# 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 |

### 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 |
| Public contact | Justin Wahlstrom, MD, Pharmacyclics LLC, +1 (650) 540-6205, jwahlstrom@pcyc.com |
| Scientific contact | Justin Wahlstrom, MD, Pharmacyclics LLC, +1 (650) 540-6205, jwahlstrom@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? | 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 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 | 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 |
|---|---|

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 |
| 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.<br>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 |
| 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.<br>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<br>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<br>Units: years | | | |
| arithmetic mean | 50.0 | 51.1 | |
| standard deviation | ± 14.48 | ± 14.99 | - |
| Gender categorical<br>Units: Subjects | | | |
| Female | 34 | 33 | 67 |
| Male | 61 | 65 | 126 |

## End points

### End points reporting groups

| Reporting group title | Ibrutinib + 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 + 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 week.

| End point type | Primary |
|---|---|

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 |
|---|---|

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 |
|---|---|

| | |
|---|---|
| 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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 | = 0.216 |
| Method | Gray`s chi-square test |

## Secondary: Withdrawal of all Immunosuppressants incl. study treatment

| End point title | Withdrawal of all Immunosuppressants incl. study treatment |
|---|---|

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 |
|---|---|

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

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|---|---|
| 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 + 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:

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 | = 0.0708 |
| 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 |

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 + 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 |

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 + 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 |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 22.1 |

### Reporting groups

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|---|---|
| Reporting group title | Ibrutinib |

Reporting group description: -

| | |
|---|---|
| Reporting group title | Placebo |

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 | | | |

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|---|---|---|---|
| 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 | | | |

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|---|---|---|---|
| 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 | | | |

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|---|---|---|---|
| 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 | | | |

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|---|---|---|---|
| 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 | |

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|---|---|---|---|
| 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 | |

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|---|---|---|---|
| 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 | | | |

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|---|---|---|---|
| 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 | |

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|---|---|---|---|
| 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 JIROVECII 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 | 10 / 94 (10.64%) | 13 / 96 (13.54%) | |
| occurrences (all) | 16 | 14 | |
| General disorders and administration site conditions | | | |
| ASTHENIA | | | |
| subjects affected / exposed | 5 / 94 (5.32%) | 6 / 96 (6.25%) | |
| occurrences (all) | 7 | 7 | |
| FATIGUE | | | |
| subjects affected / exposed | 17 / 94 (18.09%) | 18 / 96 (18.75%) | |
| occurrences (all) | 22 | 30 | |
| INFLUENZA LIKE ILLNESS | | | |
| subjects affected / exposed | 5 / 94 (5.32%) | 1 / 96 (1.04%) | |
| occurrences (all) | 6 | 1 | |
| OEDEMA PERIPHERAL | | | |
| subjects affected / exposed | 25 / 94 (26.60%) | 13 / 96 (13.54%) | |
| occurrences (all) | 37 | 17 | |
| PYREXIA | | | |
| subjects affected / exposed | 7 / 94 (7.45%) | 16 / 96 (16.67%) | |
| occurrences (all) | 7 | 22 | |
| 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 | 21 / 94 (22.34%) | 29 / 96 (30.21%) | |
| occurrences (all) | 24 | 37 | |
| DYSPNOEA | | | |
| subjects affected / exposed | 9 / 94 (9.57%) | 14 / 96 (14.58%) | |
| occurrences (all) | 12 | 16 | |

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

| | | | |
|---|---|---|---|
| BLOOD CREATININE INCREASED | | | |
| subjects affected / exposed | 5 / 94 (5.32%) | 6 / 96 (6.25%) | |
| occurrences (all) | 8 | 7 | |
| PLATELET COUNT DECREASED | | | |
| subjects affected / exposed | 7 / 94 (7.45%) | 6 / 96 (6.25%) | |
| occurrences (all) | 13 | 10 | |
| WEIGHT DECREASED | | | |
| subjects affected / exposed | 6 / 94 (6.38%) | 4 / 96 (4.17%) | |
| occurrences (all) | 6 | 4 | |
| WEIGHT INCREASED | | | |
| subjects affected / exposed | 5 / 94 (5.32%) | 6 / 96 (6.25%) | |
| occurrences (all) | 7 | 6 | |
| Injury, poisoning and procedural complications | | | |
| CONTUSION | | | |
| subjects affected / exposed | 10 / 94 (10.64%) | 4 / 96 (4.17%) | |
| occurrences (all) | 11 | 5 | |
| FALL | | | |
| subjects affected / exposed | 3 / 94 (3.19%) | 7 / 96 (7.29%) | |
| occurrences (all) | 4 | 7 | |
| 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 | 10 / 94 (10.64%) | 11 / 96 (11.46%) | |
| occurrences (all) | 10 | 16 | |
| HEADACHE | | | |
| subjects affected / exposed | 13 / 94 (13.83%) | 12 / 96 (12.50%) | |
| occurrences (all) | 19 | 17 | |
| PERIPHERAL SENSORY NEUROPATHY | | | |
| subjects affected / exposed | 6 / 94 (6.38%) | 2 / 96 (2.08%) | |
| occurrences (all) | 7 | 5 | |
| TREMOR | | | |
| subjects affected / exposed | 5 / 94 (5.32%) | 9 / 96 (9.38%) | |
| occurrences (all) | 5 | 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 | 13 / 94 (13.83%) | 13 / 96 (13.54%) | |
| occurrences (all) | 20 | 15 | |
| VOMITING | | | |
| subjects affected / exposed | 15 / 94 (15.96%) | 8 / 96 (8.33%) | |
| occurrences (all) | 20 | 8 | |
| Hepatobiliary disorders | | | |
| HEPATIC FUNCTION ABNORMAL | | | |
| subjects affected / exposed | 6 / 94 (6.38%) | 6 / 96 (6.25%) | |
| occurrences (all) | 19 | 10 | |
| 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 | | | |
| ARTHRALGIA | | | |
| subjects affected / exposed | 12 / 94 (12.77%) | 13 / 96 (13.54%) | |
| occurrences (all) | 19 | 16 | |
| BACK PAIN | | | |
| subjects affected / exposed | 6 / 94 (6.38%) | 11 / 96 (11.46%) | |
| occurrences (all) | 7 | 12 | |
| MUSCLE SPASMS | | | |
| subjects affected / exposed | 17 / 94 (18.09%) | 16 / 96 (16.67%) | |
| occurrences (all) | 20 | 27 | |
| MUSCULAR WEAKNESS | | | |
| subjects affected / exposed | 5 / 94 (5.32%) | 9 / 96 (9.38%) | |
| occurrences (all) | 7 | 9 | |
| 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 | | | |
| BRONCHITIS | | | |
| subjects affected / exposed | 2 / 94 (2.13%) | 7 / 96 (7.29%) | |
| occurrences (all) | 2 | 8 | |
| CONJUNCTIVITIS | | | |
| subjects affected / exposed | 4 / 94 (4.26%) | 5 / 96 (5.21%) | |
| occurrences (all) | 5 | 6 | |
| HERPES ZOSTER | | | |
| subjects affected / exposed | 5 / 94 (5.32%) | 5 / 96 (5.21%) | |
| occurrences (all) | 6 | 5 | |
| NASOPHARYNGITIS | | | |
| subjects affected / exposed | 6 / 94 (6.38%) | 8 / 96 (8.33%) | |
| occurrences (all) | 6 | 11 | |
| INFLUENZA | | | |
| subjects affected / exposed | 5 / 94 (5.32%) | 6 / 96 (6.25%) | |
| occurrences (all) | 5 | 7 | |
| PARONYCHIA | | | |
| subjects affected / exposed | 5 / 94 (5.32%) | 2 / 96 (2.08%) | |
| occurrences (all) | 5 | 2 | |
| RHINOVIRUS INFECTION | | | |
| subjects affected / exposed | 1 / 94 (1.06%) | 7 / 96 (7.29%) | |
| occurrences (all) | 1 | 7 | |
| SINUSITIS | | | |
| subjects affected / exposed | 1 / 94 (1.06%) | 5 / 96 (5.21%) | |
| occurrences (all) | 1 | 8 | |
| UPPER RESPIRATORY TRACT INFECTION | | | |
| subjects affected / exposed | 15 / 94 (15.96%) | 15 / 96 (15.63%) | |
| occurrences (all) | 24 | 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 | · 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).<br>· Dose modification guidance changes included<br>o Addition of text stating that AEs considered related to concomitant high dose steroids do not require dose modification or holding of ibrutinib.<br>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.<br>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.<br>· Summary of clinical safety was updated to align with current IB.<br>· Infection surveillance monitoring guidance added that subjects should be monitored closely for signs or symptoms of aspergillus infection. |

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| 03 October 2017 | ·Clarified that treatment can be discontinued after response in disease symptoms and withdrawal of other systemic immunosuppressants<br>·Inclusion criterion changed to allow "Total bilirubin of >1.5 x ULN to 3.0 x ULN if due to GVHD".<br>·Immunosuppressants dosing for treatment of aGVHD to be stable for 2 weeks prior to screening was removed<br>·Exclusion criteria updated to:<br>o Allow subjects who received systemic corticosteroid treatment for cGVHD for a short period of time prior to signing consent<br>o Exclude subjects with presence of single-organ, genito-urinary involvement with cGVHD as the only manifestation of cGVHD<br>o Exclude only subjects with hepatic impairment Child Pugh Class C (previously excluded Class B or C)<br>o Exclude subjects who had received a DLI 56 days before randomization<br>o Clarify that subjects on secondary prophylaxis for fungal infections and some other low grade infections can be enrolled<br>o Exclude subjects requiring treatment with a strong CYP3A inducer<br>o Remove exclusion of subjects who are on strong CYP inhibitors<br>·Updated the dose modification guidelines for adverse reactions for subjects with hepatic impairment and for subjects using a CYP3A inhibitor<br>·Allowed prednisone to treat cGVHD to start prior to randomization<br>·Clarified restart of original blinded study therapy in the event of cGVHD worsening following ibrutinib/placebo withdrawal<br>·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<br>improvement from exploratory to secondary endpoints<br>·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<br>NIH criteria.<br>· Specified that tapering of an increased prednisone dose for flares should begin within 4 weeks<br>· Updated statistical methods & analyis 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.<br>· 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).<br>· 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.<br>· 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<br>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