18
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 9 study centers in the United States, 1 study center in Austria, and 1 study center in the Netherlands.

Pre-assignment

Screening details:

A total of 23 participants with Myelofibrosis (MF) were enrolled in the study and received itacitinib + ruxolitinib (Cohort A) or itacitinib monotherapy (Cohort B).

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 A

Arm description:

Participants with MF who were tolerating a ruxolitinib dose of less than 20 milligrams (mg) daily with no dose increase or no dose modification in the 8 weeks before screening visit received a combination of itacitinib at the dose of 200 mg, orally, once daily (QD) and ruxolitinib, orally, twice daily (BID) at their previous stable dose (must had been < 20 mg daily). Participants continued study treatment until disease progression, unacceptable toxicity, withdrawal of consent, or other Protocol-specified criteria to stop treatment were met.

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

Dosage and administration details:

5, 10, and 15 mg tablets

Investigational medicinal product name	Itacitinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Modified-release tablet
Routes of administration	Oral use

Dosage and administration details:

100 mg tablets

Arm title	Cohort B

Arm description:

Participants with MF who progressed after initial reduction in spleen with ruxolitinib treatment, progressed or discontinued for hematologic toxicities received treatment with itacitinib alone at the dose of 600 mg QD. Participants continued study treatment until disease progression, unacceptable toxicity, withdrawal of consent, or other Protocol-specified criteria to stop treatment were met.

Arm type	Experimental

Investigational medicinal product name	Itacitinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Modified-release tablet
Routes of administration	Oral use

Dosage and administration details:

100 mg tablets

Number of subjects in period 1	Cohort A	Cohort B
Started	13	10
Completed	10	3
Not completed	3	7
Adverse event, serious fatal	-	2
Consent withdrawn by subject	1	3
Physician decision	-	1
Not Reported	2	-
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Cohort A
Reporting group description:	
Participants with MF who were tolerating a ruxolitinib dose of less than 20 milligrams (mg) daily with no dose increase or no dose modification in the 8 weeks before screening visit received a combination of itacitinib at the dose of 200 mg, orally, once daily (QD) and ruxolitinib, orally, twice daily (BID) at their previous stable dose (must had been < 20 mg daily). Participants continued study treatment until disease progression, unacceptable toxicity, withdrawal of consent, or other Protocol-specified criteria to stop treatment were met.	
Reporting group title	Cohort B
Reporting group description:	
Participants with MF who progressed after initial reduction in spleen with ruxolitinib treatment, progressed or discontinued for hematologic toxicities received treatment with itacitinib alone at the dose of 600 mg QD. Participants continued study treatment until disease progression, unacceptable toxicity, withdrawal of consent, or other Protocol-specified criteria to stop treatment were met.	

Reporting group values	Cohort A	Cohort B	Total
Number of subjects	13	10	23
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	3	1	4
From 65-84 years	10	8	18
85 years and over	0	1	1
Age Continuous Units: years			
arithmetic mean	69.8	72.0	
standard deviation	± 6.20	± 7.33	-
Sex: Female, Male Units: participants			
Female	6	7	13
Male	7	3	10
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	1	0	1
Not Hispanic or Latino	12	9	21
Unknown or Not Reported	0	1	1
Race/Ethnicity, Customized Units: Subjects			
White/Caucasian	13	8	21
Other	0	2	2

End points

End points reporting groups

Reporting group title	Cohort A

Reporting group description:

Participants with MF who were tolerating a ruxolitinib dose of less than 20 milligrams (mg) daily with no dose increase or no dose modification in the 8 weeks before screening visit received a combination of itacitinib at the dose of 200 mg, orally, once daily (QD) and ruxolitinib, orally, twice daily (BID) at their previous stable dose (must had been < 20 mg daily). Participants continued study treatment until disease progression, unacceptable toxicity, withdrawal of consent, or other Protocol-specified criteria to stop treatment were met.

Reporting group title	Cohort B

Reporting group description:

Participants with MF who progressed after initial reduction in spleen with ruxolitinib treatment, progressed or discontinued for hematologic toxicities received treatment with itacitinib alone at the dose of 600 mg QD. Participants continued study treatment until disease progression, unacceptable toxicity, withdrawal of consent, or other Protocol-specified criteria to stop treatment were met.

Subject analysis set title	PK: Cohort A (Itacitinib)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received itacitinib at the dose of 200 mg, orally, QD. Participants continued study treatment until disease progression, unacceptable toxicity, withdrawal of consent, or other Protocol-specified criteria to stop treatment were met.

Subject analysis set title	PK: Cohort A (Ruxolitinib)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received ruxolitinib, orally, BID at their previous stable dose (must have been < 20 mg daily). Participants continued study treatment until disease progression, unacceptable toxicity, withdrawal of consent, or other Protocol-specified criteria to stop treatment were met.

Subject analysis set title	PK: Cohort B (Itacitinib)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received itacitinib alone at the dose of 600 mg QD. Participants continued study treatment until disease progression, unacceptable toxicity, withdrawal of consent, or other Protocol-specified criteria to stop treatment were met.

Primary: Change in spleen volume at Week 24 compared to baseline

End point title	Change in spleen volume at Week 24 compared to baseline[1]

End point description:

Spleen volume was measured using magnetic resonance imaging (MRI) or CT scan in participants who were not candidates for MRI or when MRI was not readily available. The MRIs or CTs were read in the central imaging laboratory. Spleen volume was obtained by outlining the circumference of the organ and determining the volume using the technique of least squares. The same method (MRI or CT) was used for a given participant unless a new contraindication to the use of MRI (eg, pacemaker insertion) occurred. A positive value indicates an increase in spleen volume and a negative value indicates a decrease in spleen volume. Here, Overall Number of participants analyzed ("N") signifies participants who were evaluable for this outcome measure.

End point type	Primary

End point timeframe:

Baseline and Week 24

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: Statistical analysis was not conducted.

End point values	Cohort A	Cohort B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	5		
Units: cubic centimeter (cm^3)				
arithmetic mean (standard deviation)	88.7 (± 563.5)	-207 (± 571.3)		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage change in spleen volume at Week 24 compared to baseline

End point title	Percentage change in spleen volume at Week 24 compared to baseline[2]

End point description:

Spleen volume was measured using MRI or CT scan in participants who were not candidates for MRI or when MRI was not readily available. The MRIs or CTs were read in the central imaging laboratory. Spleen volume was obtained by outlining the circumference of the organ and determining the volume using the technique of least squares. The same method (MRI or CT) was used for a given participant unless a new contraindication to the use of MRI (eg, pacemaker insertion) occurred. A positive value indicates an increase in spleen volume and a negative value indicates a decrease in spleen volume. Here, "N" signifies participants who were evaluable for this outcome measure.

End point type	Primary

End point timeframe:

Baseline and Week 24

Notes:

[2] - 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: Statistical analysis was not conducted.

End point values	Cohort A	Cohort B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	5		
Units: percentage change				
arithmetic mean (standard deviation)	6.9 (± 27.49)	-3.0 (± 34.67)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Treatment Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)

End point title	Number of Participants with Treatment Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)

End point description:

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether considered drug related, that occurs after a participant provides informed consent. A TEAE is any AE either reported for the first time or worsening of a pre-existing event after first dose of study drug. An SAE is an AE resulting in: death; initial/prolonged inpatient hospitalization; life-threatening; persistent or significant disability/incapacity; congenital anomaly.

End point type	Secondary

End point timeframe:

up to approximately 40 months (3.3 years)

End point values	Cohort A	Cohort B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	10		
Units: participants				
TEAE	13	10		
SAE	3	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Clinically Significant Changes From Baseline in Laboratory Parameters

End point title	Number of Participants With Clinically Significant Changes From Baseline in Laboratory Parameters

End point description:

Laboratory investigation included hematology, clinical chemistry, coagulation and urinalysis. Clinical significance was determined by the investigator. The number of participants with clinically significant changes from baseline in laboratory parameters were reported.

End point type	Secondary

End point timeframe:

up to approximately 40 months (3.3 years)

End point values	Cohort A	Cohort B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	10		
Units: participants				
Hemoglobin: High Direction	0	0		
Hemoglobin: Low Direction	4	4		
Leukocytes: High Direction	0	1		
Leukocytes: Low Direction	0	0		
Lymphocytes: High Direction	0	0		
Lymphocytes: Low Direction	3	1		
Neutrophils	0	1		
Platelets	3	4		
Alanine Aminotransferase	0	0		
Albumin	0	0		
Alkaline Phosphatase	0	0		
Aspartate Aminotransferase	0	0		
Bilirubin	1	0		
Calcium: High Direction	0	0		

Calcium: Low Direction	0	0		
Cholesterol	0	0		
Creatinine	0	0		
Glucose: High Direction	0	0		
Glucose: Low Direction	0	0		
Phosphate	0	1		
Potassium: High Direction	0	0		
Potassium: Low Direction	0	0		
Sodium: High Direction	0	0		
Sodium: Low Direction	0	0		
Triglycerides	0	1		
Urate	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Clinically Significant Changes From Baseline in Vital Signs

End point title	Number of Participants With Clinically Significant Changes From Baseline in Vital Signs

End point description:

Vital signs included body temperature, systolic and diastolic blood pressure, pulse rate, respiratory rate, weight and height. Clinical significance was determined by the investigator. The number of participants with clinically significant changes from baseline in vital signs were reported.

End point type	Secondary

End point timeframe:

up to approximately 40 months (3.3 years)

End point values	Cohort A	Cohort B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	10		
Units: participants				
Systolic blood pressure, Week 12	1	1		
Systolic blood pressure, Week 24	0	1		
Systolic blood pressure, Week 36	0	1		
Systolic blood pressure, End of Treatment	1	0		
Diastolic blood pressure, Week 12	0	1		
Pulse, Week 84	1	0		
Pulse, Follow-up	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline Through Week 12 in SVR as Measured by MRI (or CT Scan in Applicable Participants)

End point title	Change from Baseline Through Week 12 in SVR as Measured by MRI (or CT Scan in Applicable Participants)

End point description:

Spleen volume was measured using magnetic resonance imaging (or CT scan in applicable participants). MRI of the upper and lower abdomen and pelvis was performed, to assess spleen volumes. MRI was performed with a body coil. The MRIs were read in the central imaging laboratory. Spleen volume was obtained by outlining the circumference of the organ and determining the volume using the technique of least squares. MRI was the preferred method for obtaining spleen volume data. The CT scans were processed by the same central laboratory used for MRIs. The same method (MRI or CT) was used for a given participant unless a new contraindication to the use of MRI (eg, pacemaker insertion) occurred. Here, "N" signifies participants who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline through Week 12

End point values	Cohort A	Cohort B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	8		
Units: cm^3				
arithmetic mean (standard deviation)	-29.2 (± 349.3)	-608 (± 669.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Change From Baseline Through Week 12 in SVR as Measured by MRI (or CT Scan in Applicable Participants)

End point title	Percentage Change From Baseline Through Week 12 in SVR as Measured by MRI (or CT Scan in Applicable Participants)

End point description:

Spleen volume was measured using magnetic resonance imaging (or CT scan in applicable participants). MRI of the upper and lower abdomen and pelvis was performed, to assess spleen volumes. MRI was performed with a body coil. The MRIs were read in the central imaging laboratory. Spleen volume was obtained by outlining the circumference of the organ and determining the volume using the technique of least squares. MRI was the preferred method for obtaining spleen volume data. The CT scans were processed by the same central laboratory used for MRIs. The same method (MRI or CT) was used for a given participant unless a new contraindication to the use of MRI (eg, pacemaker insertion) occurred. Here, "N" signifies participants who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline through Week 12

End point values	Cohort A	Cohort B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	8		
Units: percentage change				
arithmetic mean (standard deviation)	-1.6 (± 14.69)	-24.6 (± 21.72)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline Through Week 12 and Week 24 on Spleen Length as Measured by Palpation

End point title	Change from Baseline Through Week 12 and Week 24 on Spleen Length as Measured by Palpation

End point description:

Measurement of spleen length below the left costal margin was measured by palpation. Spleen size was determined at every physical examination with the participant in the recumbent (not left decubitus) position. The edge of the spleen was determined by palpation, and measured in centimeters, using a soft ruler, from the costal margin to the point of greatest splenic protrusion. The measurements should be noted and the site at which it was determined listed (eg, anterior axillary line, midclavicular line, and/or subxiphoid). A positive value indicates an increase in spleen volume and a negative value indicates a decrease in spleen volume. Here, "N "signifies number of participants analyzed for this outcome measure and "n" signifies number of participants with data available at a particular time point.

End point type	Secondary

End point timeframe:

Baseline through Weeks 12 and 24

End point values	Cohort A	Cohort B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	7		
Units: cm				
arithmetic mean (standard deviation)				
Week 12, n=12, 7	-0.2 (± 2.17)	-3.6 (± 6.73)		
Week 24, n=9, 5	-0.4 (± 5.41)	-2.6 (± 3.44)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Change From Baseline Through Week 12 and Week 24 on Spleen Length as Measured by Palpation

End point title	Percentage Change From Baseline Through Week 12 and Week 24 on Spleen Length as Measured by Palpation

End point description:

Measurement of spleen length below the left costal margin was measured by palpation. Spleen size was determined at every physical examination with the participant in the recumbent (not left decubitus)

position. The edge of the spleen was determined by palpation, and measured in centimeters, using a soft ruler, from the costal margin to the point of greatest splenic protrusion. The measurements should be noted and the site at which it was determined listed (eg, anterior axillary line, midclavicular line, and/or subxiphoid). A positive value indicates an increase in spleen volume and a negative value indicates a decrease in spleen volume. Here, "N" signifies number of participants analyzed for this outcome measure and "n" signifies number of participants with data available at a particular time point.

End point type	Secondary

End point timeframe:

Baseline through Weeks 12 and 24

End point values	Cohort A	Cohort B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	7		
Units: percentage change				
arithmetic mean (standard deviation)				
Week 12, n=12, 7	8.8 (± 40.83)	-14.4 (± 49.89)		
Week 24, n=9, 5	2.5 (± 50.72)	-21.3 (± 27.94)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline Through Week 12 and Week 24 in Total Symptom Score as Measured by the Myelofibrosis Symptom Assessment Form (MFSAF) v2.0 Symptom Diary

End point title	Change From Baseline Through Week 12 and Week 24 in Total Symptom Score as Measured by the Myelofibrosis Symptom Assessment Form (MFSAF) v2.0 Symptom Diary

End point description:

Symptoms of myelofibrosis were assessed using a modified MFSAF Version 2.0 diary. Using the diary, participants rated the following symptoms on a scale from 0 (absent/as good as it can be) to 10 (worst imaginable/as bad as it can be): itching, night sweats, abdominal discomfort/bloating, early satiety, pain under the ribs on left side and bone/muscle pain. The total symptom score ranged from 0-60 and was calculated as the sum of the 6 symptom scores. A higher score indicates worse symptoms. Here, "N" signifies number of participants analyzed for this outcome measure and "n" signifies number of participants with data available at a particular time point.

End point type	Secondary

End point timeframe:

Baseline through Week 12 and 24

End point values	Cohort A	Cohort B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	7		
Units: score on scale				
arithmetic mean (standard deviation)				
Change at Week 12, n=12, 7	1.4 (± 6.06)	-4.7 (± 12.50)		
Change at Week 24, n=9, 5	-1.0 (± 9.88)	-0.3 (± 10.14)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Change From Baseline Through Week 12 and Week 24 in Total Symptom Score as measured by the MFSAF v2.0 Symptom Diary

End point title	Percentage Change From Baseline Through Week 12 and Week 24 in Total Symptom Score as measured by the MFSAF v2.0 Symptom Diary

End point description:

Symptoms of myelofibrosis were assessed using a modified MFSAF Version 2.0 diary. Using the diary, participants rated the following symptoms on a scale from 0 (absent/as good as it can be) to 10 (worst imaginable/as bad as it can be): itching, night sweats, abdominal discomfort/bloating, early satiety, pain under the ribs on left side and bone/muscle pain. The total symptom score ranged from 0-60 and was calculated as the sum of the 6 symptom scores. A higher score indicates worse symptoms. Here, "N" signifies number of participants analyzed for this outcome measure and "n" signifies number of participants with data available at a particular time point.

End point type	Secondary

End point timeframe:

Baseline through Week 12 and 24

End point values	Cohort A	Cohort B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	6		
Units: percentage change				
arithmetic mean (standard deviation)				
Percentage Change at Week 12, n=12, 6	0.7 (± 69.57)	-1.8 (± 116.6)		
Percentage Change at Week 24, n=9, 4	-5.6 (± 95.56)	33.7 (± 142.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline Through Week 12 and Week 24 in Total Symptom Score as Measured by the Myeloproliferative Neoplasm-Symptom Assessment Form (MPN-SAF)

End point title	Change From Baseline Through Week 12 and Week 24 in Total Symptom Score as Measured by the Myeloproliferative

	Neoplasm-Symptom Assessment Form (MPN-SAF)

End point description:

Symptoms are evaluated by the MPN-SAF TSS. The MPN-SAF TSS assessed by the participants themselves and this includes fatigue, concentration, early satiety, inactivity, night sweats, itching, bone pain, abdominal discomfort, weight loss, and fevers. Scoring is from 0 (absent/as good as it can be) to 10 (worst imaginable/as bad as it can be) for each item. The MPN-SAF TSS is the summation of all the individual scores (0-100 scale). A higher score indicates worse symptoms. Here, "N" signifies number of participants analyzed for this outcome measure and "n" signifies number of participants with data available at a particular time point.

End point type	Secondary

End point timeframe:

Baseline through Week 12 and Week 24

End point values	Cohort A	Cohort B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	7		
Units: score on scale				
arithmetic mean (standard deviation)				
Change at Week 12, n=11, 7	2.0 (± 9.76)	-3.7 (± 12.91)		
Change at Week 24, n=9, 4	-1.6 (± 11.11)	-6.0 (± 8.76)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Change From Baseline Through Week 12 and Week 24 in Total Symptom Score as Measured by the MPN-SAF

End point title	Percentage Change From Baseline Through Week 12 and Week 24 in Total Symptom Score as Measured by the MPN-SAF

End point description:

Symptoms are evaluated by the MPN-SAF TSS. The MPN-SAF TSS assessed by the participants themselves and this includes fatigue, concentration, early satiety, inactivity, night sweats, itching, bone pain, abdominal discomfort, weight loss, and fevers. Scoring is from 0 (absent/as good as it can be) to 10 (worst imaginable/as bad as it can be) for each item. The MPN-SAF TSS is the summation of all the individual scores (0-100 scale). A higher score indicates worse symptoms. Note that the mean percentage change can vary in direction from the mean absolute change because percent increases (but not decreases) can exceed 100%. Here, "N" signifies number of participants analyzed for this outcome measure and "n" signifies number of participants with data available at a particular time point.

End point type	Secondary

End point timeframe:

Baseline through Week 12 and Week 24

End point values	Cohort A	Cohort B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	7		
Units: percentage change				
arithmetic mean (standard deviation)				
Percentage Change at Week 12, n=11, 7	3.8 (± 47.25)	-6.1 (± 51.24)		
Percentage Change at Week 24, n=9, 4	5.8 (± 46.85)	-22.7 (± 29.62)		

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Global Impression of Change (PGIC) Score at Each Visit

End point title	Patient Global Impression of Change (PGIC) Score at Each Visit

End point description:

Symptoms of myelofibrosis were assessed using the PGIC questionnaire. Using the questionnaire, participants rated the overall sense of treatment effect on their symptoms on a scale of 1 (very much improved)- 7(very much worse). The specific wording was: Since the start of the treatment you have received in this study, your myelofibrosis symptoms are: 1) Very much improved, 2) Much improved, 3) Minimally improved, 4) No change, 5) Minimally worse, 6) Much worse, 7) Very much worse. A higher score indicates worse symptoms. 9999=no participants were analyzed at this time point. 99999=Standard deviation was not estimable since only 1 participant was evaluable. Here, "N" signifies number of participants analyzed for this outcome measure and "n" signifies number of participants with data available at a particular time point. Here, "N" signifies number of participants analyzed for this outcome measure and "n" signifies number of participants with data available at a particular time point.

End point type	Secondary

End point timeframe:

Weeks 4, 8, 12, 16, 20, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, and 168

End point values	Cohort A	Cohort B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	9		
Units: score on scale				
arithmetic mean (standard deviation)				
Week 4, n=11, 8	3.6 (± 0.81)	3.5 (± 0.93)		
Weeks 8, n=11, 9	3.3 (± 0.90)	3.3 (± 1.22)		
Weeks 12, n=11, 7	3.2 (± 0.98)	3.6 (± 0.98)		
Weeks 16, n=9, 6	3.0 (± 1.00)	4.2 (± 1.47)		
Weeks 20, n=8, 6	3.3 (± 0.71)	3.2 (± 0.75)		
Weeks 24, n=9, 4	3.2 (± 1.09)	2.8 (± 0.96)		
Weeks 36, n=6, 3	3.2 (± 0.98)	3.0 (± 1.00)		
Weeks 48, n=4, 1	2.5 (± 1.00)	2.0 (± 99999)		
Weeks 60, n=3, 1	3.0 (± 1.73)	3.0 (± 99999)		
Weeks 72, n=4, 1	3.3 (± 1.50)	3.0 (± 99999)		
Weeks 84, n=1, 1	2.0 (± 99999)	3.0 (± 99999)		
Weeks 96, n=0, 1	9999 (± 9999)	2.0 (± 99999)		
Weeks 108, n=0, 1	9999 (± 9999)	4.0 (± 99999)		

Week 120, n=0, 1	9999 (± 9999)	3.0 (± 99999)		
Week 132, n=0, 1	9999 (± 9999)	3.0 (± 99999)		
Week 168, n=0, 1	9999 (± 9999)	3.0 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Responses According to the 2013 International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) Consensus Criteria for Treatment Response

End point title	Number of Participants with Responses According to the 2013 International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) Consensus Criteria for Treatment Response

End point description:

Treatment response (complete remission [CR] or partial remission [PR]) graded per IWG-MRT. CR: Bone marrow (BM): < 5% blasts; ≤ Grade 1 MF, Peripheral blood: Hemoglobin (Hb) ≥ 100 grams per liter (g/L), < upper normal limit (UNL); neutrophil count ≥ 1 × 10^9/L and < UNL; Platelet count ≥ 100 × 10^9/L and < UNL; < 2% immature myeloid cells (IMCs) and Clinical: Resolution of disease symptoms; spleen, liver not palpable; no evidence of extramedullary hematopoeisis (EMH). PR: Peripheral blood: Hb ≥ 100 g/L and < UNL; neutrophil count ≥ 1 × 10^9/L and < UNL; platelet count ≥ 100 × 10^9/L and < UNL; < 2% IMCs and Clinical: Resolution of symptoms; spleen and liver not palpable; no evidence of EMH or BM: < 5% blasts; ≤ Grade 1 MF; and peripheral blood: Hb≥ 85 g/L but < 100 g/L and < UNL; neutrophil count ≥ 1 × 10^9/L and < UNL; platelet count ≥ 50 × 10^9/L but < 100 × 10^9/L and < UNL; < 2% IMCs and Clinical: Resolution of symptoms; spleen, liver not palpable; no evidence of EMH.

End point type	Secondary

End point timeframe:

up to approximately 40 months (3.3 years)

End point values	Cohort A	Cohort B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	10		
Units: participants	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration-time Curve Over a Dosing Interval (AUCtau) for Itacitinib

End point title	Area Under the Concentration-time Curve Over a Dosing Interval (AUCtau) for Itacitinib

End point description:

AUCtau defined as area under the concentration-time curve over a dosing interval for Itacitinib. The concentrations of itacitinib in plasma were determined using a validated Liquid Chromatography with tandem mass spectrometry (LC/MS/MS) method with an assay range of 5 to 5000 nM. The PK parameters were calculated using standard noncompartmental analysis in Phoenix WinNonlin® v8.2 (Certara USA Inc., Princeton, NJ). 9999=itacitinib PK data for Cohort A on Week 2 were not available as

itacitinib was to be held until the completion of PK sample collection. Here, "N " signifies number of participants analyzed for this outcome measure.

End point type	Secondary

End point timeframe:

0 (pre-dose), 1, 2, 5 and 8 hours post-dose on Week 2 and Week 4

End point values	PK: Cohort A (Itacitinib)	PK: Cohort B (Itacitinib)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12	8		
Units: nanomolar* hour (nM*h)				
arithmetic mean (standard deviation)				
Week 2, n=0, 8	9999 (± 9999)	24100 (± 6600)		
Week 4, n=12, 7	2540 (± 2020)	28900 (± 11200)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration-time Curve Over a Dosing Interval (AUCtau) for Ruxolitinib

End point title	Area Under the Concentration-time Curve Over a Dosing Interval (AUCtau) for Ruxolitinib

End point description:

AUCtau defined as area under the concentration-time curve over a dosing interval for ruxolitinib. The concentrations of ruxolitinib in plasma were determined using a validated LC/MS/MS method with an assay range of 1 to 1000 nM. The PK parameters were calculated using standard noncompartmental analysis in Phoenix WinNonlin® v8.2 (Certara USA Inc., Princeton, NJ). Here, "N " signifies number of participants analyzed for this outcome measure. Only the data from 15 mg QD is shown as it is the only dose level with at least 3 participants at both Week 2 and Week 4.

End point type	Secondary

End point timeframe:

0 (pre-dose), 1, 2, 5 and 8 hours post-dose on Week 2 and Week 4

End point values	PK: Cohort A (Ruxolitinib)			
Subject group type	Subject analysis set			
Number of subjects analysed	4			
Units: nM*h				
arithmetic mean (standard deviation)				
Week 2	2930 (± 486)			
Week 4	2350 (± 635)			

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Oral Dose Clearance (CL/F) of Itacitinib

End point title	Apparent Oral Dose Clearance (CL/F) of Itacitinib

End point description:

Clearance of a drug was measure of the rate at which a drug is metabolized or eliminated by normal biological processes. The concentrations of itacitinib in plasma were determined using a validated LC/MS/MS method with an assay range of 5 to 5000 nM. The PK parameters were calculated using standard noncompartmental analysis in Phoenix WinNonlin® v8.2 (Certara USA Inc., Princeton, NJ). 9999=Data for Cohort A (Itacitinib) on Week 2 was not available as Cohort A, itacitinib was to be held on Week 2 until the completion of the PK sample collection. Here, "N " signifies number of participants analyzed for this outcome measure.

End point type	Secondary

End point timeframe:

0 (pre-dose), 1, 2, 5 and 8 hours post-dose on Week 2 and Week 4

End point values	PK: Cohort A (Itacitinib)	PK: Cohort B (Itacitinib)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12	8		
Units: liters per hour (L/h)				
arithmetic mean (standard deviation)				
Week 2, n=0, 8	9999 (± 9999)	48.5 (± 14.9)		
Week 4, n=12, 7	203 (± 97.4)	42.4 (± 15.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Oral Dose Clearance (CL/F) of Ruxolitinib

End point title	Apparent Oral Dose Clearance (CL/F) of Ruxolitinib

End point description:

Clearance of a drug was measure of the rate at which a drug is metabolized or eliminated by normal biological processes. The concentrations of ruxolitinib in plasma were determined using a validated LC/MS/MS method with an assay range of 1 to 1000 nM. The PK parameters were calculated using standard noncompartmental analysis in Phoenix WinNonlin® v8.2 (Certara USA Inc., Princeton, NJ). Only the data from 15 mg QD is shown as it is the only dose level with at least 3 participants at both Week 2 and Week 4.

End point type	Secondary

End point timeframe:

0 (pre-dose), 1, 2, 5 and 8 hours post-dose on Week 2 and Week 4

End point values	PK: Cohort A (Ruxolitinib)			
Subject group type	Subject analysis set			
Number of subjects analysed	4			
Units: L/h				
arithmetic mean (standard deviation)				
Week 2, n=3	17.0 (± 3.12)			
Week 4, n=4	22.2 (± 6.82)			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Plasma Concentration (Cmax) of Itacitinib

End point title	Maximum Observed Plasma Concentration (Cmax) of Itacitinib

End point description:

The concentrations of itacitinib in plasma were determined using a validated LC/MS/MS method with an assay range of 5 to 5000 nM. The PK parameters were calculated using standard noncompartmental analysis in Phoenix WinNonlin® v8.2 (Certara USA Inc., Princeton, NJ). 9999=Data for Cohort A (Itacitinib) on Week 2 was not available as Cohort A, itacitinib was to be held on Week 2 until the completion of the PK sample collection. Here, "N " signifies number of participants analyzed for this outcome measure.

End point type	Secondary

End point timeframe:

0 (pre-dose), 1, 2, 5 and 8 hours post-dose on Week 2 and Week 4

End point values	PK: Cohort A (Itacitinib)	PK: Cohort B (Itacitinib)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12	8		
Units: nanometer (nM)				
arithmetic mean (standard deviation)				
Week 2, n=0, 8	9999 (± 9999)	3570 (± 1280)		
Week 4, n=12, 7	559 (± 518)	4460 (± 2470)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Plasma Concentration (Cmax) of Ruxolitinib

End point title	Maximum Observed Plasma Concentration (Cmax) of Ruxolitinib

End point description:

The concentrations of ruxolitinib in plasma were determined using a validated LC/MS/MS method with an assay range of 1 to 1000 nM. The PK parameters were calculated using standard noncompartmental analysis in Phoenix WinNonlin® v8.2 (Certara USA Inc., Princeton, NJ). Only the data from 15 mg QD is shown as it is the only dose level with at least 3 participants at both Week 2 and Week 4.

End point type	Secondary

End point timeframe:

0 (pre-dose), 1, 2, 5 and 8 hours post-dose on Week 2 and Week 4

End point values	PK: Cohort A (Ruxolitinib)			
Subject group type	Subject analysis set			
Number of subjects analysed	4			
Units: nM				
arithmetic mean (standard deviation)				
Week 2, n=3	695 (± 111)			
Week 4, n=4	677 (± 118)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Maximum Concentration (Tmax) of Itacitinib

End point title	Time to Maximum Concentration (Tmax) of Itacitinib

End point description:

The concentrations of itacitinib in plasma were determined using a validated LC/MS/MS method with an assay range of 5 to 5000 nM. The PK parameters were calculated using standard noncompartmental analysis in Phoenix WinNonlin® v8.2 (Certara USA Inc., Princeton, NJ). 9999=Data for Cohort A (Itacitinib) on Week 2 was not available as Cohort A, itacitinib was to be held on Week 2 until the completion of the PK sample collection. Here, "N " signifies number of participants analyzed for this outcome measure.

End point type	Secondary

End point timeframe:

0 (pre-dose), 1, 2, 5 and 8 hours post-dose on Week 2 and Week 4

End point values	PK: Cohort A (Itacitinib)	PK: Cohort B (Itacitinib)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12	8		
Units: hour (hr)				
median (full range (min-max))				
Week 2, n=0, 8	9999 (9999 to 9999)	2.0 (1.0 to 5.0)		
Week 4, n=12, 7	2.0 (1.0 to 2.3)	2.0 (2.0 to 4.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Maximum Concentration (Tmax) of Ruxolitinib

End point title	Time to Maximum Concentration (Tmax) of Ruxolitinib

End point description:

The concentrations of ruxolitinib in plasma were determined using a validated LC/MS/MS method with an assay range of 1 to 1000 nM. The PK parameters were calculated using standard noncompartmental analysis in Phoenix WinNonlin® v8.2 (Certara USA Inc., Princeton, NJ). Only the data from 15 mg QD is shown as it is the only dose level with at least 3 participants at both Week 2 and Week 4.

End point type	Secondary

End point timeframe:

0 (pre-dose), 1, 2, 5 and 8 hours post-dose on Week 2 and Week 4

End point values	PK: Cohort A (Ruxolitinib)			
Subject group type	Subject analysis set			
Number of subjects analysed	4			
Units: hr				
median (full range (min-max))				
Week 2, n=3	1.0 (1.0 to 1.1)			
Week 4, n=4	1.0 (1.0 to 1.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Concentration at the end of the Dosing Interval (Ctau) of Itacitinib

End point title	Concentration at the end of the Dosing Interval (Ctau) of Itacitinib

End point description:

Ctau is defined as concentration at the end of the dosing interval of ruxolitinib.The concentrations of itacitinib in plasma were determined using a validated LC/MS/MS method with an assay range of 5 to 5000 nM. The PK parameters were calculated using standard noncompartmental analysis in Phoenix WinNonlin® v8.2 (Certara USA Inc., Princeton, NJ). 9999=Data for Cohort A (Itacitinib) on Week 2 was not available as Cohort A, itacitinib was to be held on Week 2 until the completion of the PK sample collection. Here, "N " signifies number of participants analyzed for this outcome measure.

End point type	Secondary

End point timeframe:

0 (pre-dose), 1, 2, 5 and 8 hours post-dose on Week 2 and Week 4

End point values	PK: Cohort A (Itacitinib)	PK: Cohort B (Itacitinib)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12	9		
Units: nM				
arithmetic mean (standard deviation)				
Week 2, n=0, 8	9999 (± 9999)	102 (± 120)		
Week 4, n=12, 9	10.2 (± 8.67)	108 (± 85.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Concentration at the End of the Dosing Interval (Ctau) of Ruxolitinib

End point title	Concentration at the End of the Dosing Interval (Ctau) of Ruxolitinib

End point description:

Ctau is defined as concentration at the end of the dosing interval of ruxolitinib. The concentrations of ruxolitinib in plasma were determined using a validated LC/MS/MS method with an assay range of 1 to 1000 nM. The PK parameters were calculated using standard noncompartmental analysis in Phoenix WinNonlin® v8.2 (Certara USA Inc., Princeton, NJ). Only the data from 15 mg QD is shown as it is the only dose level with at least 3 participants at both Week 2 and Week 4.

End point type	Secondary

End point timeframe:

0 (pre-dose), 1, 2, 5 and 8 hours post-dose Week 2 and Week 4

End point values	PK: Cohort A (Ruxolitinib)			
Subject group type	Subject analysis set			
Number of subjects analysed	4			
Units: nM				
arithmetic mean (standard deviation)				
Week 2, n=3	16.6 (± 14.5)			
Week 4, n=4	19.7 (± 28.6)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: up to approximately 40 months (3.3 years)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22

Reporting groups	
Reporting group title	Cohort A
Reporting group description: Participants with MF who were tolerating a ruxolitinib dose of less than 20 milligrams (mg) daily with no dose increase or no dose modification in the 8 weeks before screening visit received a combination of itacitinib at the dose of 200 mg, orally, once daily (QD) and ruxolitinib, orally, twice daily (BID) at their previous stable dose (must had been < 20 mg daily). Participants continued study treatment until disease progression, unacceptable toxicity, withdrawal of consent, or other Protocol-specified criteria to stop treatment were met.	
Reporting group title	Total
Reporting group description: Total	
Reporting group title	Cohort B
Reporting group description: Participants with MF who progressed after initial reduction in spleen with ruxolitinib treatment, progressed or discontinued for hematologic toxicities received treatment with itacitinib alone at the dose of 600 mg QD. Participants continued study treatment until disease progression, unacceptable toxicity, withdrawal of consent, or other Protocol-specified criteria to stop treatment were met.	

Serious adverse events	Cohort A	Total	Cohort B
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 13 (23.08%)	8 / 23 (34.78%)	5 / 10 (50.00%)
number of deaths (all causes)	0	2	2
number of deaths resulting from adverse events			
Investigations			
Blood creatinine increased			
subjects affected / exposed	1 / 13 (7.69%)	1 / 23 (4.35%)	0 / 10 (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
Pulse absent			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Injury, poisoning and procedural complications			

Subdural haematoma			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	1 / 13 (7.69%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Stent removal			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 13 (7.69%)	1 / 23 (4.35%)	0 / 10 (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
Non-cardiac chest pain			

subjects affected / exposed	1 / 13 (7.69%)	1 / 23 (4.35%)	0 / 10 (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
Pyrexia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 13 (7.69%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic cyst			
subjects affected / exposed	1 / 13 (7.69%)	1 / 23 (4.35%)	0 / 10 (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
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1

Respiratory failure			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wheezing			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatic lesion			
subjects affected / exposed	1 / 13 (7.69%)	1 / 23 (4.35%)	0 / 10 (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
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 13 (7.69%)	1 / 23 (4.35%)	0 / 10 (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
Haematoma muscle			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Campylobacter gastroenteritis			

subjects affected / exposed	1 / 13 (7.69%)	1 / 23 (4.35%)	0 / 10 (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
Cellulitis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile infection			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Cohort A	Total	Cohort B
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 13 (100.00%)	23 / 23 (100.00%)	10 / 10 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm malignant			
subjects affected / exposed	1 / 13 (7.69%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Skin papilloma			
subjects affected / exposed	1 / 13 (7.69%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Squamous cell carcinoma of skin			

subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 13 (7.69%)	2 / 23 (8.70%)	1 / 10 (10.00%)
occurrences (all)	1	2	1
Hypotension			
subjects affected / exposed	2 / 13 (15.38%)	4 / 23 (17.39%)	2 / 10 (20.00%)
occurrences (all)	2	4	2
Thrombophlebitis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
General disorders and administration site conditions			
Calcinosis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Chest discomfort			
subjects affected / exposed	1 / 13 (7.69%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Chills			
subjects affected / exposed	1 / 13 (7.69%)	2 / 23 (8.70%)	1 / 10 (10.00%)
occurrences (all)	1	2	1
Exercise tolerance decreased			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Fatigue			
subjects affected / exposed	3 / 13 (23.08%)	8 / 23 (34.78%)	5 / 10 (50.00%)
occurrences (all)	3	9	6
Influenza like illness			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Malaise			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Oedema			

subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Oedema peripheral			
subjects affected / exposed	2 / 13 (15.38%)	3 / 23 (13.04%)	1 / 10 (10.00%)
occurrences (all)	2	3	1
Peripheral swelling			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Pyrexia			
subjects affected / exposed	1 / 13 (7.69%)	5 / 23 (21.74%)	4 / 10 (40.00%)
occurrences (all)	1	7	6
Thirst			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 13 (7.69%)	2 / 23 (8.70%)	1 / 10 (10.00%)
occurrences (all)	2	4	2
Dyspnoea			
subjects affected / exposed	2 / 13 (15.38%)	5 / 23 (21.74%)	3 / 10 (30.00%)
occurrences (all)	2	5	3
Epistaxis			
subjects affected / exposed	0 / 13 (0.00%)	2 / 23 (8.70%)	2 / 10 (20.00%)
occurrences (all)	0	2	2
Haemoptysis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Hypoxia			
subjects affected / exposed	1 / 13 (7.69%)	2 / 23 (8.70%)	1 / 10 (10.00%)
occurrences (all)	1	2	1
Oropharyngeal pain			

subjects affected / exposed	1 / 13 (7.69%)	2 / 23 (8.70%)	1 / 10 (10.00%)
occurrences (all)	1	2	1
Pleural effusion			
subjects affected / exposed	1 / 13 (7.69%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Rhinorrhoea			
subjects affected / exposed	2 / 13 (15.38%)	2 / 23 (8.70%)	0 / 10 (0.00%)
occurrences (all)	2	2	0
Upper-airway cough syndrome			
subjects affected / exposed	1 / 13 (7.69%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Psychiatric disorders			
Depressive symptom			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Dysphoria			
subjects affected / exposed	1 / 13 (7.69%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 13 (7.69%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	2	2	0
Blood bilirubin increased			
subjects affected / exposed	2 / 13 (15.38%)	3 / 23 (13.04%)	1 / 10 (10.00%)
occurrences (all)	3	4	1
Blood chloride increased			
subjects affected / exposed	1 / 13 (7.69%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Blood creatinine increased			
subjects affected / exposed	1 / 13 (7.69%)	2 / 23 (8.70%)	1 / 10 (10.00%)
occurrences (all)	2	4	2
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Blood triglycerides increased			

subjects affected / exposed	1 / 13 (7.69%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Blood uric acid increased			
subjects affected / exposed	2 / 13 (15.38%)	2 / 23 (8.70%)	0 / 10 (0.00%)
occurrences (all)	2	2	0
C-reactive protein increased			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Neutrophil count decreased			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Platelet count decreased			
subjects affected / exposed	1 / 13 (7.69%)	2 / 23 (8.70%)	1 / 10 (10.00%)
occurrences (all)	1	3	2
Reticulocyte count increased			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Serum ferritin increased			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Weight decreased			
subjects affected / exposed	1 / 13 (7.69%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
White blood cell count decreased			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	2	2
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	2 / 13 (15.38%)	4 / 23 (17.39%)	2 / 10 (20.00%)
occurrences (all)	2	5	3
Fall			
subjects affected / exposed	1 / 13 (7.69%)	4 / 23 (17.39%)	3 / 10 (30.00%)
occurrences (all)	1	4	3
Skin abrasion			

subjects affected / exposed	1 / 13 (7.69%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Skin laceration			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Cardiac failure			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Left ventricular hypertrophy			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Tachycardia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Nervous system disorders			
Balance disorder			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Diabetic neuropathy			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Dizziness			
subjects affected / exposed	4 / 13 (30.77%)	6 / 23 (26.09%)	2 / 10 (20.00%)
occurrences (all)	4	6	2
Dysarthria			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Headache			
subjects affected / exposed	2 / 13 (15.38%)	3 / 23 (13.04%)	1 / 10 (10.00%)
occurrences (all)	2	3	1
Hypoaesthesia			

subjects affected / exposed	1 / 13 (7.69%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Lethargy			
subjects affected / exposed	1 / 13 (7.69%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Paraesthesia			
subjects affected / exposed	1 / 13 (7.69%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Presyncope			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 13 (30.77%)	8 / 23 (34.78%)	4 / 10 (40.00%)
occurrences (all)	4	14	10
Hypofibrinogenaemia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Increased tendency to bruise			
subjects affected / exposed	1 / 13 (7.69%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Leukocytosis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Splenic infarction			
subjects affected / exposed	1 / 13 (7.69%)	2 / 23 (8.70%)	1 / 10 (10.00%)
occurrences (all)	1	2	1
Thrombocytopenia			
subjects affected / exposed	2 / 13 (15.38%)	4 / 23 (17.39%)	2 / 10 (20.00%)
occurrences (all)	5	7	2
Thrombocytosis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Ear and labyrinth disorders			
Vertigo			

subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Eye disorders			
Visual impairment			
subjects affected / exposed	1 / 13 (7.69%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Abdominal distension			
subjects affected / exposed	2 / 13 (15.38%)	2 / 23 (8.70%)	0 / 10 (0.00%)
occurrences (all)	2	2	0
Abdominal pain			
subjects affected / exposed	4 / 13 (30.77%)	7 / 23 (30.43%)	3 / 10 (30.00%)
occurrences (all)	4	7	3
Abdominal pain upper			
subjects affected / exposed	1 / 13 (7.69%)	3 / 23 (13.04%)	2 / 10 (20.00%)
occurrences (all)	1	5	4
Constipation			
subjects affected / exposed	1 / 13 (7.69%)	3 / 23 (13.04%)	2 / 10 (20.00%)
occurrences (all)	1	4	3
Diarrhoea			
subjects affected / exposed	4 / 13 (30.77%)	8 / 23 (34.78%)	4 / 10 (40.00%)
occurrences (all)	4	12	8
Dry mouth			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Flatulence			
subjects affected / exposed	1 / 13 (7.69%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Gingival bleeding			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Haemorrhoidal haemorrhage			

subjects affected / exposed	1 / 13 (7.69%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Mouth ulceration			
subjects affected / exposed	1 / 13 (7.69%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Nausea			
subjects affected / exposed	2 / 13 (15.38%)	5 / 23 (21.74%)	3 / 10 (30.00%)
occurrences (all)	2	7	5
Stomatitis			
subjects affected / exposed	1 / 13 (7.69%)	2 / 23 (8.70%)	1 / 10 (10.00%)
occurrences (all)	1	2	1
Tooth disorder			
subjects affected / exposed	1 / 13 (7.69%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Vomiting			
subjects affected / exposed	1 / 13 (7.69%)	3 / 23 (13.04%)	2 / 10 (20.00%)
occurrences (all)	1	3	2
Hepatobiliary disorders			
Hepatomegaly			
subjects affected / exposed	1 / 13 (7.69%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Dermatitis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Dermatitis acneiform			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Hyperhidrosis			
subjects affected / exposed	1 / 13 (7.69%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Night sweats			

subjects affected / exposed	1 / 13 (7.69%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Pruritus			
subjects affected / exposed	3 / 13 (23.08%)	3 / 23 (13.04%)	0 / 10 (0.00%)
occurrences (all)	4	4	0
Rash			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Skin exfoliation			
subjects affected / exposed	1 / 13 (7.69%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Skin lesion			
subjects affected / exposed	1 / 13 (7.69%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 13 (0.00%)	2 / 23 (8.70%)	2 / 10 (20.00%)
occurrences (all)	0	2	2
Chronic kidney disease			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Dysuria			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Micturition urgency			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Nephrolithiasis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Pollakiuria			
subjects affected / exposed	1 / 13 (7.69%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	2	2	0
Urinary incontinence			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1

Urinary retention			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Urinary tract pain			
subjects affected / exposed	1 / 13 (7.69%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 13 (7.69%)	2 / 23 (8.70%)	1 / 10 (10.00%)
occurrences (all)	2	3	1
Back pain			
subjects affected / exposed	1 / 13 (7.69%)	2 / 23 (8.70%)	1 / 10 (10.00%)
occurrences (all)	1	2	1
Bone pain			
subjects affected / exposed	2 / 13 (15.38%)	3 / 23 (13.04%)	1 / 10 (10.00%)
occurrences (all)	2	3	1
Chondrocalcinosis pyrophosphate			
subjects affected / exposed	1 / 13 (7.69%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	2	2	0
Muscle spasms			
subjects affected / exposed	3 / 13 (23.08%)	3 / 23 (13.04%)	0 / 10 (0.00%)
occurrences (all)	3	3	0
Muscular weakness			
subjects affected / exposed	1 / 13 (7.69%)	2 / 23 (8.70%)	1 / 10 (10.00%)
occurrences (all)	1	2	1
Musculoskeletal chest pain			
subjects affected / exposed	1 / 13 (7.69%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Musculoskeletal pain			
subjects affected / exposed	1 / 13 (7.69%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Myalgia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Pain in extremity			

subjects affected / exposed	1 / 13 (7.69%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Posterior tibial tendon dysfunction			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Clostridium difficile colitis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Conjunctivitis			
subjects affected / exposed	1 / 13 (7.69%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Fungal skin infection			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Gastrointestinal viral infection			
subjects affected / exposed	1 / 13 (7.69%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Herpes simplex			
subjects affected / exposed	1 / 13 (7.69%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Pneumonia			
subjects affected / exposed	1 / 13 (7.69%)	2 / 23 (8.70%)	1 / 10 (10.00%)
occurrences (all)	1	2	1
Rash pustular			
subjects affected / exposed	1 / 13 (7.69%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Tooth abscess			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Upper respiratory tract infection			
subjects affected / exposed	1 / 13 (7.69%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	3	3	0

Urinary tract infection			
subjects affected / exposed	3 / 13 (23.08%)	5 / 23 (21.74%)	2 / 10 (20.00%)
occurrences (all)	6	9	3
Vaginal infection			
subjects affected / exposed	1 / 13 (7.69%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 13 (15.38%)	4 / 23 (17.39%)	2 / 10 (20.00%)
occurrences (all)	2	4	2
Dehydration			
subjects affected / exposed	2 / 13 (15.38%)	2 / 23 (8.70%)	0 / 10 (0.00%)
occurrences (all)	2	2	0
Gout			
subjects affected / exposed	0 / 13 (0.00%)	2 / 23 (8.70%)	2 / 10 (20.00%)
occurrences (all)	0	2	2
Hyperglycaemia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Hyperkalaemia			
subjects affected / exposed	1 / 13 (7.69%)	2 / 23 (8.70%)	1 / 10 (10.00%)
occurrences (all)	1	2	1
Hyperuricaemia			
subjects affected / exposed	1 / 13 (7.69%)	2 / 23 (8.70%)	1 / 10 (10.00%)
occurrences (all)	1	2	1
Hypoalbuminaemia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Hypocalcaemia			
subjects affected / exposed	1 / 13 (7.69%)	3 / 23 (13.04%)	2 / 10 (20.00%)
occurrences (all)	2	5	3
Hypokalaemia			
subjects affected / exposed	1 / 13 (7.69%)	3 / 23 (13.04%)	2 / 10 (20.00%)
occurrences (all)	1	3	2
Hypomagnesaemia			

subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Hypophosphataemia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Iron deficiency			
subjects affected / exposed	1 / 13 (7.69%)	2 / 23 (8.70%)	1 / 10 (10.00%)
occurrences (all)	1	2	1
Lactic acidosis			
subjects affected / exposed	1 / 13 (7.69%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Vitamin D deficiency			
subjects affected / exposed	1 / 13 (7.69%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	1	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 August 2017	The primary purpose of this amendment was to clarify exclusion criterion 16 and correct discrepancies between the Protocol text and the schedule of assessments.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported