



Clinical trial results:

Randomized, Double-blind, Placebo-controlled Phase 3 Study of Ibrutinib, a Bruton's Tyrosine Kinase (BTK) Inhibitor, in Combination with Bendamustine and Rituximab (BR) in Subjects With Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

Summary

| | |
|--------------------------|-------------------------|
| EudraCT number | 2012-000600-15 |
| Trial protocol | SE BE ES PT GB DE GR PL |
| Global end of trial date | 23 January 2019 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 08 February 2020 |
| First version publication date | 08 February 2020 |

Trial information

Trial identification

| | |
|-----------------------|------------------|
| Sponsor protocol code | PCI-32765CLL3001 |
|-----------------------|------------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01611090 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--------------------------------------------------------------------------------------------|
| Sponsor organisation name | Janssen Research & Development, LLC |
| Sponsor organisation address | 920 Route 202, Raritan, United States, NJ 08869 |
| Public contact | Janssen Research & Development, LLC, Clinical Registry Group, ClinicalTrialsEU@its.jnj.com |
| Scientific contact | Janssen Research & Development, LLC, Clinical Registry Group, ClinicalTrialsEU@its.jnj.com |

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|------------------------------------------------------|-----------------|
| Analysis stage | Final |
| Date of interim/final analysis | 23 January 2019 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 23 January 2019 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The purpose of the study was to determine whether the addition of ibrutinib to bendamustine/rituximab (BR) significantly improved progression-free survival (PFS) compared with BR in subjects with relapsed or refractory chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL).

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practices and applicable regulatory requirements. The safety assessments included adverse events, clinical laboratory tests (hematology and chemistry), vital signs, physical examination results and electrocardiograms.

Background therapy:

Bendamustine hydrochloride and Rituximab

Evidence for comparator: -

| | |
|-----------------------------------------------------------|-------------------|
| Actual start date of recruitment | 19 September 2012 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------------|
| Country: Number of subjects enrolled | Argentina: 6 |
| Country: Number of subjects enrolled | Belgium: 28 |
| Country: Number of subjects enrolled | Brazil: 22 |
| Country: Number of subjects enrolled | Canada: 62 |
| Country: Number of subjects enrolled | Colombia: 1 |
| Country: Number of subjects enrolled | Czech Republic: 23 |
| Country: Number of subjects enrolled | Germany: 21 |
| Country: Number of subjects enrolled | Spain: 18 |
| Country: Number of subjects enrolled | France: 27 |
| Country: Number of subjects enrolled | United Kingdom: 14 |
| Country: Number of subjects enrolled | Greece: 17 |
| Country: Number of subjects enrolled | Israel: 26 |
| Country: Number of subjects enrolled | Korea, Republic of: 1 |
| Country: Number of subjects enrolled | Mexico: 3 |
| Country: Number of subjects enrolled | Poland: 39 |
| Country: Number of subjects enrolled | Portugal: 19 |
| Country: Number of subjects enrolled | Russian Federation: 100 |
| Country: Number of subjects enrolled | Sweden: 6 |

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Turkey: 51 |
| Country: Number of subjects enrolled | Ukraine: 30 |
| Country: Number of subjects enrolled | United States: 64 |
| Worldwide total number of subjects | 578 |
| EEA total number of subjects | 212 |

Notes:

| Subjects enrolled per age group | |
|-------------------------------------------|-----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 305 |
| From 65 to 84 years | 272 |
| 85 years and over | 1 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 578 subjects were enrolled in the study. Among these, 289 subjects were randomized in each ibrutinib + bendamustine/rituximab (BR) treatment group and placebo+BR treatment group.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

Arms

| | |
|------------------------------|--------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Ibrutinib+BR |

Arm description:

Subjects received ibrutinib 420 milligram (mg) (3 * 140 mg capsules) orally once daily starting on Cycle 1 Day 2 for a maximum of 6 cycles (each cycle of 28 days except Cycle 1 which was of 29 days) along with BR. After 6 cycles ibrutinib alone was administered until disease progression or unacceptable toxicity.

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

Dosage and administration details:

Subjects received ibrutinib 420 milligram (mg) (3 * 140 mg capsules) oral once daily.

| | |
|------------------|------------|
| Arm title | Placebo+BR |
|------------------|------------|

Arm description:

Subjects received placebo (3 capsules) orally once daily starting on Cycle 1 Day 2 for a maximum of 6 cycles (each cycle of 28 days except Cycle 1 which was of 29 days) along with BR. After 6 cycles placebo alone was administered until disease progression or unacceptable toxicity.

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

Dosage and administration details:

Subjects received placebo (3 capsules) oral once daily.

| Number of subjects in period 1 | Ibrutinib+BR | Placebo+BR |
|---------------------------------------|------------------|--------------------|
| Started | 289 | 289 |
| Crossover: Placebo to Ibrutinib | 0 ^[1] | 183 ^[2] |
| Treated | 287 | 287 |
| Completed | 259 | 260 |
| Not completed | 30 | 29 |
| Consent withdrawn by subject | 22 | 26 |
| Lost to follow-up | 8 | 3 |

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Only 183 subjects from Placebo+BR group were crossed over to Ibrutinib group.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Only 183 subjects from Placebo+BR group were crossed over to Ibrutinib group.

Baseline characteristics

Reporting groups

| | |
|-----------------------|--------------|
| Reporting group title | Ibrutinib+BR |
|-----------------------|--------------|

Reporting group description:

Subjects received ibrutinib 420 milligram (mg) (3 * 140 mg capsules) orally once daily starting on Cycle 1 Day 2 for a maximum of 6 cycles (each cycle of 28 days except Cycle 1 which was of 29 days) along with BR. After 6 cycles ibrutinib alone was administered until disease progression or unacceptable toxicity.

| | |
|-----------------------|------------|
| Reporting group title | Placebo+BR |
|-----------------------|------------|

Reporting group description:

Subjects received placebo (3 capsules) orally once daily starting on Cycle 1 Day 2 for a maximum of 6 cycles (each cycle of 28 days except Cycle 1 which was of 29 days) along with BR. After 6 cycles placebo alone was administered until disease progression or unacceptable toxicity.

| Reporting group values | Ibrutinib+BR | Placebo+BR | Total |
|---------------------------------------------|--------------|------------|-------|
| Number of subjects | 289 | 289 | 578 |
| Title for AgeCategorical Units: subjects | | | |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 145 | 160 | 305 |
| From 65 to 84 years | 143 | 129 | 272 |
| 85 years and over | 1 | 0 | 1 |
| Title for AgeContinuous Units: years | | | |
| arithmetic mean | 63.7 | 63.3 | |
| standard deviation | ± 9.82 | ± 9.3 | - |
| Title for Gender Units: subjects | | | |
| Female | 96 | 100 | 196 |
| Male | 193 | 189 | 382 |

End points

End points reporting groups

| | |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|
| Reporting group title | Ibrutinib+BR |
| Reporting group description: | |
| Subjects received ibrutinib 420 milligram (mg) (3 * 140 mg capsules) orally once daily starting on Cycle 1 Day 2 for a maximum of 6 cycles (each cycle of 28 days except Cycle 1 which was of 29 days) along with BR. After 6 cycles ibrutinib alone was administered until disease progression or unacceptable toxicity. | |
| Reporting group title | Placebo+BR |
| Reporting group description: | |
| Subjects received placebo (3 capsules) orally once daily starting on Cycle 1 Day 2 for a maximum of 6 cycles (each cycle of 28 days except Cycle 1 which was of 29 days) along with BR. After 6 cycles placebo alone was administered until disease progression or unacceptable toxicity. | |

