Clinical trial results:
A Randomized, Double-Blind Phase 3 Study of Ibrutinib in Combination With Corticosteroids versus Placebo in Combination With Corticosteroids in Subjects with New Onset Chronic Graft Versus Host Disease (cGVHD)

Summary

EudraCT number	2016-003286-26
Trial protocol	HU DE ES AT HR IT FR
Global end of trial date	

Results information

Result version number	v1
This version publication date	31 March 2021
First version publication date	31 March 2021

Trial information

Trial identification

Sponsor protocol code	PCYC-1140-IM

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02959944
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pharmacyclics LLC
Sponsor organisation address	999 East Arques Ave, Sunnyvale, United States, 94085
Public contact	Clinical Trial Information, Pharmacyclics LLC, +1 408774 0330, info@pcyc.com
Scientific contact	Clinical Trial Information, Pharmacyclics LLC, +1 408774 0330, info@pcyc.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	30 March 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 March 2020
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of ibrutinib in combination with prednisone (Arm A) versus placebo in combination with prednisone (Arm B) based on the response rate at 48 weeks (the proportion of responders [CR or PR]) as determined by NIH Consensus Development Project criteria in subjects with new onset moderate to severe cGVHD.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 May 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	15 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	Croatia: 2
Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	France: 22
Country: Number of subjects enrolled	Germany: 9
Country: Number of subjects enrolled	Hungary: 1
Country: Number of subjects enrolled	Italy: 10
Country: Number of subjects enrolled	United States: 79
Country: Number of subjects enrolled	Canada: 5
Country: Number of subjects enrolled	Australia: 18
Country: Number of subjects enrolled	Korea, Republic of: 14
Country: Number of subjects enrolled	Japan: 11
Country: Number of subjects enrolled	Taiwan: 9
Country: Number of subjects enrolled	China: 5
Country: Number of subjects enrolled	Singapore: 2
Worldwide total number of subjects	193
EEA total number of subjects	50

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)	2
Adults (18-64 years)	156
From 65 to 84 years	35
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a Phase 3, multicenter, international, randomized, double-blind study of oral ibrutinib in combination with prednisone vs. placebo in combination with prednisone in subjects with treatment-naive, cGVHD. Subjects participated at 66 sites overall; 24 sites in North America, 18 sites in the EU, and 24 sites in the rest of the world.

Pre-assignment

Screening details:

Eligible patients had to be 12 years or older and had to present with treatment-naive, moderate or severe cGVHD requiring systemic treatment with corticosteroids following allogeneic hematopeietic cell transplant.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

Treatment was allocated using an interactive web response system (IWRS). Subjects, investigators, and the Sponsor were blinded to the treatment assignment. Sponsor team members did not have access to any data that might reveal treatment assignment. Data that may potentially unblind the treatment assignment (ie, study drug plasma concentrations) were handled with special care to ensure that the integrity of the blind was maintained and the potential for bias was minimized.

Arms

Are arms mutually exclusive?	Yes
Arm title	Ibrutinib plus prednisone

Arm description:

Ibrutinib (420 mg) was given orally once daily continuously starting on Week 1, Day 1 until cGVHD progression, progression of underlying malignancy, the initiation of another systemic treatment for cGVHD, or unacceptable toxicity.
Prednisone 1 mg/kg/day was given orally once daily continuously starting on Week 1, Day 1 until unacceptable toxicity or until the subject was successfully tapered from the prednisone. The starting prednisone dose could be as low as 0.5 mg/kg/day if a subject could not tolerate higher doses.

Arm type	Experimental
Investigational medicinal product name	Ibrutinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Ibrutinib (420 mg) was administered using 3 capsule (each containing 140 mg ibrutinib). Ibrutinib (adjusted for cytochrome P450 [CYP] inhibitors or hepatic dysfunction as applicable) was given orally once daily continuously until cGVHD progression, progression of underlying malignancy, the initiation of another systemic treatment for cGVHD, or unacceptable toxicity. Ibrutinib could be withdrawn if cGVHD response was maintained after all immunosuppressants were withdrawn.

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

Dosage and administration details:

Prednisone tablets for oral administration supplied by the Sponsor were available in multiple strengths.

Prednisone 1 mg/kg/day was given orally once daily continuously starting on Week 1, Day 1 until unacceptable toxicity or until the subject was successfully tapered from the prednisone. The starting prednisone dose could be as low as 0.5 mg/kg/day if a subject could not tolerate higher doses.

Arm title	Placebo plus prednisone

Arm description:

Placebo (matching ibrutinib) was given orally once daily continuously starting on Week 1, Day 1 until cGVHD progression, progression of underlying malignancy, the initiation of another systemic treatment for cGVHD, or unacceptable toxicity.
Prednisone 1 mg/kg/day was given orally once daily continuously starting on Week 1, Day 1 until unacceptable toxicity or until the subject was successfully tapered from the prednisone. The starting prednisone dose could be as low as 0.5 mg/kg/day if a subject could not tolerate higher doses.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Placebo (identical to ibrutinib) was administered using 3 capsule. Placebo (adjusted for cytochrome P450 [CYP] inhibitors or hepatic dysfunction as applicable) was given orally once daily continuously until cGVHD progression, progression of underlying malignancy, the initiation of another systemic treatment for cGVHD, or unacceptable toxicity. Placebo could be withdrawn if cGVHD response was maintained after all immunosuppressants were withdrawn.

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

Dosage and administration details:

Prednisone tablets for oral administration supplied by the Sponsor were available in multiple strengths. Prednisone 1 mg/kg/day was given orally once daily continuously starting on Week 1, Day 1 until unacceptable toxicity or until the subject was successfully tapered from the prednisone. The starting prednisone dose could be as low as 0.5 mg/kg/day if a subject could not tolerate higher doses.

Number of subjects in period 1	Ibrutinib plus prednisone	Placebo plus prednisone
Started	95	98
Completed	29	22
Not completed	66	76
Physician decision	11	12
Consent withdrawn by subject	9	6
Subject started another GVHD therapy	2	7
Death	3	2
cGVHD progression	21	30
Progression or relapse of the underlying disease	1	5
Did not receive study drug	1	-

Adverse event not related to disease progression	18	14

Baseline characteristics

Reporting groups	
Reporting group title	Ibrutinib plus prednisone
Reporting group description:	
Ibrutinib (420 mg) was given orally once daily continuously starting on Week 1, Day 1 until cGVHD progression, progression of underlying malignancy, the initiation of another systemic treatment for cGVHD, or unacceptable toxicity. Prednisone 1 mg/kg/day was given orally once daily continuously starting on Week 1, Day 1 until unacceptable toxicity or until the subject was successfully tapered from the prednisone. The starting prednisone dose could be as low as 0.5 mg/kg/day if a subject could not tolerate higher doses.	
Reporting group title	Placebo plus prednisone
Reporting group description:	
Placebo (matching ibrutinib) was given orally once daily continuously starting on Week 1, Day 1 until cGVHD progression, progression of underlying malignancy, the initiation of another systemic treatment for cGVHD, or unacceptable toxicity. Prednisone 1 mg/kg/day was given orally once daily continuously starting on Week 1, Day 1 until unacceptable toxicity or until the subject was successfully tapered from the prednisone. The starting prednisone dose could be as low as 0.5 mg/kg/day if a subject could not tolerate higher doses.	

Reporting group values	Ibrutinib plus prednisone	Placebo plus prednisone	Total
Number of subjects	95	98	193
Age categorical Units: Subjects			
Adolescents (12-17 years)	2	0	2
Adults (18-64 years)	77	79	156
From 65-84 years	16	19	35
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	50.0	51.1	
standard deviation	± 14.48	± 14.99	-
Gender categorical Units: Subjects			
Female	34	33	67
Male	61	65	126

End points

End points reporting groups

Reporting group title	Ibrutinib plus prednisone

Reporting group description:

Ibrutinib (420 mg) was given orally once daily continuously starting on Week 1, Day 1 until cGVHD progression, progression of underlying malignancy, the initiation of another systemic treatment for cGVHD, or unacceptable toxicity.
Prednisone 1 mg/kg/day was given orally once daily continuously starting on Week 1, Day 1 until unacceptable toxicity or until the subject was successfully tapered from the prednisone. The starting prednisone dose could be as low as 0.5 mg/kg/day if a subject could not tolerate higher doses.

Reporting group title	Placebo plus prednisone

Reporting group description:

Placebo (matching ibrutinib) was given orally once daily continuously starting on Week 1, Day 1 until cGVHD progression, progression of underlying malignancy, the initiation of another systemic treatment for cGVHD, or unacceptable toxicity.
Prednisone 1 mg/kg/day was given orally once daily continuously starting on Week 1, Day 1 until unacceptable toxicity or until the subject was successfully tapered from the prednisone. The starting prednisone dose could be as low as 0.5 mg/kg/day if a subject could not tolerate higher doses.

Primary: Response Rate at 48 Weeks

End point title	Response Rate at 48 Weeks

End point description:

Response rate is estimated using the crude proportion of responders. Responders are subjects who had a response (PR or CR) at 48 weeks (study day 296-379) without starting any subsequent therapy for cGVHD or having evidence of relapse of their underlying disease that was indication for transplant prior to response assessment at 48 weeks.

End point type	Primary

End point timeframe:

Number of responders with a CR or PR at 48 weeks.

End point values	Ibrutinib plus prednisone	Placebo plus prednisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	98		
Units: Number of Subjects	39	36		

Statistical analyses

Statistical analysis title	Response Rate at 48 Weeks

Statistical analysis description:

Response rate is estimated using the crude proportion of responders. Responders are subjects who had a response (PR or CR) at 48 weeks (study day 296-379) without starting any subsequent therapy for cGVHD or having evidence of relapse of their underlying disease that was indication for transplant prior to response assessment at 48 weeks. Confidence interval is computed using normal approximation and p-value are computed using non-stratified Chi-Square test.

Comparison groups	Ibrutinib plus prednisone v Placebo plus prednisone

Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5384
Method	Chi-squared
Parameter estimate	Normal approximation
Point estimate	0.043
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.094
upper limit	0.181

Secondary: Number of Subjects with Withdrawal of all Corticosteroids

End point title	Number of Subjects with Withdrawal of all Corticosteroids

End point description:

Time to withdrawal of corticosteroids is computed from randomization date to the first date of withdrawal of all corticosteroids for treatment of cGVHD to 0 mg daily for at least 30 days.

End point type	Secondary

End point timeframe:

Assessments were made every 3 months for 2 years.

End point values	Ibrutinib plus prednisone	Placebo plus prednisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	98		
Units: Number of Patients	40	36		

Statistical analyses

Statistical analysis title	Withdrawal of all Corticosteroids
Comparison groups	Ibrutinib plus prednisone v Placebo plus prednisone
Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.324
Method	Chi-squared

Secondary: Number of Subjects with Withdrawal of all Immunosuppressants

End point title	Number of Subjects with Withdrawal of all Immunosuppressants

End point description:

Time to withdrawal of all immunosuppressants is computed from randomization date to the first date of withdrawal of all immunosuppressants for treatment of cGVHD and it sustains for at least 30 days. All immunosuppressants include corticosteroid but they do not include ibrutinib.

End point type	Secondary

End point timeframe:

Assessments were made every 3 months for 2 years.

End point values	Ibrutinib plus prednisone	Placebo plus prednisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	98		
Units: Number of Subjects	29	24		

Statistical analyses

Statistical analysis title	Withdrawal of all Immunosuppressants
Comparison groups	Ibrutinib plus prednisone v Placebo plus prednisone
Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.275
Method	Chi-squared

Secondary: Response Rate at 24 Weeks

End point title	Response Rate at 24 Weeks

End point description:

Response rate is estimated using the crude proportion of responders. Responders are subjects who had a response (PR or CR) at 24 weeks (Study Day 156-211) without starting any subsequent therapy for cGVHD or having evidence of relapse of their underlying disease that was indication for transplant prior to response assessment at 24 weeks.

End point type	Secondary

End point timeframe:

Number of responders with a CR or PR at 24 weeks.

End point values	Ibrutinib plus prednisone	Placebo plus prednisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	98		
Units: Number of Subjects	45	53		

Statistical analyses

Statistical analysis title	Response Rate at 24 Weeks
Comparison groups	Ibrutinib plus prednisone v Placebo plus prednisone
Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.351
Method	Chi-squared
Parameter estimate	Differences in Rates
Point estimate	-0.067
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.208
upper limit	0.074

Secondary: Improvement in Lee cGVHD Symptom Scale

End point title	Improvement in Lee cGVHD Symptom Scale

End point description:

Clinically meaningful improvement on the Lee cGVHD symptom scale was defined as at least a 7-point decrease in Lee Symptom Scale overall summary score on at least 2 consecutive visits, not preceded by progressive disease, relapse of underlying disease or start of subsequent cGVHD treatment.
The Lee cGVD Symptoms Scale score has 7 subscales (Skin, Energy, Lung, Eye, Nutrition, Mouth and Psychological) with ratings as follows: 0 - Not at all, 1- Slightly, 2 - Moderately, 3 - Quite a bit, 4 - Extremely, with lower values representing better outcome. A score is calculated for each subscale by taking the mean of all items completed if more than 50% were answered and normalizing to a 0 to 100 scale. An overall score is calculated as the average of these 7 subscales if at least 4 subscales have valid scores.

End point type	Secondary

End point timeframe:

Lee cGVHD Symptom Scale was assessed at screening, during treatment (Weeks 5, 13, 25, 37, 49 and every 12 weeks thereafter) and if applicable, at the progressive disease visit and the end-of-treatment visit.

End point values	Ibrutinib plus prednisone	Placebo plus prednisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	98		
Units: Number of Subjects	37	26		

Statistical analyses

Statistical analysis title	Improvement in Overall Lee Score
Comparison groups	Ibrutinib plus prednisone v Placebo plus prednisone
Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0659
Method	Chi-squared
Parameter estimate	Differences in Rates
Point estimate	0.124
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.007
upper limit	0.256

Secondary: Reduction in Corticosteroid Dose Level	
End point title	Reduction in Corticosteroid Dose Level
End point description:	
Reduction in Corticosteroid Dose Level to Less than 0.15 mg/kg/day at 24 Weeks Sustained for at Least 30 Days	
End point type	Secondary
End point timeframe:	
Assessment at 24 weeks.	

End point values	Ibrutinib plus prednisone	Placebo plus prednisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	98		
Units: Number of Subjects	38	45		

Statistical analyses

Statistical analysis title	Reduction in Corticosteroid Dose Level
Comparison groups	Ibrutinib plus prednisone v Placebo plus prednisone

Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4064
Method	Chi-squared
Parameter estimate	Differences in Rates
Point estimate	-0.059
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.199
upper limit	0.08

Secondary: Overall Survival

End point title	Overall Survival

End point description:

End point type	Secondary

End point timeframe:

As the median overall survival was not reached in either arm, landmark analysis data at 24 months are provided.

End point values	Ibrutinib plus prednisone	Placebo plus prednisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	98		
Units: percent				
number (confidence interval 95%)	80.1 (68.9 to 87.6)	80.5 (70.1 to 87.6)		

Statistical analyses

Statistical analysis title	Overall Survival
Comparison groups	Ibrutinib plus prednisone v Placebo plus prednisone
Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.994
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.507
upper limit	1.949

Secondary: Duration of Response

End point title	Duration of Response

End point description:

End point type	Secondary

End point timeframe:

Response assessments were performed during the treatment phase at Weeks 5, 13, 25, 37, 49 and every 12 weeks thereafter, and if applicable, at the progressive disease visit, and the end-of-treatment visit.

End point values	Ibrutinib plus prednisone	Placebo plus prednisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74[1]	80[2]		
Units: months				
number (not applicable)	19.8	10.0		

Notes:

[1] - N = number of subjects who had response of CR/PR at any time during the study

[2] - N = number of subjects who had response of CR/PR at any time during the study

Statistical analyses

Statistical analysis title	Duration of Response
Comparison groups	Placebo plus prednisone v Ibrutinib plus prednisone
Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.101
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.697
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.451
upper limit	1.076

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug up to 30 days after the last dose of study drug or the day before initiation of subsequent cGVHD treatment, whichever comes first.

Adverse event reporting additional description:

As of the date of the data cutoff (20 March 2020), the median time on treatment in the ibrutinib plus prednisone arm was 5.4 months and in the placebo plus prednisone arm was 6.4 months.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Ibrutinib plus Prednisone Safety Population

Reporting group description:

All patients who received at least one dose of study treatment.

Reporting group title	Placebo plus Prednisone Safety Population

Reporting group description:

All patients who received at least one dose of study treatment.

Serious adverse events	Ibrutinib plus Prednisone Safety Population	Placebo plus Prednisone Safety Population	
Total subjects affected by serious adverse events			
subjects affected / exposed	44 / 94 (46.81%)	46 / 96 (47.92%)	
number of deaths (all causes)	17	16	
number of deaths resulting from adverse events	9	6	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia recurrent			
subjects affected / exposed	1 / 94 (1.06%)	3 / 96 (3.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Leukaemia recurrent			
subjects affected / exposed	0 / 94 (0.00%)	2 / 96 (2.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer			
subjects affected / exposed	0 / 94 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Primary myelofibrosis			
subjects affected / exposed	0 / 94 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 94 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phlebitis			
subjects affected / exposed	0 / 94 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 94 (1.06%)	2 / 96 (2.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	0 / 94 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 94 (1.06%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Malaise			
subjects affected / exposed	1 / 94 (1.06%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Chronic graft versus host disease			

subjects affected / exposed	1 / 94 (1.06%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Graft versus host disease			
subjects affected / exposed	0 / 94 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypogammaglobulinaemia			
subjects affected / exposed	1 / 94 (1.06%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Metrorrhagia			
subjects affected / exposed	0 / 94 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scrotal oedema			
subjects affected / exposed	0 / 94 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 94 (0.00%)	3 / 96 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	0 / 94 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 94 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hypoxia			
subjects affected / exposed	0 / 94 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 94 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis chronic			
subjects affected / exposed	1 / 94 (1.06%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary mass			
subjects affected / exposed	1 / 94 (1.06%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	1 / 94 (1.06%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	2 / 94 (2.13%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 94 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Substance-induced psychotic disorder			
subjects affected / exposed	0 / 94 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Tic			
subjects affected / exposed	0 / 94 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mania			
subjects affected / exposed	1 / 94 (1.06%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 94 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 94 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased			
subjects affected / exposed	1 / 94 (1.06%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	0 / 94 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	1 / 94 (1.06%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			

subjects affected / exposed	1 / 94 (1.06%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 94 (1.06%)	2 / 96 (2.08%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	0 / 94 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 94 (1.06%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 94 (1.06%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 94 (1.06%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocarditis			
subjects affected / exposed	1 / 94 (1.06%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	2 / 94 (2.13%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			

Ischaemic stroke			
subjects affected / exposed	1 / 94 (1.06%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Posterior reversible encephalopathy syndrome			
subjects affected / exposed	1 / 94 (1.06%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 94 (1.06%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	2 / 94 (2.13%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 94 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coagulopathy			
subjects affected / exposed	0 / 94 (0.00%)	10 / 96 (10.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombotic microangiopathy			
subjects affected / exposed	0 / 94 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 94 (1.06%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Eye disorders			
Diplopia			
subjects affected / exposed	1 / 94 (1.06%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 94 (0.00%)	2 / 96 (2.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 94 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	2 / 94 (2.13%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 94 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 94 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 94 (1.06%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	1 / 94 (1.06%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Ileus			
subjects affected / exposed	1 / 94 (1.06%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	1 / 94 (1.06%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	1 / 94 (1.06%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic enzyme abnormality			
subjects affected / exposed	1 / 94 (1.06%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 94 (1.06%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 94 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cirrhosis			
subjects affected / exposed	1 / 94 (1.06%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 94 (1.06%)	2 / 96 (2.08%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cystitis haemorrhagic			
subjects affected / exposed	0 / 94 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 94 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Haematuria			
subjects affected / exposed	2 / 94 (2.13%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	1 / 94 (1.06%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive nephropathy			
subjects affected / exposed	1 / 94 (1.06%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureterolithiasis			
subjects affected / exposed	1 / 94 (1.06%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Muscle atrophy			
subjects affected / exposed	1 / 94 (1.06%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myopathy			
subjects affected / exposed	1 / 94 (1.06%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Rhabdomyolysis			
subjects affected / exposed	1 / 94 (1.06%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	6 / 94 (6.38%)	8 / 96 (8.33%)	
occurrences causally related to treatment / all	2 / 7	4 / 9	
deaths causally related to treatment / all	0 / 1	0 / 0	
Influenza			
subjects affected / exposed	4 / 94 (4.26%)	3 / 96 (3.13%)	
occurrences causally related to treatment / all	0 / 4	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia respiratory syncytial viral			
subjects affected / exposed	0 / 94 (0.00%)	2 / 96 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 94 (1.06%)	2 / 96 (2.08%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	1 / 1	0 / 1	
Bacteraemia			
subjects affected / exposed	0 / 94 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 94 (1.06%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	0 / 94 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus infection			

subjects affected / exposed	0 / 94 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye infection			
subjects affected / exposed	0 / 94 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemophilus infection			
subjects affected / exposed	0 / 94 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella sepsis			
subjects affected / exposed	0 / 94 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 94 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parainfluenzae virus infection			
subjects affected / exposed	0 / 94 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parotitis			
subjects affected / exposed	0 / 94 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	0 / 94 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia haemophilus			

subjects affected / exposed	0 / 94 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia parainfluenzae viral			
subjects affected / exposed	0 / 94 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	0 / 94 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 94 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	2 / 94 (2.13%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 1	
Sinusitis			
subjects affected / exposed	0 / 94 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	0 / 94 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 94 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			

subjects affected / exposed	3 / 94 (3.19%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dacryocystitis			
subjects affected / exposed	1 / 94 (1.06%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis			
subjects affected / exposed	1 / 94 (1.06%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epstein-Barr virus infection			
subjects affected / exposed	1 / 94 (1.06%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella bacteraemia			
subjects affected / exposed	1 / 94 (1.06%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mastoiditis			
subjects affected / exposed	1 / 94 (1.06%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periorbital cellulitis			
subjects affected / exposed	1 / 94 (1.06%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia fungal			
subjects affected / exposed	1 / 94 (1.06%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia legionella			

subjects affected / exposed	1 / 94 (1.06%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	2 / 94 (2.13%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Sinusitis fungal			
subjects affected / exposed	1 / 94 (1.06%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	1 / 94 (1.06%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	2 / 94 (2.13%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 94 (1.06%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 94 (1.06%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	1 / 94 (1.06%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperglycaemia			

subjects affected / exposed	2 / 94 (2.13%)	2 / 96 (2.08%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 94 (0.00%)	2 / 96 (2.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Steroid diabetes			
subjects affected / exposed	0 / 94 (0.00%)	2 / 96 (2.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 94 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Ibrutinib plus Prednisone Safety Population	Placebo plus Prednisone Safety Population	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	93 / 94 (98.94%)	95 / 96 (98.96%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	10 / 94 (10.64%)	13 / 96 (13.54%)	
occurrences (all)	16	14	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	16 / 94 (17.02%)	17 / 96 (17.71%)	
occurrences (all)	21	26	
Pyrexia			
subjects affected / exposed	8 / 94 (8.51%)	15 / 96 (15.63%)	
occurrences (all)	10	20	
Oedema peripheral			

subjects affected / exposed	25 / 94 (26.60%)	12 / 96 (12.50%)	
occurrences (all)	38	16	
Asthenia			
subjects affected / exposed	5 / 94 (5.32%)	6 / 96 (6.25%)	
occurrences (all)	6	7	
Immune system disorders			
Hypogammaglobulinaemia			
subjects affected / exposed	5 / 94 (5.32%)	3 / 96 (3.13%)	
occurrences (all)	5	3	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	20 / 94 (21.28%)	29 / 96 (30.21%)	
occurrences (all)	22	37	
Dyspnoea			
subjects affected / exposed	9 / 94 (9.57%)	13 / 96 (13.54%)	
occurrences (all)	11	15	
Rhinorrhoea			
subjects affected / exposed	3 / 94 (3.19%)	8 / 96 (8.33%)	
occurrences (all)	5	8	
Epistaxis			
subjects affected / exposed	7 / 94 (7.45%)	3 / 96 (3.13%)	
occurrences (all)	8	4	
Productive cough			
subjects affected / exposed	5 / 94 (5.32%)	3 / 96 (3.13%)	
occurrences (all)	8	3	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	25 / 94 (26.60%)	17 / 96 (17.71%)	
occurrences (all)	27	19	
Anxiety			
subjects affected / exposed	4 / 94 (4.26%)	6 / 96 (6.25%)	
occurrences (all)	4	7	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	7 / 94 (7.45%)	17 / 96 (17.71%)	
occurrences (all)	11	30	

Aspartate aminotransferase increased			
subjects affected / exposed	1 / 94 (1.06%)	14 / 96 (14.58%)	
occurrences (all)	1	18	
Blood alkaline phosphatase increased			
subjects affected / exposed	3 / 94 (3.19%)	6 / 96 (6.25%)	
occurrences (all)	3	11	
Platelet count decreased			
subjects affected / exposed	7 / 94 (7.45%)	6 / 96 (6.25%)	
occurrences (all)	13	9	
Weight increased			
subjects affected / exposed	5 / 94 (5.32%)	6 / 96 (6.25%)	
occurrences (all)	7	6	
Blood creatinine increased			
subjects affected / exposed	5 / 94 (5.32%)	5 / 96 (5.21%)	
occurrences (all)	8	6	
Weight decreased			
subjects affected / exposed	5 / 94 (5.32%)	4 / 96 (4.17%)	
occurrences (all)	5	4	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	3 / 94 (3.19%)	7 / 96 (7.29%)	
occurrences (all)	4	7	
Contusion			
subjects affected / exposed	9 / 94 (9.57%)	4 / 96 (4.17%)	
occurrences (all)	10	5	
Cardiac disorders			
Palpitations			
subjects affected / exposed	5 / 94 (5.32%)	3 / 96 (3.13%)	
occurrences (all)	5	3	
Nervous system disorders			
Dizziness			
subjects affected / exposed	9 / 94 (9.57%)	11 / 96 (11.46%)	
occurrences (all)	9	16	
Headache			
subjects affected / exposed	12 / 94 (12.77%)	10 / 96 (10.42%)	
occurrences (all)	17	16	

Tremor			
subjects affected / exposed	5 / 94 (5.32%)	9 / 96 (9.38%)	
occurrences (all)	5	10	
Peripheral sensory neuropathy			
subjects affected / exposed	6 / 94 (6.38%)	2 / 96 (2.08%)	
occurrences (all)	7	4	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	18 / 94 (19.15%)	15 / 96 (15.63%)	
occurrences (all)	30	25	
Anaemia			
subjects affected / exposed	4 / 94 (4.26%)	12 / 96 (12.50%)	
occurrences (all)	17	23	
Increased tendency to bruise			
subjects affected / exposed	9 / 94 (9.57%)	8 / 96 (8.33%)	
occurrences (all)	10	8	
Neutropenia			
subjects affected / exposed	1 / 94 (1.06%)	6 / 96 (6.25%)	
occurrences (all)	1	10	
Eye disorders			
Vision blurred			
subjects affected / exposed	7 / 94 (7.45%)	9 / 96 (9.38%)	
occurrences (all)	7	10	
Cataract			
subjects affected / exposed	0 / 94 (0.00%)	6 / 96 (6.25%)	
occurrences (all)	0	6	
Dry eye			
subjects affected / exposed	5 / 94 (5.32%)	4 / 96 (4.17%)	
occurrences (all)	6	4	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	7 / 94 (7.45%)	14 / 96 (14.58%)	
occurrences (all)	7	14	
Diarrhoea			
subjects affected / exposed	16 / 94 (17.02%)	13 / 96 (13.54%)	
occurrences (all)	26	19	
Nausea			

subjects affected / exposed	11 / 94 (11.70%)	12 / 96 (12.50%)	
occurrences (all)	18	14	
Vomiting			
subjects affected / exposed	15 / 94 (15.96%)	8 / 96 (8.33%)	
occurrences (all)	19	8	
Abdominal pain			
subjects affected / exposed	6 / 94 (6.38%)	6 / 96 (6.25%)	
occurrences (all)	8	6	
Dyspepsia			
subjects affected / exposed	6 / 94 (6.38%)	5 / 96 (5.21%)	
occurrences (all)	6	5	
Hepatobiliary disorders			
Hepatic function abnormal			
subjects affected / exposed	7 / 94 (7.45%)	6 / 96 (6.25%)	
occurrences (all)	15	11	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	6 / 94 (6.38%)	7 / 96 (7.29%)	
occurrences (all)	7	10	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	3 / 94 (3.19%)	8 / 96 (8.33%)	
occurrences (all)	7	9	
Endocrine disorders			
Cushingoid			
subjects affected / exposed	3 / 94 (3.19%)	6 / 96 (6.25%)	
occurrences (all)	3	6	
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	17 / 94 (18.09%)	16 / 96 (16.67%)	
occurrences (all)	20	27	
Back pain			
subjects affected / exposed	6 / 94 (6.38%)	10 / 96 (10.42%)	
occurrences (all)	6	11	
Muscular weakness			

subjects affected / exposed	5 / 94 (5.32%)	9 / 96 (9.38%)	
occurrences (all)	7	9	
Arthralgia			
subjects affected / exposed	10 / 94 (10.64%)	8 / 96 (8.33%)	
occurrences (all)	16	10	
Musculoskeletal pain			
subjects affected / exposed	2 / 94 (2.13%)	5 / 96 (5.21%)	
occurrences (all)	2	6	
Myalgia			
subjects affected / exposed	1 / 94 (1.06%)	5 / 96 (5.21%)	
occurrences (all)	1	6	
Pain in extremity			
subjects affected / exposed	5 / 94 (5.32%)	5 / 96 (5.21%)	
occurrences (all)	6	5	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	15 / 94 (15.96%)	13 / 96 (13.54%)	
occurrences (all)	22	19	
Nasopharyngitis			
subjects affected / exposed	6 / 94 (6.38%)	9 / 96 (9.38%)	
occurrences (all)	6	12	
Rhinovirus infection			
subjects affected / exposed	1 / 94 (1.06%)	7 / 96 (7.29%)	
occurrences (all)	1	7	
Bronchitis			
subjects affected / exposed	3 / 94 (3.19%)	6 / 96 (6.25%)	
occurrences (all)	3	7	
Cytomegalovirus infection			
subjects affected / exposed	3 / 94 (3.19%)	6 / 96 (6.25%)	
occurrences (all)	3	7	
Conjunctivitis			
subjects affected / exposed	4 / 94 (4.26%)	5 / 96 (5.21%)	
occurrences (all)	4	6	
Herpes zoster			
subjects affected / exposed	3 / 94 (3.19%)	5 / 96 (5.21%)	
occurrences (all)	3	5	

Influenza			
subjects affected / exposed	5 / 94 (5.32%)	4 / 96 (4.17%)	
occurrences (all)	5	5	
Paronychia			
subjects affected / exposed	5 / 94 (5.32%)	2 / 96 (2.08%)	
occurrences (all)	5	2	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	4 / 94 (4.26%)	14 / 96 (14.58%)	
occurrences (all)	6	23	
Hypokalaemia			
subjects affected / exposed	11 / 94 (11.70%)	13 / 96 (13.54%)	
occurrences (all)	20	18	
Hypophosphataemia			
subjects affected / exposed	3 / 94 (3.19%)	8 / 96 (8.33%)	
occurrences (all)	5	10	
Hyperkalaemia			
subjects affected / exposed	3 / 94 (3.19%)	7 / 96 (7.29%)	
occurrences (all)	3	9	
Hypomagnesaemia			
subjects affected / exposed	4 / 94 (4.26%)	7 / 96 (7.29%)	
occurrences (all)	10	9	
Hyponatraemia			
subjects affected / exposed	9 / 94 (9.57%)	7 / 96 (7.29%)	
occurrences (all)	10	12	
Decreased appetite			
subjects affected / exposed	7 / 94 (7.45%)	6 / 96 (6.25%)	
occurrences (all)	8	7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 October 2016	• Inclusion criterion requirement for bilirubin was revised from "direct bilirubin ≤1.5 x ULN" to "total bilirubin ≤1.5 x ULN" and requirement for highly effective methods of birth control was revised from "for 30 days" to "for 90 days" after the last dose of study drug (ibrutinib/placebo). • Dose modification guidance changes included o Addition of text stating that AEs considered related to concomitant high dose steroids do not require dose modification or holding of ibrutinib. o Addition of text stating that for subjects who are at 140 mg on a CYP3A inhibitor, the subject may resume that dose on the second occurrence of a toxicity after resolution of that toxicity. Study drug (ibrutinib/placebo) will be discontinued after a third occurrence of that toxicity. o Revision of text for hepatic impaired subjects; ie, revised from "for subjects with direct bilirubin" to "for subjects with total bilirubin" >3 x ULN (Grade 3 CTCAE), ibrutinib will be held until the "total" bilirubin returns to ≤1.5 x ULN (Grade 1 CTCAE) or baseline. Added that subjects who are on 140 mg dose at the first occurrence of hepatic impairment, the subject may re-start at the 140 mg dose but will discontinue study drug (ibrutinib/placebo) at the second occurrence of hepatic impairment. • Summary of clinical safety was updated to align with current IB. • Infection surveillance monitoring guidance added that subjects should be monitored closely for signs or symptoms of aspergillus infection.
03 October 2017	• Clarified that treatment can be discontinued after response in disease symptoms and withdrawal of other systemic immunosuppressants • Inclusion criterion changed to allow "Total bilirubin of >1.5 x ULN to 3.0 x ULN if due to GVHD". • Immunosuppressants dosing for treatment of aGVHD to be stable for 2 weeks prior to screening was removed • Exclusion criteria updated to o Allow subjects who received systemic corticosteroid treatment for cGVHD for a short period of time prior to signing consent o Exclude subjects with presence of single-organ, genito-urinary involvement with cGVHD as the only manifestation of cGVHD o Exclude only subjects with hepatic impairment Child Pugh Class C (previously excluded Class B or C) o Exclude subjects who had received a DLI ≤56 days before randomization o Clarify that subjects on secondary prophylaxis for fungal infections and some other low grade infections can be enrolled o Exclude subjects requiring treatment with a strong CYP3A inducer o Remove exclusion of subjects who are on strong CYP inhibitors • Updated the dose modification guidelines for adverse reactions for subjects with hepatic impairment and for subjects using a CYP3A inhibitor • Allowed prednisone to treat cGVHD to start prior to randomization • Clarified restart of original blinded study therapy in the event of cGVHD worsening following ibrutinib/placebo withdrawal • Clarified that the secondary endpoint of "withdrawal of all immunosuppressants at 48 weeks" was "time to withdrawal of all immunosuppressants"; revised DOR and Lee cGVHD Symptom Scale improvement from exploratory to secondary endpoints • Updated the study evaluation requirements: added late effects surveillance for adolescents up to 5 years post randomization; simplified ECG procedure; clarified the overall response definition per NIH criteria. • Specified that tapering of an increased prednisone dose for flares should begin within 4 weeks • Updated statistical methods and analysis plans

06 February 2019	• The primary objective/primary endpoint revised from evaluating the efficacy based on response rate at 24 weeks, to evaluating the efficacy based on response rate at 48 weeks; evaluation of response rate at 24 weeks added as a secondary objective/endpoint. • Efficacy analyses were to be performed on the ITT population (all randomized subjects), rather than the mITT population (which excludes randomized subjects who had evidence of disease progression before randomization but was not identified until after randomization). • Clarified that cGVHD flares were expected but if they occurred during response assessments, the clinician had discretion to re-evaluate response when flare had resolved or disease had progressed. • Expected length of follow-up for adolescents (<22 years of age at the time of randomization) revised from 5 years after randomization to up to 5 years after randomization; however, the study may close after the last subject below 18 years of age has exited the study if all other participating subjects have completed a minimum of 1 year of follow-up.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported