Clinical trial results:
A phase III randomized open-label multi-center study of ruxolitinib vs. best available therapy in patients with corticosteroid-refractory chronic graft versus host disease after allogeneic stem cell transplantation.

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

Summary

EudraCT number	2016-004432-38
Trial protocol	GB SE DE AT ES BE DK NL IT FR PT HU PL BG NO GR RO
Global end of trial date	15 December 2022

Results information

Result version number	v1 (current)
This version publication date	01 July 2023
First version publication date	01 July 2023

Trial information

Trial identification

Sponsor protocol code	CINC424D2301 (INCB 18424-365)

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03112603
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma, AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma, AG, 41 613241111, novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma, AG, 41 613241111, novartis.email@novartis.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000901-PIP04-17

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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	15 December 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 December 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy of ruxolitinib vs. Investigator’s choice Best Available Therapy (BAT) in patients with moderate or severe SR-cGvHD assessed by Overall Response Rate (ORR) at the Cycle 7 Day 1 visit.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 June 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 6
Country: Number of subjects enrolled	Austria: 8
Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	Bulgaria: 3
Country: Number of subjects enrolled	Canada: 6
Country: Number of subjects enrolled	Czechia: 3
Country: Number of subjects enrolled	Denmark: 4
Country: Number of subjects enrolled	France: 11
Country: Number of subjects enrolled	Germany: 35
Country: Number of subjects enrolled	United Kingdom: 18
Country: Number of subjects enrolled	Greece: 6
Country: Number of subjects enrolled	India: 6
Country: Number of subjects enrolled	Israel: 18

Country: Number of subjects enrolled	Italy: 50
Country: Number of subjects enrolled	Japan: 37
Country: Number of subjects enrolled	Jordan: 3
Country: Number of subjects enrolled	Korea, Republic of: 4
Country: Number of subjects enrolled	Netherlands: 3
Country: Number of subjects enrolled	Norway: 1
Country: Number of subjects enrolled	Poland: 11
Country: Number of subjects enrolled	Portugal: 1
Country: Number of subjects enrolled	Russian Federation: 8
Country: Number of subjects enrolled	Saudi Arabia: 10
Country: Number of subjects enrolled	Spain: 19
Country: Number of subjects enrolled	Switzerland: 5
Country: Number of subjects enrolled	Turkey: 15
Country: Number of subjects enrolled	United States: 34
Worldwide total number of subjects	329
EEA total number of subjects	159

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)	12
Adults (18-64 years)	267
From 65 to 84 years	50
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted in 29 countries globally. During the main treatment period, participants were randomly assigned to a ruxolitinib arm or a Best Available Therapy (BAT) arm for 6 cycles of treatment. On Cycle 7 Day 1 and thereafter, participants in the BAT arm could cross over to ruxolitinib treatment.

Pre-assignment

Screening details:

A total of 404 participants were screened, of whom 72 were screen failures and 3 were not randomized for various reasons. Out of the 329 participants randomized, 6 did not receive BAT due to logistical reasons. A total of 329 participants were included in the Full Analysis Set (FAS); 165 were in the ruxolitinib arm and 164 were in the BAT arm.

Period 1

Period 1 title	End of Randomization/Crossover Periods (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	Ruxolitinib

Arm description:

Ruxolitinib was administered orally twice per day at a dose of 10 milligrams (mg).

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

Dosage and administration details:

Ruxolitinib was administered orally twice per day at a dose of 10 mg bid, as two 5-mg tablets and was taken without regard to food.

Arm title	Best Available Therapy

Arm description:

Subjects received best available therapies (BATs), including, but not limited to, extracorporeal photopheresis (ECP), low-dose methotrexate (MTX), mycophenolate mofetil (MMF), mTOR inhibitors (everolimus or sirolimus), infliximab, rituximab, pentostatin, imatinib, and ibrutinib based on the investigator's decision.

Arm type	Active comparator
Investigational medicinal product name	extracorporeal photopheresis (ECP)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Blood fraction modifier
Routes of administration	Intravenous use

Dosage and administration details:

0 mg weekly/every 2 weeks, taken intravenously. As these treatments varied from administered tablets to cellular therapy and photopheresis, the open-label design of this study was inevitable to accommodate the variety of treatments that were considered by investigators for these patients. Additionally, there was a necessity for modifications and dose adjustments in these therapies depending on the subject’s response made utilizing a placebo operationally impossible and would have presented an undue burden to the patient.

Investigational medicinal product name	low-dose methotrexate (MTX)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

10 mg weekly, 1 week on/1 week off, taken orally. As these treatments varied from administered tablets to cellular therapy and photopheresis, the open-label design of this study was inevitable to accommodate the variety of treatments that were considered by investigators for these patients. Additionally, there was a necessity for modifications and dose adjustments in these therapies depending on the subject's response made utilizing a placebo operationally impossible and would have presented an undue burden to the patient.

Investigational medicinal product name	mycophenolate mofetil (MMF)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

2000 mg per day, taken orally. As these treatments varied from administered tablets to cellular therapy and photopheresis, the open-label design of this study was inevitable to accommodate the variety of treatments that were considered by investigators for these patients. Additionally, there was a necessity for modifications and dose adjustments in these therapies depending on the subject's response made utilizing a placebo operationally impossible and would have presented an undue burden to the patient.

Investigational medicinal product name	Everolimus
Investigational medicinal product code	RAD001
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

2 mg per day, taken orally. As these treatments varied from administered tablets to cellular therapy and photopheresis, the open-label design of this study was inevitable to accommodate the variety of treatments that were considered by investigators for these patients. Additionally, there was a necessity for modifications and dose adjustments in these therapies depending on the subject's response made utilizing a placebo operationally impossible and would have presented an undue burden to the patient.

Investigational medicinal product name	Infliximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Blood fraction modifier
Routes of administration	Intravenous use

Dosage and administration details:

400 mg every 2 weeks, taken intravenously. As these treatments varied from administered tablets to cellular therapy and photopheresis, the open-label design of this study was inevitable to accommodate the variety of treatments that were considered by investigators for these patients. Additionally, there was a necessity for modifications and dose adjustments in these therapies depending on the subject's response made utilizing a placebo operationally impossible and would have presented an undue burden to the patient.

Investigational medicinal product name	Sirolimus
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

0.5 mg every 2 weeks, taken orally. As these treatments varied from administered tablets to cellular therapy and photopheresis, the open-label design of this study was inevitable to accommodate the variety of treatments that were considered by investigators for these patients. Additionally, there was a necessity for modifications and dose adjustments in these therapies depending on the subject's response made utilizing a placebo operationally impossible and would have presented an undue burden to the patient.

Investigational medicinal product name	Ibrutinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

420 mg per day, taken orally. As these treatments varied from administered tablets to cellular therapy and photopheresis, the open-label design of this study was inevitable to accommodate the variety of treatments that were considered by investigators for these patients. Additionally, there was a necessity for modifications and dose adjustments in these therapies depending on the subject's response made utilizing a placebo operationally impossible and would have presented an undue burden to the patient.

Investigational medicinal product name	Imatinib
Investigational medicinal product code	STI571
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

200 mg per day, taken orally. As these treatments varied from administered tablets to cellular therapy and photopheresis, the open-label design of this study was inevitable to accommodate the variety of treatments that were considered by investigators for these patients. Additionally, there was a necessity for modifications and dose adjustments in these therapies depending on the subject's response made utilizing a placebo operationally impossible and would have presented an undue burden to the patient.

Arm title	Ruxolitinib Cross-Over Period (Other)

Arm description:

Participants from the BAT arm at the end of Cycle 6 crossed over to ruxolitinib treatment.

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

Dosage and administration details:

Ruxolitinib was administered orally twice per day at a dose of 10 milligrams (mg).