Primary: Progression-free Survival (PFS)

| | |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|
| End point title | Progression-free Survival (PFS) |
| End point description: | |
| PFS was defined as the interval between the date of randomization and the date of disease progression or death, whichever was first reported. IWCLL 2008 criteria for PD: New enlarged nodes >1.5 cm, new hepatomegaly or splenomegaly, or other new organ infiltrates, bone lesion, ascites, or pleural effusion confirmed due to chronic lymphocytic leukemia (CLL); $\geq 50\%$ increase in existing lymph nodes; $\geq 50\%$ increase in enlargement of liver or spleen; $\geq 50\%$ increase from baseline in lymphocyte count (and to $\geq 5 \times 10^9/L$) or $\geq 50\%$ increase from nadir count confirmed on ≥ 2 serial assessments if absolute lymphocyte count (ALC) $\geq 30,000$ per microliter and lymphocyte doubling time is rapid, unless considered treatment-related lymphocytosis; new cytopenia (Hemoglobin b [Hgb] or platelets) attributable to CLL; and transformation to a more aggressive histology. ITT population included. Here, 99999 indicates that upper limit of CI was not evaluable due to insufficient number of events. | |
| End point type | Primary |
| End point timeframe: | |
| Up to 5 years | |

| End point values | Ibrutinib+BR | Placebo+BR | | |
|----------------------------------|------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 289 | 289 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 65.12 (55.43 to 99999) | 14.32 (13.86 to 16.62) | | |

Statistical analyses

| | |
|----------------------------|---------------------------|
| Statistical analysis title | Statistical analysis 1 |
| Comparison groups | Ibrutinib+BR v Placebo+BR |

| | |
|-----------------------------------------|-------------------|
| Number of subjects included in analysis | 578 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.229 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.183 |
| upper limit | 0.286 |

Secondary: Overall Response Rate (ORR)

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|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|
| End point title | Overall Response Rate (ORR) |
| End point description: | |
| ORR defined as number of subjects achieving a complete response (CR), complete response with incomplete marrow recovery (CRi), nodular partial response (nPR) or partial response (PR). IWCLL 2008 criteria: CR- No lymphadenopathy and hepatosplenomegaly, no constitutional symptoms, neutrophils $>1.5 \times 10^9/\text{liter}$ (L), platelets $>100 \times 10^9/\text{L}$, Hgb >11 gram per deciliter (g/dL) and absolute lymphocyte count $<4000/\text{microliter}$ (mcL); CRi- CR with incomplete recovery of bone marrow; nPR- subjects meet criteria for CR, but the bone marrow biopsy shows B-lymphoid nodules, may represent a clonal infiltrate; PR-2 of the following when abnormal at baseline: $\geq 50\%$ decrease in ALC, $\geq 50\%$ decrease in sum products of up to 6 lymph nodes, $\geq 50\%$ decrease in enlargement of spleen or liver; and 1 of the following: neutrophils $>1.5 \times 10^9/\text{L}$, Platelets $>100 \times 10^9/\text{L}$ and Hgb >11 g/dL or $\geq 50\%$ improvement over baseline in any of these; no new enlarged nodes or new hepatosplenomegaly. ITT population included. | |
| End point type | Secondary |
| End point timeframe: | |
| Up to 5 years | |

| End point values | Ibrutinib+BR | Placebo+BR | | |
|-------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 289 | 289 | | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | 87.2 | 66.1 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

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|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| End point title | Overall Survival (OS) |
| End point description: | |
| OS was defined as the interval between the date of randomization and the date of death from any cause. ITT population included all subjects randomized into the study regardless of treatment actually received. Here, '99999' indicates that the data was not estimable due to insufficient number of events. | |

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Up to 5 years | |

| End point values | Ibrutinib+BR | Placebo+BR | | |
|----------------------------------|------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 289 | 289 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 99999 (70.93 to 99999) | 99999 (99999 to 99999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Minimal Residual Disease (MRD)-negative Response

| | |
|-----------------|------------------------------------------------------------------------------|
| End point title | Percentage of Subjects with Minimal Residual Disease (MRD)-negative Response |
|-----------------|------------------------------------------------------------------------------|

End point description:

MRD-negative response was defined as the percentage of subjects who reach MRD negative disease status (less than 1 chronic lymphocytic leukemia [CLL] cell per 10,000 leukocytes) in either bone marrow or peripheral blood. All randomized subjects were included in this analysis. Subjects with missing MRD data were considered non-responders. ITT population included all subjects randomized into the study regardless of treatment actually received.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Up to 5 years | |

| End point values | Ibrutinib+BR | Placebo+BR | | |
|-------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 289 | 289 | | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | 28.7 | 5.9 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Sustained Hematologic Improvement

| | |
|-----------------|---------------------------------------------------------------|
| End point title | Percentage of Subjects with Sustained Hematologic Improvement |
|-----------------|---------------------------------------------------------------|

End point description:

Sustained hematologic improvement was defined as hematological improvement that was sustained continuously for greater than or equal to (\geq) 56 days without blood transfusion or growth factors: 1) Platelet counts greater than ($>$) 100×10^9 /liter (L) if baseline less than or equal to (\leq) 100×10^9 /L or increase ≥ 50 percent (%) over baseline; 2) Hemoglobin >11 gram per deciliters (g/dL) if baseline ≤ 11 g/dL or increase ≥ 2 g/dL over baseline. ITT population included all subjects randomized into the study regardless of treatment actually received.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

At disease progression, up to 5 years after the last subject was randomized

| End point values | Ibrutinib+BR | Placebo+BR | | |
|-------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 289 | 289 | | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |
| Hemoglobin | 36.7 | 29.1 | | |
| Platelets | 30.8 | 21.8 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Median Time to Clinically Meaningful Improvement in FACIT-Fatigue Scale

| | |
|-----------------|-------------------------------------------------------------------------|
| End point title | Median Time to Clinically Meaningful Improvement in FACIT-Fatigue Scale |
|-----------------|-------------------------------------------------------------------------|

End point description:

Time to improvement is defined as the time interval (months) from randomization to the first observation of improvement. FACIT-Fatigue is an instrument for use as a measure of the effect of fatigue in patients with cancer and other chronic diseases. Responses to the 13-item FACIT Fatigue Scale are reported on a 5-point categorical response scale ranging from 0 (not at all) to 4 (very much). The sum of all responses resulted in the FACIT-Fatigue score for a total possible score of 0 (worst score) to 52 (best score). ITT population included all subjects randomized into the study regardless of treatment actually received.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to 2 years

| End point values | Ibrutinib+BR | Placebo+BR | | |
|----------------------------------|-------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 289 | 289 | | |
| Units: Months | | | | |
| number (confidence interval 95%) | 6.5 (4.7 to 10.7) | 4.6 (2.8 to 6.4) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Clinically Relevant Shifts in Disease-Related Symptoms

| | |
|-----------------|--------------------------------------------------------------------------------|
| End point title | Number of Subjects With Clinically Relevant Shifts in Disease-Related Symptoms |
|-----------------|--------------------------------------------------------------------------------|

End point description:

The disease-related symptoms included fatigue, weight loss, fevers, night sweats, abdominal discomfort/splenomegaly and anorexia. ITT population included all subjects randomized into the study regardless of treatment actually received.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From the date of randomization to disease progression (Up to 2 years)

| End point values | Ibrutinib+BR | Placebo+BR | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 289 | 289 | | |
| Units: Subjects | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects who Received Subsequent Antineoplastic Therapy

| | |
|-----------------|-------------------------------------------------------------------|
| End point title | Number of Subjects who Received Subsequent Antineoplastic Therapy |
|-----------------|-------------------------------------------------------------------|

End point description:

Number of subjects who received subsequent antineoplastic therapy was reported. Safety analysis set included all the randomized subjects who received at least 1 dose of study drug or placebo.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to 5 years

| End point values | Ibrutinib+BR | Placebo+BR | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 287 | 287 | | |
| Units: Subjects | 52 | 61 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Beta2 Microglobulin at End of Treatment (EOT)

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|-----------------|-----------------------------------------------------------------------|
| End point title | Change from Baseline in Beta2 Microglobulin at End of Treatment (EOT) |
|-----------------|-----------------------------------------------------------------------|

End point description:

Change from baseline in beta2 microglobulin at end of treatment at time of primary analysis was reported. ITT population included all subjects randomized into the study regardless of treatment actually received. Here, 'N' (number of subjects analyzed) signifies number of subjects evaluable for this endpoint.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline to EOT (Up to 2 years)

| End point values | Ibrutinib+BR | Placebo+BR | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 39 | 106 | | |
| Units: milligram per liter (mg/L) | | | | |
| arithmetic mean (standard deviation) | -0.46 (± 1.77) | -0.23 (± 2.08) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in FACIT-Fatigue Scale at End of Treatment

| | |
|-----------------|-----------------------------------------------------------------|
| End point title | Change from Baseline in FACIT-Fatigue Scale at End of Treatment |
|-----------------|-----------------------------------------------------------------|

End point description:

FACIT-Fatigue is an instrument for use as a measure of the effect of fatigue in patients with cancer and other chronic diseases. Responses to the 13-item FACIT Fatigue Scale are reported on a 5point categorical response scale ranging from 0 (not at all) to 4 (very much). The sum of all responses resulted in the FACIT-Fatigue score for a total possible score of 0 (worst score) to 52 (best score). ITT population included all subjects randomized into the study regardless of treatment actually received. Here, 'N' (number of subjects analyzed) signifies number of subjects evaluable for this endpoint.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline to EOT (up to 2 years)

| End point values | Ibrutinib+BR | Placebo+BR | | |
|--------------------------------------|---------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 38 | 104 | | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | -0.9 (\pm 11.22) | 0.0 (\pm 11.01) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in EORTC QLQ-C30 Physical Functioning Score at End of Treatment

| | |
|-----------------|--------------------------------------------------------------------------------------|
| End point title | Change from Baseline in EORTC QLQ-C30 Physical Functioning Score at End of Treatment |
|-----------------|--------------------------------------------------------------------------------------|

End point description:

EORTC QLQ-C30 Physical Functioning Score is a questionnaire to assess quality of life of cancer patients. It is composed of 30 items, multi-item measure (28 items) and 2 single-item measures. For the multiple item measure, 4-point scale is used and the score for each item range from "1 = not at all" to "4 = very much". Higher scores indicate worsening. The 2 single-item measure involves question about the overall health and overall quality of life which was rated on a 7-point scale ranging from "1 = very poor" to "7 = excellent". Lower scores indicate worsening. All scale and item scores were linearly transformed to be in range from 0-100. A higher score represents a higher (better) level of functioning, or a higher (worse) level of symptoms. ITT population included all subjects randomized into the study regardless of treatment actually received. Here, 'N' (number of subjects analyzed) signifies number of subjects evaluable for this endpoint.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline to EOT (up to 2 years)

| End point values | Ibrutinib+BR | Placebo+BR | | |
|--------------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 38 | 104 | | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | -2.1 (\pm 16.34) | -4.1 (\pm 22.52) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in EORTC QLQ-CLL 16 Domain Scores at End of Treatment

| | |
|-----------------|----------------------------------------------------------------------------|
| End point title | Change from Baseline in EORTC QLQ-CLL 16 Domain Scores at End of Treatment |
|-----------------|----------------------------------------------------------------------------|

End point description:

The EORTC QLQ-CLL 16 is a 16-item disease specific module that comprises 5 domains of patient-reported health status important in CLL. There are three multi-item scales that include fatigue (2 items), treatment side effects and disease symptoms (8 items), and infection (4 items), and 2 single-item scales on social activities and future health worries. Responses are measured on a 4 point scale ranging from 1 (not at all) to 4 (very much). ITT population included all subjects randomized into the study regardless of treatment actually received. Here, 'N' (number of subjects analyzed) signifies number of subjects evaluable for this endpoint. Here, 'n' signifies the number of subjects analyzed at a specified time point.

| | |
|---------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline to EOT (up to 2 years) | |

| End point values | Ibrutinib+BR | Placebo+BR | | |
|-----------------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 38 | 104 | | |
| Units: Units on the scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Lost weight (n=38,104) | 0.1 (± 0.86) | 0.0 (± 0.74) | | |
| Dry mouth (n=38,104) | 0.3 (± 0.96) | 0.1 (± 0.85) | | |
| Bruises (n=38,104) | 0.1 (± 0.61) | 0.0 (± 0.65) | | |
| Abdominal discomfort (n=37,104) | 0.1 (± 0.81) | 0.0 (± 0.76) | | |
| Temperature going up and down (n=38,104) | 0.1 (± 0.93) | 0.0 (± 0.72) | | |
| Night sweats (n=38,103) | -0.6 (± 0.92) | -0.3 (± 1.07) | | |
| Skin problems (n=37,104) | 0.4 (± 1.14) | 0.3 (± 0.96) | | |
| Feel ill (n=38,104) | 0.1 (± 1.08) | 0.2 (± 0.98) | | |
| Feel lethargic (n=38,104) | 0.1 (± 1.01) | 0.0 (± 0.91) | | |
| Felt slowed down (n=38,103) | 0.3 (± 0.80) | 0.0 (± 0.97) | | |
| Limited in planning activities (n=38,103) | 0.2 (± 0.97) | 0.1 (± 0.90) | | |
| Worried about health in the future (n=38,103) | 0.0 (± 0.94) | 0.0 (± 0.97) | | |
| Trouble with chest infections (n=38,104) | 0.2 (± 1.05) | 0.0 (± 0.82) | | |
| Trouble with other infections (n=38,104) | 0.7 (± 1.07) | 0.1 (± 0.86) | | |
| Repeated courses of antibiotics (n=38,104) | 0.9 (± 1.22) | 0.0 (± 0.97) | | |
| Worried about picking up infection (n=38,103) | 0.3 (± 0.96) | 0.2 (± 1.00) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in EuroQol-5 Dimension-5 Level (EQ-5D-5L) Visual Analog Scale at End of Treatment

| | |
|-----------------|--------------------------------------------------------------------------------------------------------|
| End point title | Change from Baseline in EuroQol-5 Dimension-5 Level (EQ-5D-5L) Visual Analog Scale at End of Treatment |
|-----------------|--------------------------------------------------------------------------------------------------------|

End point description:

The EQ-5D questionnaire is a brief, generic health-related quality of life assessment (HRQOL) that can also be used to incorporate subject preferences into health economic evaluations. The EQ-5D questionnaire assesses HRQOL in terms of degree of limitation on 5 health dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) and as overall health using a visual analog scale with response options ranging from 0 (worst imaginable health) to 100 (best imaginable health). ITT population included all subjects randomized into the study regardless of treatment actually received. Here, 'N' (number of subjects analyzed) signifies number of subjects evaluable for this endpoint.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline to EOT (up to 2 years)

| End point values | Ibrutinib+BR | Placebo+BR | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 38 | 110 | | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | -4.3 (± 19.58) | 4.0 (± 18.21) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in EuroQol-5 Dimension-5 Level (EQ-5D-5L) Utility Score Scale at End of Treatment

| | |
|-----------------|--------------------------------------------------------------------------------------------------------|
| End point title | Change from Baseline in EuroQol-5 Dimension-5 Level (EQ-5D-5L) Utility Score Scale at End of Treatment |
|-----------------|--------------------------------------------------------------------------------------------------------|

End point description:

The EuroQol-5 is a five dimensional health state classification. Each dimension is assessed on a 3-point ordinal scale (1=no problems, 2=some problems, 3=extreme problems). The responses to the five EQ-5D dimensions were scored using a utility-weighted algorithm to derive an EQ-5D health status index score between 0 to 1. High score indicating a high level of utility. ITT population included all subjects randomized into the study regardless of treatment actually received. Here, 'N' (number of subjects analyzed) signifies number of subjects evaluable for this endpoint.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline to EOT (up to 2 years)

| End point values | Ibrutinib+BR | Placebo+BR | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 38 | 110 | | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | 0.0 (± 0.28) | 0.0 (± 0.24) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the time a signed and dated informed consent form is obtained until 30 days following the last dose of study treatment or until the start of a subsequent systemic antineoplastic therapy, if earlier (up to 5 years)

Adverse event reporting additional description:

Safety analysis set included all the randomized subjects who received at least 1 dose of study drug or placebo.

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 20.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--------------|
| Reporting group title | Ibrutinib+BR |
|-----------------------|--------------|

Reporting group description:

Subjects received ibrutinib 420 milligram (mg) (3 * 140 mg capsules) orally once daily starting on Cycle 1 Day 2 for a maximum of 6 cycles (each cycle of 28 days except Cycle 1 which was of 29 days) along with BR. After 6 cycles ibrutinib alone was administered until disease progression or unacceptable toxicity.

| | |
|-----------------------|------------|
| Reporting group title | Placebo+BR |
|-----------------------|------------|

Reporting group description:

Subjects received placebo (3 capsules) orally once daily starting on Cycle 1 Day 2 for a maximum of 6 cycles (each cycle of 28 days except Cycle 1 which was of 29 days) along with BR. After 6 cycles placebo alone was administered until disease progression or unacceptable toxicity.

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

Reporting group description:

Subjects in the placebo+BR treatment group could cross over to receive next-line ibrutinib treatment (420 mg [3 * 140 mg capsules] orally once daily on a 28-day cycle) at the discretion of the investigator at the time of disease progression or if IWCLL criteria for treatment were met.

| Serious adverse events | Ibrutinib+BR | Placebo+BR | Crossover Ibrutinib |
|---------------------------------------------------------------------|--------------------|--------------------|---------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 198 / 287 (68.99%) | 127 / 287 (44.25%) | 105 / 183 (57.38%) |
| number of deaths (all causes) | 74 | 107 | 57 |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Acute Lymphocytic Leukaemia | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 0 / 287 (0.00%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Adenosquamous Cell Lung Cancer | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anal Squamous Cell Carcinoma | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Basal Cell Carcinoma | | | |
| subjects affected / exposed | 5 / 287 (1.74%) | 1 / 287 (0.35%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 13 / 13 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bladder Cancer | | | |
| subjects affected / exposed | 2 / 287 (0.70%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchioloalveolar Carcinoma | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 0 / 287 (0.00%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chronic Myelomonocytic Leukaemia | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Intestinal Adenocarcinoma | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intraductal Papilloma of Breast | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lipoma | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung Adenocarcinoma | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 287 (0.35%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| Malignant Melanoma | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malignant Melanoma in Situ | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Maxillofacial Sinus Neoplasm | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metastases to Central Nervous System | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Metastatic Renal Cell Carcinoma | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myelodysplastic Syndrome | | | |
| subjects affected / exposed | 2 / 287 (0.70%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 3 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| Myeloproliferative Neoplasm | | | |

| | | | |
|-----------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| Neuroendocrine Carcinoma | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Prostate Cancer | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 1 / 287 (0.35%) | 2 / 183 (1.09%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal Cancer | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal Cancer Stage I | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal Oncocytoma | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Squamous Cell Carcinoma | | | |
| subjects affected / exposed | 3 / 287 (1.05%) | 1 / 287 (0.35%) | 2 / 183 (1.09%) |
| occurrences causally related to treatment / all | 5 / 5 | 1 / 1 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Squamous Cell Carcinoma of Skin | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 2 / 287 (0.70%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Superficial Spreading Melanoma Stage Unspecified | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transitional Cell Carcinoma | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Aortic Aneurysm Rupture | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Arterial Stenosis | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 0 / 287 (0.00%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Deep Vein Thrombosis | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 3 / 287 (1.05%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 3 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematoma | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertension | | | |
| subjects affected / exposed | 2 / 287 (0.70%) | 0 / 287 (0.00%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertensive Crisis | | | |
| subjects affected / exposed | 2 / 287 (0.70%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypotension | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 2 / 287 (0.70%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Jugular Vein Thrombosis | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lymphoedema | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral Arterial Occlusive Disease | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral Artery Occlusion | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral Artery Thrombosis | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral Ischaemia | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombophlebitis | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombosis | | | |

| | | | |
|------------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vasculitis | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chest Pain | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chills | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Complication Associated with Device | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Condition Aggravated | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Death | | | |
| subjects affected / exposed | 2 / 287 (0.70%) | 0 / 287 (0.00%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 2 / 2 | 0 / 0 | 1 / 1 |
| Disease Progression | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 287 (0.35%) | 2 / 287 (0.70%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 4 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 1 | 2 / 2 | 0 / 0 |
| Fatigue | | | |
| subjects affected / exposed | 3 / 287 (1.05%) | 1 / 287 (0.35%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General Physical Health Deterioration | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Hernia | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza Like Illness | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infusion Site Extravasation | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malaise | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 1 / 287 (0.35%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mucosal Inflammation | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Multiple Organ Dysfunction Syndrome | | | |

| | | | |
|-------------------------------------------------|------------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 287 (0.35%) | 3 / 287 (1.05%) | 3 / 183 (1.64%) |
| occurrences causally related to treatment / all | 2 / 2 | 4 / 4 | 5 / 5 |
| deaths causally related to treatment / all | 1 / 1 | 3 / 3 | 3 / 3 |
| Non-Cardiac Chest Pain | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oedema Peripheral | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumotosis | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyrexia | | | |
| subjects affected / exposed | 11 / 287 (3.83%) | 7 / 287 (2.44%) | 4 / 183 (2.19%) |
| occurrences causally related to treatment / all | 13 / 13 | 11 / 11 | 3 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sudden Cardiac Death | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Sudden Death | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Systemic Inflammatory Response Syndrome | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| Anaphylactic Reaction | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Benign Prostatic Hyperplasia | | | |
| subjects affected / exposed | 2 / 287 (0.70%) | 0 / 287 (0.00%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fibrocystic Breast Disease | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Genital Rash | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pelvic Floor Muscle Weakness | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 0 / 287 (0.00%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Penile Dysplasia | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Uterine Haemorrhage | | | |
| subjects affected / exposed | 2 / 287 (0.70%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Uterine Prolapse | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| Acute Respiratory Failure | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 287 (0.35%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| Chronic Obstructive Pulmonary Disease | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 287 (0.35%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 3 / 287 (1.05%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 4 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyspnoea Exertional | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemoptysis | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 287 (0.35%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemothorax | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 0 / 287 (0.00%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung Infiltration | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Pleural Effusion | | | |
| subjects affected / exposed | 3 / 287 (1.05%) | 2 / 287 (0.70%) | 2 / 183 (1.09%) |
| occurrences causally related to treatment / all | 4 / 5 | 1 / 2 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleuritic Pain | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonitis | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 1 / 287 (0.35%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 287 (0.35%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary Congestion | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary Mass | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 0 / 287 (0.00%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary Sarcoidosis | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory Failure | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 3 / 183 (1.64%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 3 / 3 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 2 / 2 |
| Respiratory Tract Oedema | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sleep Apnoea Syndrome | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Acute Stress Disorder | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Alcoholic Psychosis | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 0 / 287 (0.00%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Completed Suicide | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| Confusional State | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Delirium | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mental Status Changes | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Biopsy | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 0 / 287 (0.00%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood Creatinine Increased | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Body Temperature Increased | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 0 / 287 (0.00%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutrophil Count Decreased | | | |
| subjects affected / exposed | 2 / 287 (0.70%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Prostatic Specific Antigen Increased | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 0 / 287 (0.00%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Weight Decreased | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Abdominal Injury | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ankle Fracture | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fall | | | |
| subjects affected / exposed | 2 / 287 (0.70%) | 0 / 287 (0.00%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femoral Neck Fracture | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 2 / 287 (0.70%) | 0 / 287 (0.00%) | 2 / 183 (1.09%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femur Fracture | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hip Fracture | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 1 / 287 (0.35%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Incision Site Haemorrhage | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infusion Related Reaction | | | |
| subjects affected / exposed | 4 / 287 (1.39%) | 5 / 287 (1.74%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 4 / 4 | 5 / 5 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pelvic Fracture | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumoconiosis | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumothorax Traumatic | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post Procedural Haemorrhage | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 2 / 183 (1.09%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Post Procedural Swelling | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subdural Haematoma | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 0 / 287 (0.00%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thoracic Vertebral Fracture | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Acute Coronary Syndrome | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 0 / 287 (0.00%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute Myocardial Infarction | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 3 / 287 (1.05%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 4 / 4 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| Angina Pectoris | | | |
| subjects affected / exposed | 4 / 287 (1.39%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 4 / 4 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Angina Unstable | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arrhythmia Supraventricular | | | |

| | | | |
|-------------------------------------------------|------------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial Fibrillation | | | |
| subjects affected / exposed | 16 / 287 (5.57%) | 2 / 287 (0.70%) | 6 / 183 (3.28%) |
| occurrences causally related to treatment / all | 16 / 19 | 2 / 2 | 6 / 7 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial Flutter | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrioventricular Block | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac Arrest | | | |
| subjects affected / exposed | 2 / 287 (0.70%) | 0 / 287 (0.00%) | 3 / 183 (1.64%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 4 / 4 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 2 / 2 |
| Cardiac Failure | | | |
| subjects affected / exposed | 3 / 287 (1.05%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Cardio-Respiratory Arrest | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiopulmonary Failure | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| Cardiovascular Insufficiency | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Carditis | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coronary Artery Occlusion | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial Infarction | | | |
| subjects affected / exposed | 2 / 287 (0.70%) | 2 / 287 (0.70%) | 2 / 183 (1.09%) |
| occurrences causally related to treatment / all | 2 / 2 | 2 / 2 | 2 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| Myocarditis | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pericardial Effusion | | | |
| subjects affected / exposed | 2 / 287 (0.70%) | 1 / 287 (0.35%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sinus Node Dysfunction | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sinus Tachycardia | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tachycardia | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ventricular Fibrillation | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ventricular Flutter | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Ventricular Tachycardia | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Carotid Sinus Syndrome | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral Disorder | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 0 / 287 (0.00%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral Infarction | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 0 / 287 (0.00%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral Ischaemia | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebrovascular Accident | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 3 / 287 (1.05%) | 0 / 287 (0.00%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cognitive Disorder | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Depressed Level of Consciousness | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Encephalopathy | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 0 / 287 (0.00%) | 2 / 183 (1.09%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 3 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| Facial Paresis | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhage Intracranial | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhagic Stroke | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Headache | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 0 / 287 (0.00%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Loss of Consciousness | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Meningism | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral Sensory Neuropathy | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post Herpetic Neuralgia | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Radiculopathy | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 0 / 287 (0.00%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 287 (0.35%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transient Global Amnesia | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 0 / 287 (0.00%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular Encephalopathy | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 0 / 287 (0.00%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |

| | | | |
|-------------------------------------------------|-------------------|------------------|-----------------|
| subjects affected / exposed | 3 / 287 (1.05%) | 7 / 287 (2.44%) | 2 / 183 (1.09%) |
| occurrences causally related to treatment / all | 2 / 3 | 10 / 11 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aplasia Pure Red Cell | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aplastic Anaemia | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 0 / 287 (0.00%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Autoimmune Haemolytic Anaemia | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 5 / 287 (1.74%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 4 / 5 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bone Marrow Failure | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cytopenia | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Febrile Neutropenia | | | |
| subjects affected / exposed | 30 / 287 (10.45%) | 22 / 287 (7.67%) | 2 / 183 (1.09%) |
| occurrences causally related to treatment / all | 22 / 33 | 20 / 28 | 1 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| Haemolytic Anaemia | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune Thrombocytopenic Purpura | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutropenia | | | |
| subjects affected / exposed | 7 / 287 (2.44%) | 6 / 287 (2.09%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 8 / 9 | 6 / 6 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancytopenia | | | |
| subjects affected / exposed | 2 / 287 (0.70%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 4 / 4 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 4 / 287 (1.39%) | 2 / 287 (0.70%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 2 / 4 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 3 / 287 (1.05%) | 0 / 287 (0.00%) | 2 / 183 (1.09%) |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | 3 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Maculopathy | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Retinal Haemorrhage | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 0 / 287 (0.00%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Scleral Disorder | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vitreous Adhesions | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vitreous Haemorrhage | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal Hernia | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal Incarcerated Hernia | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 0 / 287 (0.00%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal Pain | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 0 / 287 (0.00%) | 3 / 183 (1.64%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 3 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anal Fistula | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ascites | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 2 / 287 (0.70%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis Ischaemic | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Constipation | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 4 / 287 (1.39%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 3 / 5 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Duodenal Ulcer Haemorrhage | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyspepsia | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dysphagia | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 2 / 287 (0.70%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Enterocolitis | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastric Haemorrhage | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastric Ulcer Perforation | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 287 (0.00%) | 0 / 287 (0.00%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastritis | | | |
| subjects affected / exposed | 3 / 287 (1.05%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal Disorder | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal Haemorrhage | | | |
| subjects affected / exposed | 2 / 287 (0.70%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal Inflammation | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematemesis | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematochezia | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Inguinal Hernia | | | |
| subjects affected / exposed | 4 / 287 (1.39%) | 0 / 287 (0.00%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 5 / 5 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal Obstruction | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intra-Abdominal Haemorrhage | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Large Intestine Perforation | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Lower Gastrointestinal Haemorrhage | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mouth Ulceration | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nausea | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oesophageal Ulcer | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oesophagitis | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 287 (0.35%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 287 (0.00%) | 0 / 287 (0.00%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis Acute | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Proctitis | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Small Intestinal Obstruction | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Stomatitis | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Volvulus | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 0 / 287 (0.00%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 2 / 287 (0.70%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 0 / 1 | 2 / 2 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholangitis | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 0 / 287 (0.00%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 287 (0.35%) | 1 / 287 (0.35%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis Acute | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis Chronic | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 0 / 287 (0.00%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholelithiasis | | | |
| subjects affected / exposed | 2 / 287 (0.70%) | 0 / 287 (0.00%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholestasis | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Gallbladder Obstruction | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic Cirrhosis | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 0 / 287 (0.00%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| Hepatitis Toxic | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 2 / 287 (0.70%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatocellular Injury | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 287 (0.35%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Hepatosplenomegaly | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Acute Febrile Neutrophilic Dermatositis | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 0 / 287 (0.00%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Drug Eruption | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Excessive Granulation Tissue | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypersensitivity Vasculitis | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pemphigoid | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pemphigus | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rash | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 2 / 287 (0.70%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rash Erythematous | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rash Maculo-Papular | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin Necrosis | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urticaria | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Acute Kidney Injury | | | |
| subjects affected / exposed | 2 / 287 (0.70%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Calculus Bladder | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 0 / 287 (0.00%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dysuria | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematuria | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 0 / 287 (0.00%) | 2 / 183 (1.09%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nephropathy | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nephropathy Toxic | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal Failure | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 2 / 183 (1.09%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal Impairment | | | |
| subjects affected / exposed | 2 / 287 (0.70%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ureteric Stenosis | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ureterolithiasis | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urge Incontinence | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary Incontinence | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 0 / 287 (0.00%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary Retention | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endocrine disorders | | | |
| Addison's Disease | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 0 / 287 (0.00%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Goitre | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 0 / 287 (0.00%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arthritis | | | |
| subjects affected / exposed | 2 / 287 (0.70%) | 0 / 287 (0.00%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Back Pain | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| Chondrocalcinosis Pyrophosphate | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femoroacetabular Impingement | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Groin Pain | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 0 / 287 (0.00%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lumbar Spinal Stenosis | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 0 / 287 (0.00%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Muscle Haemorrhage | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Muscular Weakness | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 0 / 287 (0.00%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal Pain | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteoarthritis | | | |
| subjects affected / exposed | 3 / 287 (1.05%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteonecrosis | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 287 (0.00%) | 0 / 287 (0.00%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pain in Extremity | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 0 / 287 (0.00%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Abscess Jaw | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Actinomycotic Pulmonary Infection | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute Sinusitis | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 2 / 183 (1.09%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arthritis Bacterial | | | |
| subjects affected / exposed | 2 / 287 (0.70%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ascariasis | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atypical Pneumonia | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bacteraemia | | | |
| subjects affected / exposed | 2 / 287 (0.70%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Brain Abscess | | | |
| subjects affected / exposed | 2 / 287 (0.70%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Breast Abscess | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 0 / 287 (0.00%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Breast Cellulitis | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchitis | | | |
| subjects affected / exposed | 8 / 287 (2.79%) | 5 / 287 (1.74%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 8 / 10 | 5 / 5 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchopulmonary Aspergillosis | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 1 / 287 (0.35%) | 2 / 183 (1.09%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| Campylobacter Infection | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 4 / 287 (1.39%) | 2 / 287 (0.70%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 4 / 4 | 2 / 2 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis Staphylococcal | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Central Nervous System Infection | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chronic Sinusitis | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Clostridium Difficile Colitis | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 287 (0.35%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Clostridium Difficile Infection | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 0 / 287 (0.00%) | 2 / 183 (1.09%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Conjunctivitis | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cystitis | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 0 / 287 (0.00%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cytomegalovirus Colitis | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cytomegalovirus Infection | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Dacryocystitis | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dermo-Hypodermatitis | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 0 / 287 (0.00%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Disseminated Cryptococcosis | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epstein-Barr Virus Infection | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 0 / 287 (0.00%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Erysipelas | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 3 / 183 (1.64%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 3 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Escherichia Sepsis | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 0 / 287 (0.00%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Escherichia Urinary Tract Infection | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fungal Infection | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis Viral | | | |
| subjects affected / exposed | 2 / 287 (0.70%) | 0 / 287 (0.00%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal Infection | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemophilus Infection | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 0 / 287 (0.00%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatitis B Reactivation | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| Herpes Zoster | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 2 / 287 (0.70%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 2 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infection | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 3 / 287 (1.05%) | 2 / 287 (0.70%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 3 / 3 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infectious Pleural Effusion | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Laryngitis | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower Respiratory Tract Infection | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 2 / 287 (0.70%) | 2 / 183 (1.09%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung Infection | | | |
| subjects affected / exposed | 3 / 287 (1.05%) | 3 / 287 (1.05%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 3 / 3 | 3 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lymphadenitis Bacterial | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 0 / 287 (0.00%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Muscle Abscess | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 0 / 287 (0.00%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutropenic Sepsis | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nocardiosis | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oral Candidiasis | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 2 / 287 (0.70%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteomyelitis | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Otitis Media | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Periodontitis | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Periorbital Cellulitis | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peritonsillar Abscess | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 0 / 287 (0.00%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pharyngeal Abscess | | | |

| | | | |
|-------------------------------------------------|-------------------|------------------|-------------------|
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pharyngitis | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pharyngitis Streptococcal | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumocystis Jirovecii Pneumonia | | | |
| subjects affected / exposed | 2 / 287 (0.70%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 48 / 287 (16.72%) | 26 / 287 (9.06%) | 34 / 183 (18.58%) |
| occurrences causally related to treatment / all | 59 / 64 | 38 / 38 | 42 / 46 |
| deaths causally related to treatment / all | 1 / 1 | 3 / 3 | 4 / 4 |
| Pneumonia Bacterial | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia Haemophilus | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia Pneumococcal | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia Streptococcal | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 287 (0.35%) | 2 / 183 (1.09%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Progressive Multifocal Leukoencephalopathy | | | |
| subjects affected / exposed | 2 / 287 (0.70%) | 0 / 287 (0.00%) | 2 / 183 (1.09%) |
| occurrences causally related to treatment / all | 4 / 4 | 0 / 0 | 4 / 4 |
| deaths causally related to treatment / all | 2 / 2 | 0 / 0 | 1 / 1 |
| Pseudomembranous Colitis | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary Tuberculoma | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary Tuberculosis | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rash Pustular | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory Syncytial Virus Infection | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 0 / 287 (0.00%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory Tract Infection | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 5 / 287 (1.74%) | 2 / 287 (0.70%) | 5 / 183 (2.73%) |
| occurrences causally related to treatment / all | 6 / 6 | 2 / 2 | 5 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 8 / 287 (2.79%) | 4 / 287 (1.39%) | 4 / 183 (2.19%) |
| occurrences causally related to treatment / all | 9 / 9 | 5 / 7 | 6 / 6 |
| deaths causally related to treatment / all | 1 / 1 | 2 / 3 | 2 / 2 |
| Septic Shock | | | |
| subjects affected / exposed | 6 / 287 (2.09%) | 2 / 287 (0.70%) | 5 / 183 (2.73%) |
| occurrences causally related to treatment / all | 9 / 9 | 1 / 3 | 7 / 7 |
| deaths causally related to treatment / all | 4 / 4 | 0 / 1 | 5 / 5 |
| Sinusitis | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 2 / 287 (0.70%) | 2 / 183 (1.09%) |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 2 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin Candida | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 0 / 287 (0.00%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin Infection | | | |
| subjects affected / exposed | 2 / 287 (0.70%) | 1 / 287 (0.35%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Soft Tissue Infection | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Splenic Abscess | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Staphylococcal Infection | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 2 / 287 (0.70%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Staphylococcal Skin Infection | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subcutaneous Abscess | | | |
| subjects affected / exposed | 3 / 287 (1.05%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 3 / 3 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tooth Abscess | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tuberculosis of Central Nervous System | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper Respiratory Tract Infection | | | |
| subjects affected / exposed | 3 / 287 (1.05%) | 3 / 287 (1.05%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 4 / 4 | 3 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary Tract Infection | | | |
| subjects affected / exposed | 6 / 287 (2.09%) | 1 / 287 (0.35%) | 2 / 183 (1.09%) |
| occurrences causally related to treatment / all | 5 / 6 | 1 / 1 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urosepsis | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Varicella | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 287 (0.35%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Varicella Zoster Virus Infection | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 0 / 287 (0.00%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Viral Infection | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 287 (0.35%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| Metabolism and nutrition disorders | | | |
| Decreased Appetite | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dehydration | | | |
| subjects affected / exposed | 2 / 287 (0.70%) | 1 / 287 (0.35%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diabetes Mellitus | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 287 (0.00%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypercalcaemia | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 0 / 287 (0.00%) | 1 / 183 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperuricaemia | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyponatraemia | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypophosphataemia | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tumour Lysis Syndrome | | | |
| subjects affected / exposed | 6 / 287 (2.09%) | 1 / 287 (0.35%) | 0 / 183 (0.00%) |
| occurrences causally related to treatment / all | 4 / 6 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| Non-serious adverse events | Ibrutinib+BR | Placebo+BR | Crossover Ibrutinib |
|-------------------------------------------------------|--------------------|--------------------|---------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 268 / 287 (93.38%) | 271 / 287 (94.43%) | 157 / 183 (85.79%) |
| Vascular disorders | | | |
| Haematoma | | | |
| subjects affected / exposed | 26 / 287 (9.06%) | 3 / 287 (1.05%) | 14 / 183 (7.65%) |
| occurrences (all) | 58 | 3 | 18 |
| Hypertension | | | |
| subjects affected / exposed | 47 / 287 (16.38%) | 14 / 287 (4.88%) | 27 / 183 (14.75%) |
| occurrences (all) | 70 | 17 | 38 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 26 / 287 (9.06%) | 24 / 287 (8.36%) | 5 / 183 (2.73%) |
| occurrences (all) | 39 | 36 | 5 |
| Chills | | | |
| subjects affected / exposed | 33 / 287 (11.50%) | 31 / 287 (10.80%) | 5 / 183 (2.73%) |
| occurrences (all) | 45 | 35 | 6 |
| Fatigue | | | |
| subjects affected / exposed | 69 / 287 (24.04%) | 66 / 287 (23.00%) | 32 / 183 (17.49%) |
| occurrences (all) | 145 | 121 | 45 |
| Influenza Like Illness | | | |

| | | | |
|-------------------------------------------------|-------------------|-------------------|-------------------|
| subjects affected / exposed | 9 / 287 (3.14%) | 10 / 287 (3.48%) | 12 / 183 (6.56%) |
| occurrences (all) | 11 | 14 | 16 |
| Mucosal Inflammation | | | |
| subjects affected / exposed | 15 / 287 (5.23%) | 7 / 287 (2.44%) | 3 / 183 (1.64%) |
| occurrences (all) | 27 | 11 | 3 |
| Non-Cardiac Chest Pain | | | |
| subjects affected / exposed | 17 / 287 (5.92%) | 13 / 287 (4.53%) | 3 / 183 (1.64%) |
| occurrences (all) | 22 | 16 | 3 |
| Oedema Peripheral | | | |
| subjects affected / exposed | 49 / 287 (17.07%) | 34 / 287 (11.85%) | 21 / 183 (11.48%) |
| occurrences (all) | 82 | 40 | 24 |
| Pyrexia | | | |
| subjects affected / exposed | 74 / 287 (25.78%) | 60 / 287 (20.91%) | 22 / 183 (12.02%) |
| occurrences (all) | 140 | 93 | 29 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 74 / 287 (25.78%) | 75 / 287 (26.13%) | 27 / 183 (14.75%) |
| occurrences (all) | 116 | 106 | 41 |
| Dyspnoea | | | |
| subjects affected / exposed | 22 / 287 (7.67%) | 29 / 287 (10.10%) | 11 / 183 (6.01%) |
| occurrences (all) | 30 | 43 | 13 |
| Epistaxis | | | |
| subjects affected / exposed | 22 / 287 (7.67%) | 10 / 287 (3.48%) | 15 / 183 (8.20%) |
| occurrences (all) | 46 | 15 | 16 |
| Nasal Congestion | | | |
| subjects affected / exposed | 16 / 287 (5.57%) | 9 / 287 (3.14%) | 4 / 183 (2.19%) |
| occurrences (all) | 21 | 14 | 5 |
| Oropharyngeal Pain | | | |
| subjects affected / exposed | 30 / 287 (10.45%) | 20 / 287 (6.97%) | 8 / 183 (4.37%) |
| occurrences (all) | 42 | 23 | 8 |
| Productive Cough | | | |
| subjects affected / exposed | 21 / 287 (7.32%) | 18 / 287 (6.27%) | 9 / 183 (4.92%) |
| occurrences (all) | 30 | 31 | 12 |
| Viral Upper Respiratory Tract Infection | | | |

| | | | |
|--------------------------------------------------|-------------------------|------------------------|------------------------|
| subjects affected / exposed occurrences (all) | 30 / 287 (10.45%) 47 | 20 / 287 (6.97%) 27 | 13 / 183 (7.10%) 19 |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 22 / 287 (7.67%) | 11 / 287 (3.83%) | 9 / 183 (4.92%) |
| occurrences (all) | 30 | 12 | 10 |
| Depression | | | |
| subjects affected / exposed | 18 / 287 (6.27%) | 8 / 287 (2.79%) | 4 / 183 (2.19%) |
| occurrences (all) | 18 | 9 | 5 |
| Insomnia | | | |
| subjects affected / exposed | 27 / 287 (9.41%) | 21 / 287 (7.32%) | 10 / 183 (5.46%) |
| occurrences (all) | 36 | 26 | 10 |
| Investigations | | | |
| Alanine Aminotransferase Increased | | | |
| subjects affected / exposed | 15 / 287 (5.23%) | 12 / 287 (4.18%) | 3 / 183 (1.64%) |
| occurrences (all) | 17 | 19 | 4 |
| Blood Creatinine Increased | | | |
| subjects affected / exposed | 17 / 287 (5.92%) | 7 / 287 (2.44%) | 6 / 183 (3.28%) |
| occurrences (all) | 24 | 7 | 7 |
| Neutrophil Count Decreased | | | |
| subjects affected / exposed | 21 / 287 (7.32%) | 16 / 287 (5.57%) | 3 / 183 (1.64%) |
| occurrences (all) | 47 | 60 | 5 |
| Platelet Count Decreased | | | |
| subjects affected / exposed | 17 / 287 (5.92%) | 9 / 287 (3.14%) | 2 / 183 (1.09%) |
| occurrences (all) | 38 | 23 | 2 |
| Weight Decreased | | | |
| subjects affected / exposed | 18 / 287 (6.27%) | 18 / 287 (6.27%) | 5 / 183 (2.73%) |
| occurrences (all) | 24 | 28 | 5 |
| Injury, poisoning and procedural complications | | | |
| Contusion | | | |
| subjects affected / exposed | 30 / 287 (10.45%) | 9 / 287 (3.14%) | 15 / 183 (8.20%) |
| occurrences (all) | 56 | 13 | 27 |
| Infusion Related Reaction | | | |
| subjects affected / exposed | 45 / 287 (15.68%) | 64 / 287 (22.30%) | 1 / 183 (0.55%) |
| occurrences (all) | 66 | 111 | 2 |
| Cardiac disorders | | | |

| | | | |
|-----------------------------------------------------------------------------------------------------|---------------------------|---------------------------|-------------------------|
| Atrial Fibrillation subjects affected / exposed occurrences (all) | 23 / 287 (8.01%) 35 | 5 / 287 (1.74%) 6 | 19 / 183 (10.38%) 23 |
| Nervous system disorders Dysgeusia subjects affected / exposed occurrences (all) | 15 / 287 (5.23%) 16 | 15 / 287 (5.23%) 15 | 3 / 183 (1.64%) 3 |
| Headache subjects affected / exposed occurrences (all) | 49 / 287 (17.07%) 81 | 47 / 287 (16.38%) 74 | 18 / 183 (9.84%) 24 |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) | 73 / 287 (25.44%) 154 | 79 / 287 (27.53%) 200 | 33 / 183 (18.03%) 56 |
| Leukopenia subjects affected / exposed occurrences (all) | 15 / 287 (5.23%) 26 | 18 / 287 (6.27%) 62 | 2 / 183 (1.09%) 3 |
| Neutropenia subjects affected / exposed occurrences (all) | 170 / 287 (59.23%) 659 | 159 / 287 (55.40%) 722 | 40 / 183 (21.86%) 82 |
| Thrombocytopenia subjects affected / exposed occurrences (all) | 90 / 287 (31.36%) 273 | 69 / 287 (24.04%) 223 | 24 / 183 (13.11%) 51 |
| Eye disorders Cataract subjects affected / exposed occurrences (all) | 20 / 287 (6.97%) 32 | 3 / 287 (1.05%) 3 | 8 / 183 (4.37%) 9 |
| Dry Eye subjects affected / exposed occurrences (all) | 15 / 287 (5.23%) 15 | 9 / 287 (3.14%) 12 | 6 / 183 (3.28%) 7 |
| Vision Blurred subjects affected / exposed occurrences (all) | 19 / 287 (6.62%) 21 | 19 / 287 (6.62%) 20 | 3 / 183 (1.64%) 3 |
| Gastrointestinal disorders Abdominal Pain subjects affected / exposed occurrences (all) | 39 / 287 (13.59%) 45 | 24 / 287 (8.36%) 35 | 3 / 183 (1.64%) 3 |

| | | | |
|----------------------------------------|--------------------|--------------------|-------------------|
| Abdominal Pain Upper | | | |
| subjects affected / exposed | 23 / 287 (8.01%) | 16 / 287 (5.57%) | 11 / 183 (6.01%) |
| occurrences (all) | 33 | 23 | 12 |
| Constipation | | | |
| subjects affected / exposed | 61 / 287 (21.25%) | 50 / 287 (17.42%) | 15 / 183 (8.20%) |
| occurrences (all) | 97 | 71 | 23 |
| Diarrhoea | | | |
| subjects affected / exposed | 115 / 287 (40.07%) | 68 / 287 (23.69%) | 47 / 183 (25.68%) |
| occurrences (all) | 248 | 115 | 87 |
| Dyspepsia | | | |
| subjects affected / exposed | 24 / 287 (8.36%) | 21 / 287 (7.32%) | 8 / 183 (4.37%) |
| occurrences (all) | 31 | 30 | 15 |
| Gastrooesophageal Reflux Disease | | | |
| subjects affected / exposed | 15 / 287 (5.23%) | 12 / 287 (4.18%) | 4 / 183 (2.19%) |
| occurrences (all) | 19 | 12 | 4 |
| Nausea | | | |
| subjects affected / exposed | 108 / 287 (37.63%) | 101 / 287 (35.19%) | 16 / 183 (8.74%) |
| occurrences (all) | 192 | 204 | 22 |
| Toothache | | | |
| subjects affected / exposed | 15 / 287 (5.23%) | 5 / 287 (1.74%) | 3 / 183 (1.64%) |
| occurrences (all) | 15 | 8 | 3 |
| Vomiting | | | |
| subjects affected / exposed | 42 / 287 (14.63%) | 45 / 287 (15.68%) | 15 / 183 (8.20%) |
| occurrences (all) | 63 | 86 | 26 |
| Skin and subcutaneous tissue disorders | | | |
| Dry Skin | | | |
| subjects affected / exposed | 27 / 287 (9.41%) | 17 / 287 (5.92%) | 7 / 183 (3.83%) |
| occurrences (all) | 32 | 17 | 8 |
| Ecchymosis | | | |
| subjects affected / exposed | 14 / 287 (4.88%) | 2 / 287 (0.70%) | 10 / 183 (5.46%) |
| occurrences (all) | 20 | 2 | 15 |
| Onychoclasia | | | |
| subjects affected / exposed | 10 / 287 (3.48%) | 0 / 287 (0.00%) | 10 / 183 (5.46%) |
| occurrences (all) | 11 | 0 | 10 |
| Pruritus | | | |

| | | | |
|-------------------------------------------------------------------------|--------------------------|-------------------------|-------------------------|
| subjects affected / exposed occurrences (all) | 34 / 287 (11.85%) 43 | 33 / 287 (11.50%) 56 | 9 / 183 (4.92%) 10 |
| Rash subjects affected / exposed occurrences (all) | 63 / 287 (21.95%) 104 | 35 / 287 (12.20%) 61 | 15 / 183 (8.20%) 18 |
| Rash Maculo-Papular subjects affected / exposed occurrences (all) | 17 / 287 (5.92%) 25 | 11 / 287 (3.83%) 16 | 7 / 183 (3.83%) 7 |
| Skin Lesion subjects affected / exposed occurrences (all) | 30 / 287 (10.45%) 40 | 5 / 287 (1.74%) 8 | 11 / 183 (6.01%) 14 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia subjects affected / exposed occurrences (all) | 47 / 287 (16.38%) 81 | 29 / 287 (10.10%) 41 | 25 / 183 (13.66%) 43 |
| Back Pain subjects affected / exposed occurrences (all) | 41 / 287 (14.29%) 55 | 22 / 287 (7.67%) 31 | 23 / 183 (12.57%) 30 |
| Muscle Spasms subjects affected / exposed occurrences (all) | 44 / 287 (15.33%) 75 | 14 / 287 (4.88%) 19 | 17 / 183 (9.29%) 26 |
| Myalgia subjects affected / exposed occurrences (all) | 28 / 287 (9.76%) 42 | 15 / 287 (5.23%) 24 | 9 / 183 (4.92%) 12 |
| Pain in Extremity subjects affected / exposed occurrences (all) | 21 / 287 (7.32%) 32 | 15 / 287 (5.23%) 20 | 12 / 183 (6.56%) 13 |
| Infections and infestations | | | |
| Bronchitis subjects affected / exposed occurrences (all) | 51 / 287 (17.77%) 75 | 29 / 287 (10.10%) 41 | 19 / 183 (10.38%) 28 |
| Cellulitis subjects affected / exposed occurrences (all) | 16 / 287 (5.57%) 21 | 8 / 287 (2.79%) 12 | 10 / 183 (5.46%) 11 |
| Conjunctivitis | | | |

| | | | |
|------------------------------------|-------------------|-------------------|-------------------|
| subjects affected / exposed | 20 / 287 (6.97%) | 15 / 287 (5.23%) | 10 / 183 (5.46%) |
| occurrences (all) | 28 | 20 | 14 |
| Herpes Zoster | | | |
| subjects affected / exposed | 24 / 287 (8.36%) | 17 / 287 (5.92%) | 7 / 183 (3.83%) |
| occurrences (all) | 31 | 23 | 7 |
| Influenza | | | |
| subjects affected / exposed | 22 / 287 (7.67%) | 16 / 287 (5.57%) | 7 / 183 (3.83%) |
| occurrences (all) | 30 | 19 | 11 |
| Oral Herpes | | | |
| subjects affected / exposed | 15 / 287 (5.23%) | 18 / 287 (6.27%) | 7 / 183 (3.83%) |
| occurrences (all) | 26 | 27 | 13 |
| Pharyngitis | | | |
| subjects affected / exposed | 18 / 287 (6.27%) | 13 / 287 (4.53%) | 2 / 183 (1.09%) |
| occurrences (all) | 19 | 13 | 3 |
| Pneumonia | | | |
| subjects affected / exposed | 40 / 287 (13.94%) | 25 / 287 (8.71%) | 21 / 183 (11.48%) |
| occurrences (all) | 55 | 29 | 34 |
| Respiratory Tract Infection | | | |
| subjects affected / exposed | 19 / 287 (6.62%) | 10 / 287 (3.48%) | 15 / 183 (8.20%) |
| occurrences (all) | 30 | 12 | 31 |
| Sinusitis | | | |
| subjects affected / exposed | 38 / 287 (13.24%) | 24 / 287 (8.36%) | 25 / 183 (13.66%) |
| occurrences (all) | 67 | 34 | 33 |
| Upper Respiratory Tract Infection | | | |
| subjects affected / exposed | 69 / 287 (24.04%) | 50 / 287 (17.42%) | 36 / 183 (19.67%) |
| occurrences (all) | 135 | 79 | 61 |
| Urinary Tract Infection | | | |
| subjects affected / exposed | 28 / 287 (9.76%) | 15 / 287 (5.23%) | 26 / 183 (14.21%) |
| occurrences (all) | 56 | 20 | 39 |
| Metabolism and nutrition disorders | | | |
| Decreased Appetite | | | |
| subjects affected / exposed | 42 / 287 (14.63%) | 42 / 287 (14.63%) | 16 / 183 (8.74%) |
| occurrences (all) | 58 | 65 | 20 |
| Hyperuricaemia | | | |
| subjects affected / exposed | 36 / 287 (12.54%) | 20 / 287 (6.97%) | 7 / 183 (3.83%) |
| occurrences (all) | 60 | 24 | 12 |

| | | | |
|-----------------------------|------------------|------------------|-----------------|
| Hypokalaemia | | | |
| subjects affected / exposed | 24 / 287 (8.36%) | 12 / 287 (4.18%) | 8 / 183 (4.37%) |
| occurrences (all) | 40 | 18 | 14 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 05 December 2012 | <ul style="list-style-type: none">• Clarified management of study drug with concomitant cytochrome (CYP) CYP3A4/5 inhibitors/inducers and warfarin or other anticoagulants during the study to reflect updated standard language across the ibrutinib development program• Removed the eligibility restriction for subjects requiring treatment with strong CYP2D6 inhibitors in the exclusion criteria• Clarified management of study drug during the perioperative periods• Incorporated feedback from investigators, health authorities, and the study steering committee with regard to the platelet cutoff eligibility criteria, and bone marrow and MRD sampling for subjects reaching CR |
| 13 September 2013 | <ul style="list-style-type: none">• Updated the protocol with safety information in the investigator's brochure• Implemented a recommendation from the DMC to use anti-microbial prophylaxis• Added that data related to the occurrence of other malignancies or transformation to a more aggressive histology (Richter's transformation) during the follow-up phase should be collected |
| 30 January 2014 | <ul style="list-style-type: none">• Provided access to next-line treatment with ibrutinib for subjects initially assigned to placebo who had IRC-confirmed disease progression (that is each subject had met the primary endpoint), at investigator's discretion, and with medical monitor approval |
| 13 April 2015 | <ul style="list-style-type: none">• Unblinded study and removed the Amendment 3 requirement for IRC-confirmed disease progression providing access to next-line treatment with ibrutinib for subjects initially assigned to placebo at the discretion of the investigator at the time the subject had progression or met IWCLL criteria for treatment• End of study definition was revised to change the length of time from last subject in study from 4 years to 5 years so that estimated median PFS could be reached• Clarified that all responding subjects were to have peripheral blood MRD evaluations performed every 12 weeks until PD |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Study was planned to end when 80% of randomized participants died or 5 years after last participant randomized, whichever was first. Sponsor terminated study on 23-Jan-2019 (5 year after last participant randomized) and study was considered completed

Notes: