

**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	12 July 2021

Results information

Result version number	v2 (current)
This version publication date	11 January 2022
First version publication date	31 March 2021
Version creation reason	

Trial information**Trial identification**

Sponsor protocol code	PCYC-1140-IM
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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	995 E Arques Ave, Sunnyvale, United States, CA 94085
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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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	12 July 2021
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	12 July 2021
Was the trial ended prematurely?	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 (CT 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	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 18
Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Canada: 5
Country: Number of subjects enrolled	China: 5
Country: Number of subjects enrolled	Croatia: 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	Japan: 11
Country: Number of subjects enrolled	Singapore: 2
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 14
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	Taiwan: 9
Country: Number of subjects enrolled	United States: 79
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 hematopoietic 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	Investigator, Subject, 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 + 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 dose.

Arm title	Placebo + Prednisone
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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 + Prednisone	Placebo + Prednisone
Started	95	98
Completed	13	2
Not completed	82	96
Physician decision	22	26
Consent withdrawn by subject	8	10
AE not related to progressive disease	19	16
Relapse of underlying disease	3	5
Death	4	1
Progressive disease - cGVHD	22	30
Did not receive study drug	1	2

Subject started another GVHD treatment	2	6
Lost to follow-up	1	-

Baseline characteristics

Reporting groups

Reporting group title	Ibrutinib + Prednisone
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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 + Prednisone
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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 + Prednisone	Placebo + Prednisone	Total
Number of subjects	95	98	193
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	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 + Prednisone
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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 + Prednisone
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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
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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 week.

End point type	Primary
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End point timeframe:

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

End point values	Ibrutinib + Prednisone	Placebo + Prednisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	98		
Units: percent				
number (not applicable)	41.1	36.7		

Statistical analyses

Statistical analysis title	Response Rate at 48 Weeks
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Statistical analysis description:

Confidence interval is computed using normal approximation and p-value are computed using non-stratified Chi-Square test.

Comparison groups	Placebo + Prednisone v Ibrutinib + Prednisone
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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: Time to Withdrawal of all Corticosteroids

End point title	Time to 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 + Prednisone	Placebo + Prednisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	98		
Units: percent				
number (not applicable)	47.4	38.8		

Statistical analyses

Statistical analysis title	Withdrawal of all Corticosteroids
Statistical analysis description: Gray's chi-square test (p-value) and the cumulative incidence function (95% CI) were calculated using SAS lifetest procedure adjusting for competing risks including death, cGVHD progression, relapse of underlying disease, and start of subsequent cGVHD therapy.	
Comparison groups	Ibrutinib + Prednisone v Placebo + Prednisone
Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.281
Method	Gray`s chi-square test

Secondary: Time to Withdrawal of all Immunosuppressants

End point title	Time to Withdrawal of all Immunosuppressants
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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 sustained for at least 30 days. All immunosuppressants include corticosteroid but they do not include ibrutinib.

End point type	Secondary
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End point timeframe:

Assessments were made every 3 months for 2 years.

End point values	Ibrutinib + Prednisone	Placebo + Prednisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	98		
Units: percent				
number (not applicable)	38.9	30.6		

Statistical analyses

Statistical analysis title	Withdrawal of all Immunosuppressants
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Statistical analysis description:

Gray's chi-square test (p-value) and the Cumulative incidence function (95% CI) were calculated using SAS lifetest procedure adjusting for competing risks including death, cGVHD progression, relapse of underlying disease, and start of subsequent cGVHD therapy.

Comparison groups	Ibrutinib + Prednisone v Placebo + Prednisone
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Number of subjects included in analysis	193
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Analysis specification	Pre-specified
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Analysis type	superiority
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P-value	= 0.216
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Method	Gray`s chi-square test
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Secondary: Withdrawal of all Immunosuppressants incl. study treatment

End point title	Withdrawal of all Immunosuppressants incl. study treatment
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End point description:

Time to withdrawal of all immunosuppressants including corticosteroid is computed from randomization date to the first date of withdrawal of all immunosuppressants for treatment of cGVHD sustained for at least 30 days. In addition, during this 30-day period, subject either should have been on 0 mg for Ibr/Pbo continued for at least 30 days OR discontinued Ibr/Pbo due to Investigator decision related to subject no longer needing treatment for cGVHD.

End point type	Secondary
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End point timeframe:

Assessments were made every 3 months for 2 years.

End point values	Ibrutinib + Prednisone	Placebo + Prednisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	98		
Units: percent				
number (not applicable)	17.9	8.2		

Statistical analyses

Statistical analysis title	Withdrawal all Immunosuppressants incl. study drug
Statistical analysis description:	
Gray's chi-square test (p-value) and the Cumulative incidence function (95% CI) were calculated using SAS lifetest procedure adjusting for competing risks including death, cGVHD progression, relapse of underlying disease, and start of subsequent cGVHD therapy.	
Comparison groups	Ibrutinib + Prednisone v Placebo + Prednisone
Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.03
Method	Gray`s chi-square test

Secondary: Response Rate at 24 Weeks

End point title	Response Rate at 24 Weeks
End point description:	
Response rate was 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:	
Percentage of responders with a CR or PR at 24 weeks.	

End point values	Ibrutinib + Prednisone	Placebo + Prednisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	98		
Units: percent				
number (not applicable)	47.4	54.1		

Statistical analyses

Statistical analysis title	Response Rate at 24 Weeks
Statistical analysis description:	
Confidence interval is computed using normal approximation and p-value are computed using non-	

stratified Chi-Square test.

Comparison groups	Ibrutinib + Prednisone v Placebo + Prednisone
Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.351
Method	Chi-squared
Parameter estimate	Normal approximation
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:	<p>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.</p> <p>The Lee cGVHD 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.</p>
End point type	Secondary
End point timeframe:	<p>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.</p>

End point values	Ibrutinib + Prednisone	Placebo + Prednisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	98		
Units: percent				
number (not applicable)	43.2	30.6		

Statistical analyses

Statistical analysis title	Improvement in Overall Lee Score
Statistical analysis description:	<p>Confidence interval is computed using normal approximation and p-value are computed using non-stratified Chi-Square test.</p>
Comparison groups	Ibrutinib + Prednisone v Placebo + Prednisone

Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0708
Method	Chi-squared
Parameter estimate	Normal approximation
Point estimate	0.125
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.01
upper limit	0.261

Secondary: Improvement in modified Lee cGVHD Symptom Scale

End point title	Improvement in modified Lee cGVHD Symptom Scale
End point description:	
Clinically meaningful improvement on Modified Lee cGVHD symptom scale is defined as at least a 5- or 6-point decrease in Modified 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.	
End point type	Secondary
End point timeframe:	
Modified 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 + Prednisone	Placebo + Prednisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	98		
Units: percent				
number (not applicable)	52.6	38.8		

Statistical analyses

Statistical analysis title	Improvement in modified Lee Score
Statistical analysis description:	
Confidence interval computed using normal approximation and p-value are computed using non-stratified Chi-Square test.	
Comparison groups	Placebo + Prednisone v Ibrutinib + Prednisone

Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0533
Method	Chi-squared
Parameter estimate	Normal approximation
Point estimate	0.139
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.001
upper limit	0.278

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 + Prednisone	Placebo + Prednisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	98		
Units: percent				
number (not applicable)	41.1	45.9		

Statistical analyses

Statistical analysis title	Reduction in Corticosteroid Dose Level
Statistical analysis description: Confidence interval is computed using normal approximation and p-value is computed using non-stratified Chi-Square test.	
Comparison groups	Ibrutinib + Prednisone v Placebo + Prednisone
Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4955
Method	Chi-squared
Parameter estimate	Normal approximation
Point estimate	-0.049

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.188
upper limit	0.091

Secondary: Overall Survival

End point title	Overall Survival
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End point description:

End point type	Secondary
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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 + Prednisone	Placebo + Prednisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	98		
Units: percent				
number (not applicable)	79.6	79.7		

Statistical analyses

Statistical analysis title	Overall Survival
Comparison groups	Ibrutinib + Prednisone v Placebo + Prednisone
Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	1.061
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.591
upper limit	1.904

Secondary: Duration of Response

End point title	Duration of Response
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End point description:

End point type	Secondary
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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 + Prednisone	Placebo + Prednisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	98		
Units: month				
number (not applicable)	19.1	10.2		

Statistical analyses

Statistical analysis title	Duration of Response
Comparison groups	Ibrutinib + Prednisone v Placebo + Prednisone
Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.717
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.482
upper limit	1.068

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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	22.1
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Reporting groups

Reporting group title	Ibrutinib
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Reporting group description: -

Reporting group title	Placebo
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Reporting group description: -

Serious adverse events	Ibrutinib	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	51 / 94 (54.26%)	49 / 96 (51.04%)	
number of deaths (all causes)	23	21	
number of deaths resulting from adverse events	13	7	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
ACUTE MYELOID LEUKAEMIA			
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	
ACUTE MYELOID LEUKAEMIA RECURRENT			
subjects affected / exposed	2 / 94 (2.13%)	4 / 96 (4.17%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 2	0 / 2	
ACUTE PROMYELOCYTIC LEUKAEMIA			
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	
BENIGN NEOPLASM OF TESTIS			

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	
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	
COLON 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	
LEUKAEMIA RECURRENT			
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 / 0	
POST TRANSPLANT LYMPHOPROLIFERATIVE DISORDER			
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	1 / 1	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%)	2 / 96 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
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			

DEATH			
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 / 2	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	
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	
PYREXIA			
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 / 0	0 / 0	
Immune system disorders			
CHRONIC GRAFT VERSUS HOST DISEASE			
subjects affected / exposed	3 / 94 (3.19%)	3 / 96 (3.13%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
GRAFT VERSUS HOST DISEASE			
subjects affected / exposed	0 / 94 (0.00%)	3 / 96 (3.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
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			
INTERMENSTRUAL BLEEDING			

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	
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			
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	
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	
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	
PULMONARY EMBOLISM			
subjects affected / exposed	0 / 94 (0.00%)	4 / 96 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
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	
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	
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	
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			
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	
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	
Cardiac disorders			
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	
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	
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	

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	
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	1 / 1	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%)	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	
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	
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			
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	
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	
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	
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	
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	
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	
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	
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	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	
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	2 / 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	
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%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEPHROLITHIASIS			
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	
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	
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	
URETEROLITHIASIS			
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	
URETHRAL STENOSIS			
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	
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			
BACTERAEMIA			
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	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	
COVID-19			
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	
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	
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 COLITIS			
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	
CYTOMEGALOVIRUS INFECTION REACTIVATION			
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	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	
DIVERTICULITIS			
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 REACTIVATION			
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 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	
INFLUENZA			
subjects affected / exposed	4 / 94 (4.26%)	4 / 96 (4.17%)	
occurrences causally related to treatment / all	0 / 4	1 / 4	
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	
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	
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
MEDIASTINITIS		
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
METAPNEUMOVIRUS 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	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
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
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
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
PNEUMOCYSTIS JIROVECI PNEUMONIA		
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
PNEUMONIA		

subjects affected / exposed	6 / 94 (6.38%)	9 / 96 (9.38%)	
occurrences causally related to treatment / all	2 / 8	4 / 10	
deaths causally related to treatment / all	0 / 1	0 / 0	
PNEUMONIA CYTOMEGALOVIRAL			
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	
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	1 / 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	
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 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	
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	
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	
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	
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	
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	
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	
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	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	
URINARY TRACT INFECTION BACTERIAL			
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	
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	
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			
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	
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	

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

Non-serious adverse events	Ibrutinib	Placebo	
Total subjects affected by non-serious adverse events subjects affected / exposed	88 / 94 (93.62%)	92 / 96 (95.83%)	
Vascular disorders HYPERTENSION subjects affected / exposed occurrences (all)	10 / 94 (10.64%) 16	13 / 96 (13.54%) 14	
General disorders and administration site conditions ASTHENIA subjects affected / exposed occurrences (all) FATIGUE subjects affected / exposed occurrences (all) INFLUENZA LIKE ILLNESS subjects affected / exposed occurrences (all) OEDEMA PERIPHERAL subjects affected / exposed occurrences (all) PYREXIA subjects affected / exposed occurrences (all)	5 / 94 (5.32%) 7 17 / 94 (18.09%) 22 5 / 94 (5.32%) 6 25 / 94 (26.60%) 37 7 / 94 (7.45%) 7	6 / 96 (6.25%) 7 18 / 96 (18.75%) 30 1 / 96 (1.04%) 1 13 / 96 (13.54%) 17 16 / 96 (16.67%) 22	
Immune system disorders HYPOGAMMAGLOBULINAEMIA subjects affected / exposed occurrences (all)	5 / 94 (5.32%) 5	3 / 96 (3.13%) 3	
Respiratory, thoracic and mediastinal disorders COUGH subjects affected / exposed occurrences (all) DYSPNOEA subjects affected / exposed occurrences (all)	21 / 94 (22.34%) 24 9 / 94 (9.57%) 12	29 / 96 (30.21%) 37 14 / 96 (14.58%) 16	

DYSпноEA EXERTIONAL subjects affected / exposed occurrences (all)	2 / 94 (2.13%) 2	5 / 96 (5.21%) 6	
EPISTAXIS subjects affected / exposed occurrences (all)	7 / 94 (7.45%) 8	4 / 96 (4.17%) 5	
OROPHARYNGEAL PAIN subjects affected / exposed occurrences (all)	5 / 94 (5.32%) 6	3 / 96 (3.13%) 3	
PRODUCTIVE COUGH subjects affected / exposed occurrences (all)	5 / 94 (5.32%) 8	3 / 96 (3.13%) 3	
RHINORRHOEA subjects affected / exposed occurrences (all)	3 / 94 (3.19%) 5	8 / 96 (8.33%) 8	
Psychiatric disorders			
ANXIETY subjects affected / exposed occurrences (all)	5 / 94 (5.32%) 5	7 / 96 (7.29%) 8	
DEPRESSION subjects affected / exposed occurrences (all)	5 / 94 (5.32%) 6	2 / 96 (2.08%) 2	
INSOMNIA subjects affected / exposed occurrences (all)	26 / 94 (27.66%) 28	18 / 96 (18.75%) 20	
Investigations			
ALANINE AMINOTRANSFERASE INCREASED subjects affected / exposed occurrences (all)	7 / 94 (7.45%) 11	16 / 96 (16.67%) 29	
ASPARTATE AMINOTRANSFERASE INCREASED subjects affected / exposed occurrences (all)	1 / 94 (1.06%) 1	13 / 96 (13.54%) 17	
BLOOD ALKALINE PHOSPHATASE INCREASED subjects affected / exposed occurrences (all)	3 / 94 (3.19%) 3	6 / 96 (6.25%) 12	

BLOOD CREATININE INCREASED subjects affected / exposed occurrences (all)	5 / 94 (5.32%) 8	6 / 96 (6.25%) 7	
PLATELET COUNT DECREASED subjects affected / exposed occurrences (all)	7 / 94 (7.45%) 13	6 / 96 (6.25%) 10	
WEIGHT DECREASED subjects affected / exposed occurrences (all)	6 / 94 (6.38%) 6	4 / 96 (4.17%) 4	
WEIGHT INCREASED subjects affected / exposed occurrences (all)	5 / 94 (5.32%) 7	6 / 96 (6.25%) 6	
Injury, poisoning and procedural complications			
CONTUSION subjects affected / exposed occurrences (all)	10 / 94 (10.64%) 11	4 / 96 (4.17%) 5	
FALL subjects affected / exposed occurrences (all)	3 / 94 (3.19%) 4	7 / 96 (7.29%) 7	
Cardiac disorders			
PALPITATIONS subjects affected / exposed occurrences (all)	5 / 94 (5.32%) 5	3 / 96 (3.13%) 3	
Nervous system disorders			
DIZZINESS subjects affected / exposed occurrences (all)	10 / 94 (10.64%) 10	11 / 96 (11.46%) 16	
HEADACHE subjects affected / exposed occurrences (all)	13 / 94 (13.83%) 19	12 / 96 (12.50%) 17	
PERIPHERAL SENSORY NEUROPATHY subjects affected / exposed occurrences (all)	6 / 94 (6.38%) 7	2 / 96 (2.08%) 5	
TREMOR subjects affected / exposed occurrences (all)	5 / 94 (5.32%) 5	9 / 96 (9.38%) 10	

Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	4 / 94 (4.26%)	11 / 96 (11.46%)	
occurrences (all)	17	21	
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	11	
THROMBOCYTOPENIA			
subjects affected / exposed	18 / 94 (19.15%)	15 / 96 (15.63%)	
occurrences (all)	30	25	
Eye disorders			
CATARACT			
subjects affected / exposed	2 / 94 (2.13%)	7 / 96 (7.29%)	
occurrences (all)	3	8	
VISION BLURRED			
subjects affected / exposed	7 / 94 (7.45%)	9 / 96 (9.38%)	
occurrences (all)	7	10	
DRY EYE			
subjects affected / exposed	5 / 94 (5.32%)	4 / 96 (4.17%)	
occurrences (all)	6	4	
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	8 / 94 (8.51%)	6 / 96 (6.25%)	
occurrences (all)	10	6	
CONSTIPATION			
subjects affected / exposed	7 / 94 (7.45%)	14 / 96 (14.58%)	
occurrences (all)	7	15	
DYSPEPSIA			
subjects affected / exposed	7 / 94 (7.45%)	4 / 96 (4.17%)	
occurrences (all)	7	4	
DIARRHOEA			
subjects affected / exposed	14 / 94 (14.89%)	13 / 96 (13.54%)	
occurrences (all)	20	19	
NAUSEA			

subjects affected / exposed occurrences (all)	13 / 94 (13.83%) 20	13 / 96 (13.54%) 15	
VOMITING subjects affected / exposed occurrences (all)	15 / 94 (15.96%) 20	8 / 96 (8.33%) 8	
Hepatobiliary disorders HEPATIC FUNCTION ABNORMAL subjects affected / exposed occurrences (all)	6 / 94 (6.38%) 19	6 / 96 (6.25%) 10	
Skin and subcutaneous tissue disorders PRURITUS subjects affected / exposed occurrences (all)	6 / 94 (6.38%) 7	7 / 96 (7.29%) 10	
Renal and urinary disorders ACUTE KIDNEY INJURY subjects affected / exposed occurrences (all)	3 / 94 (3.19%) 7	8 / 96 (8.33%) 9	
Endocrine disorders CUSHINGOID subjects affected / exposed occurrences (all)	3 / 94 (3.19%) 3	6 / 96 (6.25%) 6	
Musculoskeletal and connective tissue disorders ARTHRALGIA subjects affected / exposed occurrences (all)	12 / 94 (12.77%) 19	13 / 96 (13.54%) 16	
BACK PAIN subjects affected / exposed occurrences (all)	6 / 94 (6.38%) 7	11 / 96 (11.46%) 12	
MUSCLE SPASMS subjects affected / exposed occurrences (all)	17 / 94 (18.09%) 20	16 / 96 (16.67%) 27	
MUSCULAR WEAKNESS subjects affected / exposed occurrences (all)	5 / 94 (5.32%) 7	9 / 96 (9.38%) 9	
MYALGIA			

subjects affected / exposed occurrences (all)	1 / 94 (1.06%) 1	5 / 96 (5.21%) 6	
PAIN IN EXTREMITY subjects affected / exposed occurrences (all)	5 / 94 (5.32%) 6	5 / 96 (5.21%) 5	
Infections and infestations			
BRONCHITIS subjects affected / exposed occurrences (all)	2 / 94 (2.13%) 2	7 / 96 (7.29%) 8	
CONJUNCTIVITIS subjects affected / exposed occurrences (all)	4 / 94 (4.26%) 5	5 / 96 (5.21%) 6	
HERPES ZOSTER subjects affected / exposed occurrences (all)	5 / 94 (5.32%) 6	5 / 96 (5.21%) 5	
NASOPHARYNGITIS subjects affected / exposed occurrences (all)	6 / 94 (6.38%) 6	8 / 96 (8.33%) 11	
INFLUENZA subjects affected / exposed occurrences (all)	5 / 94 (5.32%) 5	6 / 96 (6.25%) 7	
PARONYCHIA subjects affected / exposed occurrences (all)	5 / 94 (5.32%) 5	2 / 96 (2.08%) 2	
RHINOVIRUS INFECTION subjects affected / exposed occurrences (all)	1 / 94 (1.06%) 1	7 / 96 (7.29%) 7	
SINUSITIS subjects affected / exposed occurrences (all)	1 / 94 (1.06%) 1	5 / 96 (5.21%) 8	
UPPER RESPIRATORY TRACT INFECTION subjects affected / exposed occurrences (all)	15 / 94 (15.96%) 24	15 / 96 (15.63%) 21	
Metabolism and nutrition disorders			

DECREASED APPETITE		
subjects affected / exposed	7 / 94 (7.45%)	7 / 96 (7.29%)
occurrences (all)	8	8
HYPERGLYCAEMIA		
subjects affected / exposed	4 / 94 (4.26%)	13 / 96 (13.54%)
occurrences (all)	6	23
HYPERKALAEMIA		
subjects affected / exposed	3 / 94 (3.19%)	8 / 96 (8.33%)
occurrences (all)	3	10
HYPOKALAEMIA		
subjects affected / exposed	11 / 94 (11.70%)	14 / 96 (14.58%)
occurrences (all)	21	21
HYPOMAGNESAEMIA		
subjects affected / exposed	4 / 94 (4.26%)	8 / 96 (8.33%)
occurrences (all)	10	11
HYPONATRAEMIA		
subjects affected / exposed	9 / 94 (9.57%)	6 / 96 (6.25%)
occurrences (all)	10	9
HYPOPHOSPHATAEMIA		
subjects affected / exposed	3 / 94 (3.19%)	9 / 96 (9.38%)
occurrences (all)	5	11

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 August 2016	Original Protocol
25 October 2016	<ul style="list-style-type: none">· 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<ul style="list-style-type: none">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	<ul style="list-style-type: none"> ·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: <ul style="list-style-type: none"> 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. <ul style="list-style-type: none"> · Specified that tapering of an increased prednisone dose for flares should begin within 4 weeks · Updated statistical methods & analysis plans
06 February 2019	<ul style="list-style-type: none"> · 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