Number of subjects in period 1	Ruxolitinib	Best Available Therapy	Ruxolitinib Cross-Over Period (Other)
Started	165	164	70
Completed	29	24	16
Not completed	136	140	54
Adverse event, serious fatal	10	7	2
Physician decision	43	18	29
Disease Relapse	12	7	2
Participant/Guardian Decision	7	14	7
Adverse event, non-fatal	32	12	6
Failure to Meet Protocol Continuation Criteria	4	5	-
Lost to follow-up	3	-	-
Lack of efficacy	25	77	8

Baseline characteristics

Reporting groups

Reporting group title	End of Randomization/Crossover Periods

Reporting group description: -

Reporting group values	End of Randomization/Crossover Periods	Total	
Number of subjects	329	329	
Age categorical Units: Subjects			
Adolescents (12-17 years)	12	12	
Adults (18-64 years)	267	267	
From 65-84 years	50	50	
Age Continuous Units: Years			
arithmetic mean	46.5		
standard deviation	± 15.92	-	
Sex: Female, Male Units: Participants			
Female	128	128	
Male	201	201	
Race/Ethnicity, Customized Units: Subjects			
White	248	248	
Black or African American	2	2	
Asian	54	54	
American Indian or Alaska Native	2	2	
Other	13	13	
Unknown	10	10	
Race/Ethnicity, Customized Units: Subjects			
Hispanic/Latino	26	26	
Not Hispanic/Latino	233	233	
Not Reported	51	51	
Unknown	19	19	
ECOG Performance Status			
The Eastern Cooperative Oncology Group (ECOG) Performance Score has 6 grades (0-5). 0 = Fully active, able to carry out all pre-disease activities; 1 = Restricted in strenuous activity but ambulatory and able to carry out work of light or sedentary nature; 2 = Ambulatory and capable of all self-care but unable to carry out work activities. Active about 50% of waking hours; 3 = Capable of limited self-care, confined to bed/chair more than 50% of waking hours; 4 = Completely disabled; cannot carry on self-care. Totally confined to bed/chair. 5 = Death.			
Units: Subjects			
ECOG Score - 0	81	81	
ECOG Score - 1	174	174	
ECOG Score - 2	44	44	
ECOG Score - 3	2	2	
ECOG Score - Missing	28	28	

End points

End points reporting groups

Reporting group title	Ruxolitinib
Reporting group description:	
Ruxolitinib was administered orally twice per day at a dose of 10 milligrams (mg).	
Reporting group title	Best Available Therapy
Reporting group description:	
Subjects received best available therapies (BATs), including, but not limited to, extracorporeal photopheresis (ECP), low-dose methotrexate (MTX), mycophenolate mofetil (MMF), mTOR inhibitors (everolimus or sirolimus), infliximab, rituximab, pentostatin, imatinib, and ibrutinib based on the investigator's decision.	
Reporting group title	Ruxolitinib Cross-Over Period (Other)
Reporting group description:	
Participants from the BAT arm at the end of Cycle 6 crossed over to ruxolitinib treatment.	

Primary: Efficacy of ruxolitinib versus investigator's choice best available therapy (BAT) in participants with moderate or severe Steroid Refractory Chronic Graft versus Host Disease (SR-cGvHD) assessed by overall response rate (ORR) at the Cycle 7 Day 1 visit

End point title	Efficacy of ruxolitinib versus investigator's choice best available therapy (BAT) in participants with moderate or severe Steroid Refractory Chronic Graft versus Host Disease (SR-cGvHD) assessed by overall response rate (ORR) at the Cycle 7 Day 1 visit[1]

End point description:

ORR was defined as the percentage of participants in each arm demonstrating a complete response (CR) or partial response (PR) based on chronic GvHD (cGvHD) disease assessments (National Institutes of Health Consensus Criteria) without the requirement of additional systemic therapies for an earlier progression, mixed response, or non-response. Scoring of response was relative to the organ score at the time of randomization. CR: complete resolution of all signs and symptoms of cGVHD in all evaluable organs without the initiation or addition of new systemic therapy. PR: improvement in at least one organ (e.g., improvement of 1 or more points on a 4- to 7-point scale, or an improvement of 2 or more points on a 10- to 12-point scale) without progression in other organs or sites, initiation, or addition of new systemic therapies.

End point type	Primary

End point timeframe:

Cycle 7 Day 1 (24 weeks [each cycle was comprised of 4 weeks])

Notes:

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

End point values	Ruxolitinib	Best Available Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	165	164		
Units: percentage of participants				
number (confidence interval 95%)	49.7 (41.8 to 57.6)	25.6 (19.1 to 33.0)		

Statistical analyses

Statistical analysis title	RUX vs. BAT (ORR)
Comparison groups	Ruxolitinib v Best Available Therapy
Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	2.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.86
upper limit	4.8

Secondary: Rate of failure-free survival (FFS)

End point title	Rate of failure-free survival (FFS)[2]

End point description:

Composite time to event endpoint incorporating the following FFS events: (i) relapse or recurrence of underlying disease or death due to underlying disease, (ii) nonrelapse mortality, or (iii) addition or initiation of another systemic therapy for cGvHD.

End point type	Secondary

End point timeframe:

Baseline to when the last participant reached Cycle 7 Day 1 (24 weeks [each cycle was comprised of 4 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: No statistical analysis was planned for this arm.

End point values	Ruxolitinib	Best Available Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	165	164		
Units: months				
median (confidence interval 95%)	999 (18.6 to 999)	5.7 (5.6 to 6.5)		

Statistical analyses

Statistical analysis title	RUX vs. BAT (FFS)
Comparison groups	Ruxolitinib v Best Available Therapy

Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001 [3]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.268
upper limit	0.51

Notes:

[3] - The p-value was derived from a 1-sided stratified log-rank test.

Secondary: Rate of participants with clinically relevant improvement of the modified Lee cGvHD symptom scale score

End point title	Rate of participants with clinically relevant improvement of the modified Lee cGvHD symptom scale score[4]

End point description:

To assess improvement of symptoms based on the total symptom score (TSS); a responder was defined as having achieved a clinically relevant reduction from Baseline of the TSS. The scale consists of 30 items in 7 subscales (skin, eye, mouth, lung, nutrition, energy, and psychological). Participants reported their level of symptom "bother" over the previous month on a 5-point likert scale: not at all, slightly, moderately, quite a bit, or extremely. Subscale scores and the summary score range from 0 to 100, with a higher score indicating worse symptoms.

End point type	Secondary

End point timeframe:

Baseline; Cycle 7 Day 1 (24 weeks [each cycle was comprised of 4 weeks])

Notes:

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

End point values	Ruxolitinib	Best Available Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	165	164		
Units: percentage of participants				
number (confidence interval 95%)	24.2 (17.9 to 31.5)	11.0 (6.6 to 16.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of FFS at study completion

End point title	Rate of FFS at study completion[5]

End point description:

Composite time to event endpoint incorporating the following FFS events: (i) relapse or recurrence of underlying disease or death due to underlying disease, (ii) nonrelapse mortality, or (iii) addition or initiation of another systemic therapy for cGvHD.

End point type	Secondary

End point timeframe:

up to 1348 days

Notes:

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

End point values	Ruxolitinib	Best Available Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	165	164		
Units: months				
median (confidence interval 95%)	38.4 (22.1 to 999)	5.7 (5.6 to 6.5)		

Statistical analyses

Statistical analysis title	RUX vs. BAT (FFS at study end)
Comparison groups	Ruxolitinib v Best Available Therapy
Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.361
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.268
upper limit	0.485

Secondary: Best overall response (BOR) at Cycle 7 Day 1

End point title	Best overall response (BOR) at Cycle 7 Day 1[6]

End point description:

BOR was defined as the percentage of participants who achieved an overall response (CR+PR) based on cGvHD disease assessments (National Institutes of Health Consensus Criteria) without the requirement of additional systemic therapies for an earlier progression, mixed response, or non-response at any time point (up to Cycle 7 Day 1 or the start of additional systemic therapy for cGvHD). Scoring of response was relative to the organ score at the time of randomization. CR: complete resolution of all signs and symptoms of cGVHD in all evaluable organs without the initiation or addition of new systemic therapy. PR: improvement in at least one organ (e.g., improvement of 1 or more points on a 4- to 7-point scale, or an improvement of 2 or more points on a 10- to 12-point scale) without progression in other organs or sites, initiation, or addition of new systemic therapies.

End point type	Secondary

End point timeframe:

up to Cycle 7 Day 1 (up to approximately 24 weeks [each cycle was comprised of 4 weeks])

Notes:

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

End point values	Ruxolitinib	Best Available Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	165	164		
Units: percentage of participants				
number (confidence interval 95%)	76.4 (69.1 to 82.6)	60.4 (52.4 to 67.9)		

Statistical analyses

Statistical analysis title	RUX vs. BAT (BOR)
Comparison groups	Ruxolitinib v Best Available Therapy
Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0011 [7]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	2.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.34
upper limit	3.52

Notes:

[7] - The one-sided p-value was calculated using a stratified Cochran-Mantel-Haenszel test.

Secondary: BOR during cross-over treatment with ruxolitinib

End point title	BOR during cross-over treatment with ruxolitinib[8]

End point description:

BOR was defined as the percentage of participants who achieved an overall response (CR+PR) based on cGvHD disease assessments (National Institutes of Health Consensus Criteria) without the requirement of additional systemic therapies for an earlier progression, mixed response, or non-response at any time point (up to Cycle 7 Day 1 or the start of additional systemic therapy for cGvHD). Scoring of response was relative to the organ score at the time of randomization. CR: complete resolution of all signs and symptoms of cGVHD in all evaluable organs without the initiation or addition of new systemic therapy. PR: improvement in at least one organ (e.g., improvement of 1 or more points on a 4- to 7-point scale, or an improvement of 2 or more points on a 10- to 12-point scale) without progression in other organs or sites, initiation, or addition of new systemic therapies.

End point type	Secondary

End point timeframe:

up to Day 995 of Cross-over Period

Notes:

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

End point values	Ruxolitinib Cross-Over Period (Other)			
Subject group type	Reporting group			
Number of subjects analysed	70			
Units: percentage of participants				
number (confidence interval 95%)	81.4 (70.3 to 89.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: ORR at the end of Cycle 3

End point title	ORR at the end of Cycle 3[9]

End point description:

ORR was defined as the percentage of participants in each arm demonstrating a CR or PR based on cGvHD disease assessments (National Institutes of Health Consensus Criteria) without the requirement of additional systemic therapies for an earlier progression, mixed response, or non-response. Scoring of response was relative to the organ score at the time of randomization. CR: complete resolution of all signs and symptoms of cGVHD in all evaluable organs without the initiation or addition of new systemic therapy. PR: improvement in at least one organ (e.g., improvement of 1 or more points on a 4- to 7-point scale, or an improvement of 2 or more points on a 10- to 12-point scale) without progression in other organs or sites, initiation, or addition of new systemic therapies.

End point type	Secondary

End point timeframe:

Cycle 4 Day 1 (12 weeks [each cycle was comprised of 4 weeks])

Notes:

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

End point values	Ruxolitinib	Best Available Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	165	164		
Units: percentage of participants				
number (confidence interval 95%)	54.5 (46.6 to 62.3)	31.1 (24.1 to 38.8)		

Statistical analyses

Statistical analysis title	RUX vs. BAT (ORR at end of Cycle 3)
Comparison groups	Ruxolitinib v Best Available Therapy
Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001 [10]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	2.77

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.75
upper limit	4.39

Notes:

[10] - The one-sided p-value was calculated using a stratified Cochran-Mantel-Haenszel (CMH) test.

Secondary: Duration of response through study completion

End point title	Duration of response through study completion[11]

End point description:

DOR was defined as the time from first response until cGvHD progression, death, or the date of change/addition of systemic therapies for cGvHD and as assessed for responders only. Response was based on cGvHD disease assessments (National Institutes of Health consensus criteria).

End point type	Secondary

End point timeframe:

up to 1153 days

Notes:

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

End point values	Ruxolitinib	Best Available Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	103		
Units: Months				
median (confidence interval 95%)	999 (999 to 999)	6.4 (4.9 to 11.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS)

End point title	Overall survival (OS)[12]

End point description:

Overall survival was defined as the time from the date of randomization to the date of death due to any cause.

End point type	Secondary

End point timeframe:

up to approximately 318 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: No statistical analysis was planned for this arm.

End point values	Ruxolitinib	Best Available Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	165	164		
Units: months				
median (confidence interval 95%)	999 (999 to 999)	999 (41.0 to 999)		

Statistical analyses

Statistical analysis title	RUX vs. BAT (OS)
Comparison groups	Ruxolitinib v Best Available Therapy
Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2396 [13]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.851
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.544
upper limit	1.331

Notes:

[13] - The p-value was derived from a 1-sided stratified log-rank test.

Secondary: Cumulative incidence of non-relapse mortality (NRM)

End point title	Cumulative incidence of non-relapse mortality (NRM)[14]

End point description:

Defined as the cumulative incidence rate from competing risk analysis for NRM from the date of randomization to the date of death not preceded by underlying disease relapse/recurrence.

End point type	Secondary

End point timeframe:

Months 3, 6, 12, 18, 24, 30, and 36

Notes:

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

End point values	Ruxolitinib	Best Available Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	165	164		
Units: percentage of participants				
number (confidence interval 95%)				
Month 3	5.45 (2.68 to 9.67)	4.44 (1.96 to 8.48)		
Month 6	9.13 (5.34 to 14.15)	6.43 (3.28 to 11.03)		

Month 12	15.30 (10.26 to 21.26)	15.12 (9.94 to 21.30)		
Month 18	15.93 (10.78 to 21.98)	16.48 (11.06 to 22.84)		
Month 24	17.83 (12.37 to 24.10)	19.22 (13.36 to 25.90)		
Month 30	17.83 (12.37 to 24.10)	19.22 (13.94 to 26.67)		
Month 36	17.83 (12.37 to 24.10)	22.0 (15.73 to 28.96)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with a ≥ 50% reduction in daily corticosteroid dose up to Cycle 7 Day 1

End point title	Percentage of participants with a ≥ 50% reduction in daily corticosteroid dose up to Cycle 7 Day 1[15]

End point description:

All corticosteroid dosages prescribed to the participant and all dose changes during the study were to be recorded for assessment of participants with a ≥ 50% reduction in daily corticosteroid dose. Data reported are from the start of the study to Cycle 7 Day 1 (data cutoff of 08 May 2020).

End point type	Secondary

End point timeframe:

Cycle 7 Day 1 (up to 24 weeks [each cycle was comprised of 4 weeks])

Notes:

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

End point values	Ruxolitinib	Best Available Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	165	158		
Units: percentage of participants				
number (not applicable)				
Day 15 to ≤ Day 28	12.7	13.2		
Day 29 to ≤ Day 42	35.0	33.1		
Day 43 to ≤ Day 56	48.4	41.1		
Day 57 to ≤ Day 70	58.7	47.9		
Day 71 to ≤ Day 84	62.3	51.4		
Day 85 to ≤ Day 98	69.5	54.0		
Day 99 to ≤ Day 112	71.2	60.4		
Day 113 to ≤ Day 126	73.2	66.2		
Day 127 to ≤ Day 140	72.8	68.3		
Day 141 to ≤ Day 154	70.0	68.3		
Day 155 to ≤ Day 168	74.6	71.6		
Day 169 to ≤ Day 182	81.9	88.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants successfully tapered off of all corticosteroids up to Cycle 7 Day 1

End point title	Percentage of participants successfully tapered off of all corticosteroids up to Cycle 7 Day 1[16]

End point description:

All corticosteroid dosages prescribed to the participant and all dose changes during the study were to be recorded for assessment of participants who successfully tapered off of all corticosteroids. Participants who completely tapered off corticosteroids refer to those who permanently discontinued steroids as per the dose administration panel and who did not restart steroids in the same interval. Participants who were tapered off and continued follow-up were also counted as being tapered off with 0 dose in subsequent intervals until they discontinued from the main treatment period or restarted steroid treatment.

End point type	Secondary

End point timeframe:

Cycle 7 Day 1 (up to 24 weeks [each cycle was comprised of 4 weeks])

Notes:

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

End point values	Ruxolitinib	Best Available Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	165	158		
Units: percentage of participants				
number (not applicable)				
Day 1 to ≤ Day 28	2.5	2.6		
Day 29 to ≤ Day 56	9.6	5.4		
Day 57 to ≤ Day 84	14.0	8.5		
Day 85 to ≤ Day 112	16.3	10.3		
Day 113 to ≤ Day 140	19.7	12.4		
Day 141 to ≤ Day 168	24.2	16.8		
Day 169 to ≤ Day 179	24.1	15.9		

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulative incidence of malignancy relapse/recurrence (MR)

End point title	Cumulative incidence of malignancy relapse/recurrence (MR)[17]

End point description:

Defined as the cumulative incidence rate from competing risk analysis of MR from the date of randomization to hematologic malignancy relapse/recurrence.

End point type	Secondary

End point timeframe:

Months 3, 6, 12, 18, 24, 30, and 36

Notes:

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

End point values	Ruxolitinib	Best Available Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	156	160		
Units: percentage of participants				
number (confidence interval 95%)				
0 to < 3 months	1.92 (0.52 to 5.12)	1.31 (0.26 to 4.27)		
3 to < 6 months	3.22 (1.20 to 6.93)	2.65 (0.87 to 6.21)		
6 to < 12 months	5.18 (2.42 to 9.49)	6.08 (2.98 to 10.73)		
12 to < 18 months	7.82 (4.25 to 12.77)	6.08 (2.98 to 10.73)		
18 to < 24 months	8.48 (4.74 to 13.57)	6.08 (2.98 to 10.73)		
24 to <30 months	8.48 (4.74 to 13.57)	6.78 (3.46 to 11.62)		
30 to <36 months	8.48 (4.74 to 13.57)	7.50 (3.96 to 12.52)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Functional Assessment of Cancer Therapy – Bone Marrow Transplantation (FACT-BMT)

End point title	Change from Baseline in Functional Assessment of Cancer Therapy – Bone Marrow Transplantation (FACT-BMT)[18]

End point description:

Change from Baseline was calculated as the post-Baseline value minus the Baseline value. The FACT-BMT is a 50-item self-report questionnaire that measures the effect of a therapy on domains including physical, functional, social/family, and emotional well-being, together with additional concerns relevant for bone marrow transplantation participants. The questions were based on a 5-point Likert scale, where 0 corresponds to "not at all" and 4 corresponds to "very much." The higher the final score, the better the quality of life. The FACT-BMT total score ranges from 0 to 148.

End point type	Secondary

End point timeframe:

Baseline; up to Cycle 39 Day 1 (up to 156 weeks [each cycle was comprised of 4 weeks])

Notes:

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

Justification: No statistical analysis was planned for this arm.

End point values	Ruxolitinib	Best Available Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	165	164		
Units: scores on a scale				
arithmetic mean (standard deviation)				
Cycle 2 Day 1	2.32 (± 12.191)	-0.22 (± 14.949)		
Cycle 3 Day 1	0.62 (± 14.452)	-1.82 (± 15.849)		
Cycle 4 Day 1	1.98 (± 15.888)	-1.05 (± 16.147)		
Cycle 5 Day 1	1.25 (± 14.577)	-0.23 (± 18.903)		
Cycle 6 Day 1	2.91 (± 14.562)	2.41 (± 14.766)		
Cycle 7 Day 1	4.14 (± 14.669)	0.85 (± 16.811)		
Cycle 9 Day 1	5.32 (± 16.815)	1.20 (± 17.635)		
Cycle 12 Day 1	7.26 (± 19.296)	3.74 (± 18.059)		
Cycle 15 Day 1	5.07 (± 18.220)	7.58 (± 17.063)		
Cycle 18 Day 1	4.10 (± 19.440)	8.19 (± 17.993)		
Cycle 21 Day 1	5.24 (± 19.485)	3.68 (± 17.378)		
Cycle 24 Day 1	5.90 (± 19.662)	7.84 (± 18.561)		
Cycle 27 Day 1	6.23 (± 18.880)	5.10 (± 18.885)		
Cycle 30 Day 1	7.53 (± 20.314)	5.75 (± 21.037)		
Cycle 33 Day 1	5.17 (± 20.330)	5.67 (± 22.573)		
Cycle 36 Day 1	8.72 (± 18.710)	4.77 (± 24.186)		
Cycle 39 Day 1	8.65 (± 21.669)	6.64 (± 22.384)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in EQ-5D-5L

End point title	Change from Baseline in EQ-5D-5L[19]

End point description:

The EQ-5D-5L is a descriptive classification consisting of five dimensions of health: mobility, self-care, usual activities, anxiety/depression, and pain/discomfort. The five-level version (no problems, slight problems, moderate problems, severe problems, and extreme problems) uses a 5-point Likert scale, with 1 being no problems and 5 being extreme problems.

End point type	Secondary

End point timeframe:

Baseline; up to Cycle 39 Day 1 (156 weeks [each cycle was comprised of 4 weeks])

Notes:

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

End point values	Ruxolitinib	Best Available Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	165	164		
Units: scores on a scale				
arithmetic mean (standard deviation)				
Cycle 2 Day 1	0.03 (± 0.214)	-0.01 (± 0.163)		
Cycle 3 Day 1	0.03 (± 0.221)	-0.04 (± 0.259)		
Cycle 4 Day 1	0.04 (± 0.196)	-0.01 (± 0.192)		
Cycle 5 Day 1	0.02 (± 0.210)	-0.03 (± 0.243)		
Cycle 6 Day 1	0.05 (± 0.230)	0.01 (± 0.186)		
Cycle 7 Day 1	0.07 (± 0.234)	-0.00 (± 0.225)		
Cycle 9 Day 1	0.07 (± 0.228)	-0.02 (± 0.166)		
Cycle 12 Day 1	0.07 (± 0.187)	0.02 (± 0.158)		
Cycle 15 Day 1	0.07 (± 0.250)	0.03 (± 0.140)		
Cycle 18 Day 1	0.07 (± 0.299)	0.02 (± 0.110)		
Cycle 21 Day 1	0.08 (± 0.268)	-0.00 (± 0.222)		
Cycle 24 Day 1	0.07 (± 0.272)	0.01 (± 0.164)		
Cycle 27 Day 1	0.06 (± 0.299)	0.03 (± 0.182)		
Cycle 30 Day 1	0.05 (± 0.261)	0.01 (± 0.159)		
Cycle 33 Day 1	0.00 (± 0.282)	0.05 (± 0.186)		
Cycle 36 Day 1	0.06 (± 0.231)	0.04 (± 0.216)		
Cycle 39 Day 1	0.06 (± 0.255)	0.01 (± 0.214)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax of ruxolitinib after single (Cycle 1 Day 1) and multiple (Cycle 1 Day 15) doses

End point title	Cmax of ruxolitinib after single (Cycle 1 Day 1) and multiple (Cycle 1 Day 15) doses[20]

End point description:

Cmax was defined as the maximum observed plasma concentration of ruxolitinib. Early enrolling participants (approximately the first 8 adult and first 4 adolescent participants) randomized to ruxolitinib arm followed an "extensive PK" sampling schedule. Subsequent participants randomized to ruxolitinib, any randomized participants receiving ruxolitinib after Cycle 6, and any randomized participants receiving BAT that cross over to ruxolitinib followed the "sparse PK" sampling schedule.

End point type	Secondary

End point timeframe:

Extensive Sampling Schedule: Cycle 1 Days 1 and 15: predose; 0.5, 1, 1.5, 4, 6, and 9 hours post-dose. Sparse Sampling Schedule: Cycle 1 Days 1 and 15: predose; 1.5 hours post-dose

Notes:

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

End point values	Ruxolitinib			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: nanograms per milliliter (ng/mL)				
geometric mean (geometric coefficient of variation)				
Day 1	167 (± 39.3)			
Day 15	215 (± 48.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: AUClast of ruxolitinib after single (Cycle 1 Day 1) and multiple (Cycle 1 Day 15) doses

End point title	AUClast of ruxolitinib after single (Cycle 1 Day 1) and multiple (Cycle 1 Day 15) doses[21]

End point description:

AUClast was defined as the area under the concentration-time curve up to the last measurable concentration of ruxolitinib. Early enrolling participants (approximately the first 8 adult and first 4 adolescent participants) randomized to ruxolitinib arm followed an "extensive PK" sampling schedule. Subsequent participants randomized to ruxolitinib, any randomized participants receiving ruxolitinib after Cycle 6, and any randomized participants receiving BAT that cross over to ruxolitinib followed the "sparse PK" sampling schedule.

End point type	Secondary

End point timeframe:

Extensive Sampling Schedule: Cycle 1 Days 1 and 15: predose; 0.5, 1, 1.5, 4, 6, and 9 hours post-dose. Sparse Sampling Schedule: Cycle 1 Days 1 and 15: predose; 1.5 hours post-dose

Notes:

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

End point values	Ruxolitinib			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: ng*hour/mL				
geometric mean (geometric coefficient of variation)				
Day 1	636 (± 40.8)			
Day 15	945 (± 56.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with any treatment-emergent adverse event (TEAE)

End point title	Number of participants with any treatment-emergent adverse event (TEAE)[22]

End point description:

Adverse events were defined as the appearance of (or worsening of any pre-existing) undesirable signs, symptoms, or medical conditions that occurred after the participant's signed informed consent was obtained. Abnormal laboratory values or test results occurring after informed consent constituted adverse events only if they induced clinical signs or symptoms, were considered clinically significant, required therapy (e.g., hematologic abnormality that required transfusion or hematological stem cell support), or required changes in study medication(s). TEAEs were defined as those AEs that started or worsened during the on-treatment period (either randomized or cross-over period).

End point type	Secondary

End point timeframe:

up to approximately 318 weeks

Notes:

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

End point values	Ruxolitinib	Best Available Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	165	158		
Units: participants	165	148		

Statistical analyses

No statistical analyses for this end point

Secondary: AUCinf of ruxolitinib after single (Cycle 1 Day 1) and multiple (Cycle 1 Day 15) doses

End point title	AUCinf of ruxolitinib after single (Cycle 1 Day 1) and multiple (Cycle 1 Day 15) doses[23]

End point description:

AUCinf was defined as the area under the concentration-time curve from time 0 to infinity. Early enrolling participants (approximately the first 8 adult and first 4 adolescent participants) randomized to ruxolitinib arm followed an "extensive PK" sampling schedule. Subsequent participants randomized to ruxolitinib, any randomized participants receiving ruxolitinib after Cycle 6, and any randomized participants receiving BAT that cross over to ruxolitinib followed the "sparse PK" sampling schedule.

End point type	Secondary

End point timeframe:

Extensive Sampling Schedule: Cycle 1 Days 1 and 15: predose; 0.5, 1, 1.5, 4, 6, and 9 hours post-dose. Sparse Sampling Schedule: Cycle 1 Days 1 and 15: predose; 1.5 hours post-dose

Notes:

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

End point values	Ruxolitinib			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: ng*hour/mL				
geometric mean (geometric coefficient of variation)				
Day 1	642 (± 32.7)			
Day 15	0 (± 0)			

Statistical analyses

No statistical analyses for this end point

Secondary: CL/F of ruxolitinib after single (Cycle 1 Day 1) and multiple (Cycle 1 Day 15) doses

End point title	CL/F of ruxolitinib after single (Cycle 1 Day 1) and multiple (Cycle 1 Day 15) doses[24]

End point description:

CL/F was defined as the oral dose clearance of ruxolitinib. Early enrolling participants (approximately the first 8 adult and first 4 adolescent participants) randomized to ruxolitinib arm followed an "extensive PK" sampling schedule. Subsequent participants randomized to ruxolitinib, any randomized participants receiving ruxolitinib after Cycle 6, and any randomized participants receiving BAT that cross over to ruxolitinib followed the "sparse PK" sampling schedule.

End point type	Secondary

End point timeframe:

Extensive Sampling Schedule: Cycle 1 Days 1 and 15: predose; 0.5, 1, 1.5, 4, 6, and 9 hours post-dose. Sparse Sampling Schedule: Cycle 1 Days 1 and 15: predose; 1.5 hours post-dose

Notes:

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

End point values	Ruxolitinib			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: Liters/hour				
geometric mean (geometric coefficient of variation)				
Day 1	15.6 (± 32.7)			
Day 15	15.2 (± 20.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: tmax of ruxolitinib after single (Cycle 1 Day 1) and multiple (Cycle 1 Day 15) doses

End point title	tmax of ruxolitinib after single (Cycle 1 Day 1) and multiple (Cycle 1 Day 15) doses[25]

End point description:

tmax was defined as the time to reach the maximum plasma concentration of ruxolitinib. Early enrolling participants (approximately the first 8 adult and first 4 adolescent participants) randomized to ruxolitinib arm followed an "extensive PK" sampling schedule. Subsequent participants randomized to ruxolitinib, any randomized participants receiving ruxolitinib after Cycle 6, and any randomized participants receiving BAT that cross over to ruxolitinib followed the "sparse PK" sampling schedule.

End point type	Secondary

End point timeframe:

Extensive Sampling Schedule: Cycle 1 Days 1 and 15: predose; 0.5, 1, 1.5, 4, 6, and 9 hours post-dose.
Sparse Sampling Schedule: Cycle 1 Days 1 and 15: predose; 1.5 hours post-dose

Notes:

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

End point values	Ruxolitinib			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: hours				
median (full range (min-max))				
Day 1	0.833 (0.417 to 4.08)			
Day 15	1.00 (0.417 to 2.00)			

Statistical analyses

No statistical analyses for this end point

Secondary: Vz/F of ruxolitinib after single (Cycle 1 Day 1) and multiple (Cycle 1 Day 15) doses

End point title	Vz/F of ruxolitinib after single (Cycle 1 Day 1) and multiple (Cycle 1 Day 15) doses[26]

End point description:

Vz/F was defined as the apparent oral dose volume of distribution of ruxolitinib. Early enrolling participants (approximately the first 8 adult and first 4 adolescent participants) randomized to ruxolitinib arm followed an "extensive PK" sampling schedule. Subsequent participants randomized to ruxolitinib, any randomized participants receiving ruxolitinib after Cycle 6, and any randomized participants

receiving BAT that cross over to ruxolitinib followed the "sparse PK" sampling schedule.

End point type	Secondary

End point timeframe:

Extensive Sampling Schedule: Cycle 1 Days 1 and 15: predose; 0.5, 1, 1.5, 4, 6, and 9 hours post-dose. Sparse Sampling Schedule: Cycle 1 Days 1 and 15: predose; 1.5 hours post-dose

Notes:

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

End point values	Ruxolitinib			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: Liters				
geometric mean (geometric coefficient of variation)				
Day 1	54.0 (± 25.0)			
Day 15	50.9 (± 33.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: t1/2 of ruxolitinib after single (Cycle 1 Day 1) and multiple (Cycle 1 Day 15) doses

End point title	t1/2 of ruxolitinib after single (Cycle 1 Day 1) and multiple (Cycle 1 Day 15) doses[27]

End point description:

t1/2 was defined as the apparent terminal phase disposition half-life of ruxolitinib. Early enrolling participants (approximately the first 8 adult and first 4 adolescent participants) randomized to ruxolitinib arm followed an "extensive PK" sampling schedule. Subsequent participants randomized to ruxolitinib, any randomized participants receiving ruxolitinib after Cycle 6, and any randomized participants receiving BAT that cross over to ruxolitinib followed the "sparse PK" sampling schedule.

End point type	Secondary

End point timeframe:

Extensive Sampling Schedule: Cycle 1 Days 1 and 15: predose; 0.5, 1, 1.5, 4, 6, and 9 hours post-dose. Sparse Sampling Schedule: Cycle 1 Days 1 and 15: predose; 1.5 hours post-dose

Notes:

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

End point values	Ruxolitinib			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: hours				
geometric mean (geometric coefficient of variation)				
Day 1	2.40 (± 28.9)			
Day 15	2.32 (± 19.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Utilization of medical resources

End point title	Utilization of medical resources[28]

End point description:

The percentage of participants with at least one submission to healthcare encounter was assessed.

End point type	Secondary

End point timeframe:

up to approximately 318 weeks

Notes:

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

End point values	Ruxolitinib	Best Available Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	165	158		
Units: percentage of participants				
number (not applicable)	57.0	65.8		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline to when the last participant received the last dose (+30 days); up to approximately 318 weeks

Adverse event reporting additional description:

Treatment-emergent adverse events, defined as adverse events that started or worsened during the on-treatment period (either Randomized or Cross-over Period), have been reported for the Safety Set, which included subjects who received at least one dose of drug. A total of 6 subjects in the BAT arm discontinued before receiving the first dose.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	Ruxolitinib

Reporting group description:

Ruxolitinib was administered orally twice per day at a dose of 10 milligrams (mg).

Reporting group title	Ruxolitinib Cross-Over Period

Reporting group description:

Subjects from the BAT arm at the end of Cycle 6 crossed over to ruxolitinib treatment.

Reporting group title	Best Available Therapy

Reporting group description:

Subjects received best available therapies (BATs), including, but not limited to, extracorporeal photopheresis (ECP), low-dose methotrexate (MTX), mycophenolate mofetil (MMF), mTOR inhibitors (everolimus or sirolimus), infliximab, rituximab, pentostatin, imatinib, and ibrutinib based on the investigator's decision.

Serious adverse events	Ruxolitinib	Ruxolitinib Cross-Over Period	Best Available Therapy
Total subjects affected by serious adverse events			
subjects affected / exposed	86 / 165 (52.12%)	27 / 70 (38.57%)	71 / 158 (44.94%)
number of deaths (all causes)	37	10	40
number of deaths resulting from adverse events	8	1	4
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	0 / 158 (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
Kaposi's sarcoma			
subjects affected / exposed	0 / 165 (0.00%)	1 / 70 (1.43%)	0 / 158 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Lung neoplasm			
subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin squamous cell carcinoma recurrent			
subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	0 / 158 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma			
subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	0 / 158 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	0 / 158 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post transplant lymphoproliferative disorder			
subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	0 / 158 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Venous thrombosis limb			
subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	0 / 165 (0.00%)	1 / 70 (1.43%)	0 / 158 (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
Hypotension			
subjects affected / exposed	2 / 165 (1.21%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Poor peripheral circulation			
subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vena cava thrombosis			
subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	0 / 158 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Catheter site haemorrhage			
subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	0 / 158 (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
Stenosis			
subjects affected / exposed	0 / 165 (0.00%)	1 / 70 (1.43%)	0 / 158 (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
Pyrexia			
subjects affected / exposed	11 / 165 (6.67%)	3 / 70 (4.29%)	7 / 158 (4.43%)
occurrences causally related to treatment / all	10 / 17	0 / 3	1 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	0 / 158 (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

Necrosis			
subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	1 / 158 (0.63%)
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	1 / 165 (0.61%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Hyperthermia			
subjects affected / exposed	0 / 165 (0.00%)	1 / 70 (1.43%)	0 / 158 (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
Generalised oedema			
subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	2 / 158 (1.27%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	0 / 165 (0.00%)	1 / 70 (1.43%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Catheter site pain			
subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Social circumstances			
Loss of personal independence in daily activities			
subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	0 / 158 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Reproductive system and breast disorders			
Vulvovaginal inflammation			
subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	0 / 158 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	3 / 165 (1.82%)	2 / 70 (2.86%)	3 / 158 (1.90%)
occurrences causally related to treatment / all	2 / 3	0 / 4	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Alveolar proteinosis			
subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	0 / 158 (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
Atelectasis			
subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough			
subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	0 / 158 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	2 / 165 (1.21%)	0 / 70 (0.00%)	3 / 158 (1.90%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			

subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngeal oedema			
subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obliterative bronchiolitis			
subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Organising pneumonia			
subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	0 / 158 (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
Pleural effusion			
subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachypnoea			
subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	0 / 158 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	2 / 165 (1.21%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	2 / 3	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	3 / 165 (1.82%)	0 / 70 (0.00%)	0 / 158 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			

subjects affected / exposed	3 / 165 (1.82%)	0 / 70 (0.00%)	3 / 158 (1.90%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	0 / 158 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory acidosis			
subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	2 / 165 (1.21%)	1 / 70 (1.43%)	2 / 158 (1.27%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 2
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 2
Pleuritic pain			
subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	0 / 158 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract inflammation			
subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	0 / 158 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Completed suicide			
subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	0 / 158 (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
Agitation			
subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Confusional state			

subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	0 / 158 (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
Depression			
subjects affected / exposed	0 / 165 (0.00%)	1 / 70 (1.43%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device breakage			
subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Cytomegalovirus test positive			
subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	0 / 158 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alanine aminotransferase increased			
subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	0 / 158 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatinine increased			
subjects affected / exposed	0 / 165 (0.00%)	1 / 70 (1.43%)	0 / 158 (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
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	0 / 158 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelet count decreased			
subjects affected / exposed	1 / 165 (0.61%)	1 / 70 (1.43%)	0 / 158 (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

SARS-CoV-2 test positive			
subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	0 / 158 (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
White blood cell count decreased			
subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	0 / 158 (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
Injury, poisoning and procedural complications			
Anastomotic complication			
subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	0 / 158 (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
Femur fracture			
subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infusion related reaction			
subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	0 / 158 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal compression fracture			
subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	0 / 158 (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
Fall			
subjects affected / exposed	0 / 165 (0.00%)	1 / 70 (1.43%)	0 / 158 (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			
Acute myocardial infarction			
subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Tachycardia			
subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis			
subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	0 / 165 (0.00%)	1 / 70 (1.43%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiogenic shock			
subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiac failure congestive			
subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	0 / 158 (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
Cardiac failure			
subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	0 / 165 (0.00%)	1 / 70 (1.43%)	0 / 158 (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
Aortic valve incompetence			

subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Haemorrhage intracranial			
subjects affected / exposed	1 / 165 (0.61%)	1 / 70 (1.43%)	0 / 158 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 1	0 / 0
Depressed level of consciousness			
subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	0 / 158 (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
Encephalopathy			
subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	0 / 158 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	0 / 158 (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
Intracranial pressure increased			
subjects affected / exposed	0 / 165 (0.00%)	1 / 70 (1.43%)	0 / 158 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic encephalopathy			

subjects affected / exposed	0 / 165 (0.00%)	1 / 70 (1.43%)	0 / 158 (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
Neuralgia			
subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuropathy peripheral			
subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	2 / 158 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			
subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	0 / 158 (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
Syncope			
subjects affected / exposed	2 / 165 (1.21%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somnolence			
subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	1 / 158 (0.63%)
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			
Atypical haemolytic uraemic syndrome			

subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia			
subjects affected / exposed	1 / 165 (0.61%)	3 / 70 (4.29%)	0 / 158 (0.00%)
occurrences causally related to treatment / all	3 / 3	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombotic microangiopathy			
subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 165 (0.00%)	1 / 70 (1.43%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	4 / 165 (2.42%)	1 / 70 (1.43%)	2 / 158 (1.27%)
occurrences causally related to treatment / all	3 / 5	0 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spleen disorder			
subjects affected / exposed	0 / 165 (0.00%)	1 / 70 (1.43%)	0 / 158 (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
Pancytopenia			
subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	2 / 158 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	2 / 165 (1.21%)	0 / 70 (0.00%)	0 / 158 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			

subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	0 / 158 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Splenic haemorrhage			
subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	0 / 158 (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
Eye disorders			
Angle closure glaucoma			
subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	0 / 158 (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
Corneal erosion			
subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	0 / 158 (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
Corneal perforation			
subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	0 / 158 (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
Keratitis			
subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ulcerative keratitis			
subjects affected / exposed	0 / 165 (0.00%)	2 / 70 (2.86%)	0 / 158 (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
Gastrointestinal disorders			
Intestinal obstruction			
subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			

subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	0 / 158 (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
Haematemesis			
subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	0 / 158 (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
Gastrointestinal ulcer			
subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	0 / 158 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	3 / 158 (1.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis			
subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 165 (0.61%)	1 / 70 (1.43%)	3 / 158 (1.90%)
occurrences causally related to treatment / all	0 / 1	0 / 1	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal fistula			
subjects affected / exposed	0 / 165 (0.00%)	1 / 70 (1.43%)	0 / 158 (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
Abdominal pain upper			

subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	3 / 165 (1.82%)	1 / 70 (1.43%)	0 / 158 (0.00%)
occurrences causally related to treatment / all	2 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	2 / 158 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	0 / 158 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumatosis intestinalis			
subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	0 / 158 (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
Pancreatitis			
subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophagitis			
subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Odynophagia			

subjects affected / exposed	0 / 165 (0.00%)	1 / 70 (1.43%)	0 / 158 (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
Nausea			
subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Melaena			
subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	0 / 158 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine perforation			
subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oral dysaesthesia			
subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatic cirrhosis			
subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxic epidermal necrolysis			

subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	0 / 158 (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
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 165 (1.21%)	0 / 70 (0.00%)	3 / 158 (1.90%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	2 / 158 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal impairment			
subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	0 / 158 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Back pain			
subjects affected / exposed	2 / 165 (1.21%)	1 / 70 (1.43%)	0 / 158 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone pain			
subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	0 / 165 (0.00%)	1 / 70 (1.43%)	0 / 158 (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
Muscular weakness			
subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	0 / 158 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteonecrosis			
subjects affected / exposed	4 / 165 (2.42%)	1 / 70 (1.43%)	2 / 158 (1.27%)
occurrences causally related to treatment / all	2 / 4	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	0 / 158 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendon disorder			
subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	0 / 158 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abdominal wall infection			
subjects affected / exposed	0 / 165 (0.00%)	1 / 70 (1.43%)	0 / 158 (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
Bronchopulmonary aspergillosis			

subjects affected / exposed	3 / 165 (1.82%)	0 / 70 (0.00%)	4 / 158 (2.53%)
occurrences causally related to treatment / all	3 / 4	0 / 0	0 / 4
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	1 / 165 (0.61%)	1 / 70 (1.43%)	0 / 158 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain abscess			
subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	0 / 158 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial translocation			
subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	0 / 158 (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
Bacterial sepsis			
subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	0 / 158 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19 pneumonia			
subjects affected / exposed	3 / 165 (1.82%)	0 / 70 (0.00%)	0 / 158 (0.00%)
occurrences causally related to treatment / all	3 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis bacterial			
subjects affected / exposed	0 / 165 (0.00%)	1 / 70 (1.43%)	0 / 158 (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
Anal abscess			

subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	0 / 158 (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
Adenovirus reactivation			
subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	0 / 158 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess limb			
subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			
subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	2 / 158 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Aspergillus infection			
subjects affected / exposed	0 / 165 (0.00%)	1 / 70 (1.43%)	0 / 158 (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
Fungal infection			
subjects affected / exposed	2 / 165 (1.21%)	0 / 70 (0.00%)	0 / 158 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile infection			
subjects affected / exposed	0 / 165 (0.00%)	1 / 70 (1.43%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cytomegalovirus infection			
subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	0 / 158 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cytomegalovirus infection reactivation			

subjects affected / exposed	2 / 165 (1.21%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dacryocanaliculitis			
subjects affected / exposed	0 / 165 (0.00%)	1 / 70 (1.43%)	0 / 158 (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
Device related sepsis			
subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterococcal infection			
subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	0 / 158 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis infectious			
subjects affected / exposed	0 / 165 (0.00%)	1 / 70 (1.43%)	0 / 158 (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
Erysipelas			
subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	0 / 158 (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
Escherichia bacteraemia			
subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	1 / 158 (0.63%)
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 infection			
subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	2 / 158 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia sepsis			

subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	0 / 158 (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
Febrile infection			
subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	4 / 165 (2.42%)	1 / 70 (1.43%)	0 / 158 (0.00%)
occurrences causally related to treatment / all	3 / 4	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 165 (0.00%)	1 / 70 (1.43%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine infection			
subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver abscess			
subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oral candidiasis			

subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	0 / 158 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection fungal			
subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	0 / 158 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Measles			
subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	0 / 158 (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
Meningitis cryptococcal			
subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	0 / 158 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis viral			
subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	0 / 158 (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
Metapneumovirus infection			
subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mycobacterial infection			
subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	0 / 158 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	5 / 165 (3.03%)	1 / 70 (1.43%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	4 / 6	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oral herpes			

subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngitis			
subjects affected / exposed	0 / 165 (0.00%)	1 / 70 (1.43%)	0 / 158 (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
Pneumococcal infection			
subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	0 / 158 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	24 / 165 (14.55%)	5 / 70 (7.14%)	18 / 158 (11.39%)
occurrences causally related to treatment / all	18 / 31	0 / 5	4 / 20
deaths causally related to treatment / all	4 / 5	0 / 0	2 / 3
Pneumonia bacterial			
subjects affected / exposed	3 / 165 (1.82%)	0 / 70 (0.00%)	2 / 158 (1.27%)
occurrences causally related to treatment / all	3 / 3	0 / 0	1 / 2
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Pneumonia cytomegaloviral			
subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	2 / 158 (1.27%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia klebsiella			
subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia pseudomonal			

subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	2 / 158 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia viral			
subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pseudomonal sepsis			
subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pulmonary nocardiosis			
subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	0 / 158 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory syncytial virus infection			
subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	0 / 158 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	2 / 165 (1.21%)	3 / 70 (4.29%)	0 / 158 (0.00%)
occurrences causally related to treatment / all	0 / 2	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection bacterial			
subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	0 / 158 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Respiratory tract infection fungal			

subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	0 / 158 (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
Respiratory tract infection viral			
subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	0 / 158 (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
Sepsis			
subjects affected / exposed	4 / 165 (2.42%)	1 / 70 (1.43%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	3 / 4	2 / 2	0 / 1
deaths causally related to treatment / all	1 / 1	1 / 1	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	1 / 165 (0.61%)	2 / 70 (2.86%)	2 / 158 (1.27%)
occurrences causally related to treatment / all	0 / 1	1 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinusitis			
subjects affected / exposed	0 / 165 (0.00%)	1 / 70 (1.43%)	0 / 158 (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
Skin infection			
subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Systemic infection			
subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Systemic mycosis			
subjects affected / exposed	0 / 165 (0.00%)	1 / 70 (1.43%)	0 / 158 (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
Tracheitis			

subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	0 / 158 (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
Septic shock			
subjects affected / exposed	2 / 165 (1.21%)	1 / 70 (1.43%)	4 / 158 (2.53%)
occurrences causally related to treatment / all	1 / 2	1 / 1	2 / 4
deaths causally related to treatment / all	0 / 1	0 / 0	2 / 3
Urinary tract infection			
subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection			
subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 165 (1.21%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	2 / 165 (1.21%)	0 / 70 (0.00%)	0 / 158 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			

subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	1 / 165 (0.61%)	0 / 70 (0.00%)	0 / 158 (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
Hyperkalaemia			
subjects affected / exposed	0 / 165 (0.00%)	0 / 70 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Ruxolitinib	Ruxolitinib Cross-Over Period	Best Available Therapy
Total subjects affected by non-serious adverse events			
subjects affected / exposed	158 / 165 (95.76%)	62 / 70 (88.57%)	132 / 158 (83.54%)
Vascular disorders			
Hypertension			
subjects affected / exposed	33 / 165 (20.00%)	7 / 70 (10.00%)	21 / 158 (13.29%)
occurrences (all)	37	7	25
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	4 / 165 (2.42%)	5 / 70 (7.14%)	4 / 158 (2.53%)
occurrences (all)	6	6	4
Fatigue			
subjects affected / exposed	25 / 165 (15.15%)	7 / 70 (10.00%)	15 / 158 (9.49%)
occurrences (all)	26	8	19
Oedema peripheral			
subjects affected / exposed	13 / 165 (7.88%)	4 / 70 (5.71%)	18 / 158 (11.39%)
occurrences (all)	14	6	21
Pyrexia			
subjects affected / exposed	34 / 165 (20.61%)	9 / 70 (12.86%)	16 / 158 (10.13%)
occurrences (all)	43	11	23
Respiratory, thoracic and mediastinal			

disorders			
Cough			
subjects affected / exposed	25 / 165 (15.15%)	12 / 70 (17.14%)	15 / 158 (9.49%)
occurrences (all)	37	13	17
Dyspnoea			
subjects affected / exposed	19 / 165 (11.52%)	5 / 70 (7.14%)	10 / 158 (6.33%)
occurrences (all)	21	5	11
Rhinorrhoea			
subjects affected / exposed	8 / 165 (4.85%)	0 / 70 (0.00%)	8 / 158 (5.06%)
occurrences (all)	10	0	8
Psychiatric disorders			
Insomnia			
subjects affected / exposed	13 / 165 (7.88%)	1 / 70 (1.43%)	8 / 158 (5.06%)
occurrences (all)	14	1	8
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	32 / 165 (19.39%)	5 / 70 (7.14%)	8 / 158 (5.06%)
occurrences (all)	42	8	12
Amylase increased			
subjects affected / exposed	12 / 165 (7.27%)	2 / 70 (2.86%)	4 / 158 (2.53%)
occurrences (all)	13	2	4
Aspartate aminotransferase increased			
subjects affected / exposed	19 / 165 (11.52%)	3 / 70 (4.29%)	6 / 158 (3.80%)
occurrences (all)	28	5	8
Blood alkaline phosphatase increased			
subjects affected / exposed	12 / 165 (7.27%)	3 / 70 (4.29%)	6 / 158 (3.80%)
occurrences (all)	17	4	7
Blood cholesterol increased			
subjects affected / exposed	15 / 165 (9.09%)	1 / 70 (1.43%)	7 / 158 (4.43%)
occurrences (all)	18	1	7
Blood creatine phosphokinase increased			
subjects affected / exposed	11 / 165 (6.67%)	2 / 70 (2.86%)	1 / 158 (0.63%)
occurrences (all)	17	3	1
Blood creatinine increased			
subjects affected / exposed	29 / 165 (17.58%)	4 / 70 (5.71%)	8 / 158 (5.06%)
occurrences (all)	39	4	10

Fibrin D dimer increased			
subjects affected / exposed	9 / 165 (5.45%)	0 / 70 (0.00%)	0 / 158 (0.00%)
occurrences (all)	10	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	19 / 165 (11.52%)	3 / 70 (4.29%)	7 / 158 (4.43%)
occurrences (all)	28	3	7
Lipase increased			
subjects affected / exposed	10 / 165 (6.06%)	3 / 70 (4.29%)	4 / 158 (2.53%)
occurrences (all)	14	5	4
Platelet count decreased			
subjects affected / exposed	19 / 165 (11.52%)	1 / 70 (1.43%)	11 / 158 (6.96%)
occurrences (all)	27	2	15
Nervous system disorders			
Headache			
subjects affected / exposed	17 / 165 (10.30%)	6 / 70 (8.57%)	14 / 158 (8.86%)
occurrences (all)	21	7	14
Tremor			
subjects affected / exposed	7 / 165 (4.24%)	0 / 70 (0.00%)	8 / 158 (5.06%)
occurrences (all)	7	0	9
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	21 / 165 (12.73%)	7 / 70 (10.00%)	14 / 158 (8.86%)
occurrences (all)	24	10	19
Neutropenia			
subjects affected / exposed	25 / 165 (15.15%)	8 / 70 (11.43%)	8 / 158 (5.06%)
occurrences (all)	43	12	15
Leukopenia			
subjects affected / exposed	10 / 165 (6.06%)	1 / 70 (1.43%)	2 / 158 (1.27%)
occurrences (all)	17	2	2
Anaemia			
subjects affected / exposed	56 / 165 (33.94%)	15 / 70 (21.43%)	25 / 158 (15.82%)
occurrences (all)	101	26	38
Eye disorders			
Dry eye			
subjects affected / exposed	11 / 165 (6.67%)	2 / 70 (2.86%)	10 / 158 (6.33%)
occurrences (all)	11	3	10

Cataract			
subjects affected / exposed	4 / 165 (2.42%)	5 / 70 (7.14%)	6 / 158 (3.80%)
occurrences (all)	5	5	7
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	27 / 165 (16.36%)	6 / 70 (8.57%)	23 / 158 (14.56%)
occurrences (all)	31	7	31
Constipation			
subjects affected / exposed	14 / 165 (8.48%)	5 / 70 (7.14%)	10 / 158 (6.33%)
occurrences (all)	14	5	10
Nausea			
subjects affected / exposed	19 / 165 (11.52%)	3 / 70 (4.29%)	21 / 158 (13.29%)
occurrences (all)	20	3	24
Vomiting			
subjects affected / exposed	15 / 165 (9.09%)	3 / 70 (4.29%)	12 / 158 (7.59%)
occurrences (all)	21	3	18
Dyspepsia			
subjects affected / exposed	4 / 165 (2.42%)	4 / 70 (5.71%)	4 / 158 (2.53%)
occurrences (all)	4	4	4
Abdominal pain			
subjects affected / exposed	7 / 165 (4.24%)	4 / 70 (5.71%)	9 / 158 (5.70%)
occurrences (all)	8	4	11
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	1 / 165 (0.61%)	1 / 70 (1.43%)	8 / 158 (5.06%)
occurrences (all)	1	1	9
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	20 / 165 (12.12%)	7 / 70 (10.00%)	13 / 158 (8.23%)
occurrences (all)	26	14	14
Back pain			
subjects affected / exposed	18 / 165 (10.91%)	5 / 70 (7.14%)	10 / 158 (6.33%)
occurrences (all)	18	5	10
Myalgia			
subjects affected / exposed	17 / 165 (10.30%)	1 / 70 (1.43%)	7 / 158 (4.43%)
occurrences (all)	18	1	8

Pain in extremity			
subjects affected / exposed	10 / 165 (6.06%)	1 / 70 (1.43%)	5 / 158 (3.16%)
occurrences (all)	10	1	5
Infections and infestations			
Pneumonia			
subjects affected / exposed	8 / 165 (4.85%)	6 / 70 (8.57%)	11 / 158 (6.96%)
occurrences (all)	9	11	11
Urinary tract infection			
subjects affected / exposed	13 / 165 (7.88%)	4 / 70 (5.71%)	9 / 158 (5.70%)
occurrences (all)	21	5	17
Upper respiratory tract infection			
subjects affected / exposed	19 / 165 (11.52%)	12 / 70 (17.14%)	15 / 158 (9.49%)
occurrences (all)	22	21	23
BK virus infection			
subjects affected / exposed	9 / 165 (5.45%)	3 / 70 (4.29%)	2 / 158 (1.27%)
occurrences (all)	9	3	2
Bronchitis			
subjects affected / exposed	7 / 165 (4.24%)	7 / 70 (10.00%)	3 / 158 (1.90%)
occurrences (all)	8	8	5
COVID-19			
subjects affected / exposed	8 / 165 (4.85%)	5 / 70 (7.14%)	1 / 158 (0.63%)
occurrences (all)	9	6	2
Conjunctivitis			
subjects affected / exposed	13 / 165 (7.88%)	2 / 70 (2.86%)	6 / 158 (3.80%)
occurrences (all)	17	2	6
Cytomegalovirus infection reactivation			
subjects affected / exposed	8 / 165 (4.85%)	4 / 70 (5.71%)	15 / 158 (9.49%)
occurrences (all)	10	5	23
Influenza			
subjects affected / exposed	16 / 165 (9.70%)	2 / 70 (2.86%)	10 / 158 (6.33%)
occurrences (all)	18	2	12
Nasopharyngitis			
subjects affected / exposed	17 / 165 (10.30%)	1 / 70 (1.43%)	10 / 158 (6.33%)
occurrences (all)	24	3	14
Metabolism and nutrition disorders			

Hypokalaemia			
subjects affected / exposed	15 / 165 (9.09%)	2 / 70 (2.86%)	22 / 158 (13.92%)
occurrences (all)	25	2	47
Hypophosphataemia			
subjects affected / exposed	4 / 165 (2.42%)	4 / 70 (5.71%)	8 / 158 (5.06%)
occurrences (all)	7	9	8
Hypomagnesaemia			
subjects affected / exposed	8 / 165 (4.85%)	2 / 70 (2.86%)	11 / 158 (6.96%)
occurrences (all)	11	2	16
Hyperuricaemia			
subjects affected / exposed	9 / 165 (5.45%)	2 / 70 (2.86%)	1 / 158 (0.63%)
occurrences (all)	9	2	1
Hypertriglyceridaemia			
subjects affected / exposed	16 / 165 (9.70%)	4 / 70 (5.71%)	14 / 158 (8.86%)
occurrences (all)	21	6	15
Hyperkalaemia			
subjects affected / exposed	12 / 165 (7.27%)	5 / 70 (7.14%)	4 / 158 (2.53%)
occurrences (all)	14	6	4
Hyperglycaemia			
subjects affected / exposed	13 / 165 (7.88%)	1 / 70 (1.43%)	6 / 158 (3.80%)
occurrences (all)	20	1	8
Hypercholesterolaemia			
subjects affected / exposed	13 / 165 (7.88%)	8 / 70 (11.43%)	2 / 158 (1.27%)
occurrences (all)	15	8	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 December 2017	The main purpose of the amendment was to extend the available patient population. Due to protracted enrollment and feedback from health authorities and investigators, several inclusion and exclusion criteria were revised. Additionally, with the recent approval of ibrutinib the original protocol-defined list of BAT options would not allow for a complete comparative assessment versus ruxolitinib. Therefore, adding ibrutinib to this list was necessary to reflect the complete list of treatment options for this patient population. Lastly, a Data Monitoring Committee was added based on health authority feedback to include an independent review group.
07 October 2021	The main purpose of the amendment was to restrict the use of live attenuated vaccines (specifically against SARS-CoV-2) in this population with immunocompromised state while on study treatment. Due to feedback from health authorities and based on a risk assessment, protocol language was revised for prohibited concomitant medication. These changes did not add risk to the subject population.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

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

Notes: