# Clinical trial results:
# A Prospective, Open-Label, Multicenter Randomized Phase III Trial to Compare The Efficacy and Safety of A Combined Regimen of Obinutuzumab and Venetoclax (GDC-0199/ABT-199) Versus Obinutuzumab and Chlorambucil in Previously Untreated Patients With CLL and Coexisting Medical Conditions

## Summary

| | |
|---|---|
| EudraCT number | 2014-001810-24 |
| Trial protocol | DE DK GB EE AT BG ES HR IT FR PL |
| Global end of trial date | |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 01 September 2019 |
| First version publication date | 01 September 2019 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | BO25323 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02242942 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | F. Hoffmann-La Roche AG |
| Sponsor organisation address | Grenzacherstrasse 124, Basel, Switzerland, CH-4070 |
| Public contact | F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com |
| Scientific contact | F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com |

Notes:

**Paediatric regulatory details**

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

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Interim |
| Date of interim/final analysis | 17 August 2018 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 17 August 2018 |
| Global end of trial reached? | No |

Notes:

## General information about the trial

Main objective of the trial:

This study compared the efficacy and safety of a combined regimen of obinutuzumab and venetoclax versus obinutuzumab + chlorambucil in subjects with previously untreated chronic lymphocytic leukemia (CLL) and coexisting medical conditions. The study had a safety run-in phase and a main randomized phase with two treatment arms.

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 24 December 2014 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety, Efficacy |
| Long term follow-up duration | 5 Years |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Australia: 47 |
| Country: Number of subjects enrolled | New Zealand: 20 |
| Country: Number of subjects enrolled | Austria: 6 |
| Country: Number of subjects enrolled | Bulgaria: 33 |
| Country: Number of subjects enrolled | Croatia: 12 |
| Country: Number of subjects enrolled | Estonia: 5 |
| Country: Number of subjects enrolled | Poland: 16 |
| Country: Number of subjects enrolled | Romania: 7 |
| Country: Number of subjects enrolled | Russian Federation: 41 |
| Country: Number of subjects enrolled | Argentina: 1 |
| Country: Number of subjects enrolled | Brazil: 22 |
| Country: Number of subjects enrolled | Canada: 16 |
| Country: Number of subjects enrolled | Mexico: 3 |
| Country: Number of subjects enrolled | United States: 30 |
| Country: Number of subjects enrolled | Denmark: 21 |
| Country: Number of subjects enrolled | France: 39 |
| Country: Number of subjects enrolled | Germany: 58 |
| Country: Number of subjects enrolled | Italy: 26 |
| Country: Number of subjects enrolled | Spain: 31 |
| Country: Number of subjects enrolled | Switzerland: 3 |

| | |
|---|---|
| Country: Number of subjects enrolled | United Kingdom: 8 |
| Worldwide total number of subjects | 445 |
| EEA total number of subjects | 262 |

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) | 74 |
| From 65 to 84 years | 356 |
| 85 years and over | 15 |

## Subject disposition

### Recruitment

Recruitment details:

A total of 445 subjects were enrolled in the study in 130 centers in 21 countries. The safety run-in cohort enrolled 13 subjects and the main randomized main part of the trial enrolled 432 subjects.

### Pre-assignment

Screening details:

Subjects with previously untreated CLL and coexisting medical conditions were enrolled in the study.

### Period 1

| | |
|---|---|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Obinutuzumab + Chlorambucil |

Arm description:

Subjects received obinutuzumab for 6 cycles and chlorambucil for 12 cycles. Cycles comprised of 28 days.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Chlorambucil |
| Investigational medicinal product code | RO0059978 |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Chlorambucil was administered orally at a dose of 0.5 mg/kg on Day 1 and Day 15 of each 28-day cycle for 12 cycles.

| | |
|---|---|
| Investigational medicinal product name | Obinutuzumab |
| Investigational medicinal product code | RO5072759 |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Subjects received obinutuzumab 1000 mg on Days 1, 8 and 15 of Cycle 1 and 1000 mg on Day 1 through Cycles 2-6.

| | |
|---|---|
| **Arm title** | Obinutuzumab + Venetoclax |

Arm description:

Subjects received obinutuzumab for 6 cycles and venetoclax for 12 cycles. Cycles comprised of 28 days.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Obinutuzumab |
| Investigational medicinal product code | RO5072759 |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Subjects received obinutuzumab 1000 mg on Days 1, 8 and 15 of Cycle 1 and 1000 mg on Day 1 through Cycles 2-6.

| | |
|---|---|
| Investigational medicinal product name | Venetoclax |
| Investigational medicinal product code | RO553-7382 |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects received venetoclax 400 mg daily orally for twelve 28-day cycles.

| **Arm title** | Safety Run-in Obinutuzumab + Venetoclax |
|---|---|

Arm description:

Subjects received obinutuzumab for 6 cycles and venetoclax for 12 cycles. Cycles comprised of 28 days.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Obinutuzumab |
| Investigational medicinal product code | RO5072759 |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Subjects received obinutuzumab intravenously for six 28-day cycles.

| | |
|---|---|
| Investigational medicinal product name | Venetoclax |
| Investigational medicinal product code | RO553-7382 |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects received venetoclax 400 mg orally daily for twelve 28-day cycles.

| **Number of subjects in period 1** | Obinutuzumab + Chlorambucil | Obinutuzumab + Venetoclax | Safety Run-in Obinutuzumab + Venetoclax |
|---|---|---|---|
| Started | 216 | 216 | 13 |
| Treated | 214 | 212 | 13 |
| Completed | 0 | 0 | 0 |
| Not completed | 216 | 216 | 13 |
| Adverse event, serious fatal | 17 | 20 | 2 |
| Physician decision | 1 | - | - |
| Consent withdrawn by subject | 8 | 10 | - |
| On-going in Study | 190 | 186 | 11 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Obinutuzumab + Chlorambucil |
| Reporting group description: | |
| Subjects received obinutuzumab for 6 cycles and chlorambucil for 12 cycles. Cycles comprised of 28 days. | |
| Reporting group title | Obinutuzumab + Venetoclax |
| Reporting group description: | |
| Subjects received obinutuzumab for 6 cycles and venetoclax for 12 cycles. Cycles comprised of 28 days. | |
| Reporting group title | Safety Run-in Obinutuzumab + Venetoclax |
| Reporting group description: | |
| Subjects received obinutuzumab for 6 cycles and venetoclax for 12 cycles. Cycles comprised of 28 days. | |

| Reporting group values | Obinutuzumab + Chlorambucil | Obinutuzumab + Venetoclax | Safety Run-in Obinutuzumab + Venetoclax |
|---|---|---|---|
| Number of subjects | 216 | 216 | 13 |
| Age categorical<br>Units: Subjects | | | |
| Adults (18-64 years) | 37 | 36 | 1 |
| Elderly (From 65-84 years) | 174 | 172 | 10 |
| Elderly 85 years and over | 5 | 8 | 2 |
| Age Continuous<br>Units: Years | | | |
| arithmetic mean | 71.1 | 71.1 | 75.4 |
| standard deviation | ± 8.0 | ± 8.2 | ± 7.8 |
| Sex: Female, Male<br>Units: Subjects | | | |
| Female | 73 | 70 | 5 |
| Male | 143 | 146 | 8 |

| Reporting group values | Total | | |
|---|---|---|---|
| Number of subjects | 445 | | |
| Age categorical<br>Units: Subjects | | | |
| Adults (18-64 years) | 74 | | |
| Elderly (From 65-84 years) | 356 | | |
| Elderly 85 years and over | 15 | | |
| Age Continuous<br>Units: Years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Sex: Female, Male<br>Units: Subjects | | | |
| Female | 148 | | |
| Male | 297 | | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Obinutuzumab + Chlorambucil |
| Reporting group description: | |
| Subjects received obinutuzumab for 6 cycles and chlorambucil for 12 cycles. Cycles comprised of 28 days. | |
| Reporting group title | Obinutuzumab + Venetoclax |
| Reporting group description: | |
| Subjects received obinutuzumab for 6 cycles and venetoclax for 12 cycles. Cycles comprised of 28 days. | |
| Reporting group title | Safety Run-in Obinutuzumab + Venetoclax |
| Reporting group description: | |
| Subjects received obinutuzumab for 6 cycles and venetoclax for 12 cycles. Cycles comprised of 28 days. | |

### Primary: Progression Free Survival (PFS) Based on Investigator Assessment According to IWCLL Criteria

| | |
|---|---|
| End point title | Progression Free Survival (PFS) Based on Investigator Assessment According to IWCLL Criteria[1] |
| End point description: | |
| PFS was determined according to IWCLL 2008 criteria and defined as the time from randomisation to the first occurrence of PD or death from any cause. Disease progression was characterized by at least one of the following: 1) >/= 50% increase in the absolute number of circulating lymphocytes to at least 5*10^9/L, 2) Appearance of new palpable lymph nodes (> 15 mm in longest diameter) or any new extra-nodal lesion; 3) >/= 50% increase in the longest diameter of any previous site of lymphadenopathy; 4) >/= 50% increase in the enlargement of the liver and/or spleen; 5) Transformation to a more aggressive histology. Intent to treat (ITT) population was defined as all randomised subjects. Here, 9999 indicates that the data for the specific time point were not evaluable due to insufficient number of subjects with events. | |
| End point type | Primary |
| End point timeframe: | |
| Baseline until disease progression or death up to approximately 3.75 years | |
| Notes: | |
| [1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Efficacy data were analysed only for the randomised arms in the main study. | |

| End point values | Obinutuzumab + Chlorambucil | Obinutuzumab + Venetoclax | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 216 | 216 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 9999 (31.1 to 9999) | 9999 (9999 to 9999) | | |

### Statistical analyses

| | |
|---|---|
| **Statistical analysis title** | Main study analysis |
| Comparison groups | Obinutuzumab + Venetoclax v Obinutuzumab + Chlorambucil |

| | |
|---|---|
| Number of subjects included in analysis | 432 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.35 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.23 |
| upper limit | 0.53 |

## Secondary: Progression Free Survival (PFS) Based on Institutional Review Committee (IRC)-Assessments According to International Workshop on Chronic Lymphocytic Leukemia (IWCLL) Criteria

| | |
|---|---|
| End point title | Progression Free Survival (PFS) Based on Institutional Review Committee (IRC)-Assessments According to International Workshop on Chronic Lymphocytic Leukemia (IWCLL) Criteria[2] |

End point description:

PFS was determined according to IWCLL 2008 criteria and defined as the time from randomisation to the first occurrence of progressive disease (PD) or death from any cause. Disease progression was characterised by at least one of the following: 1) >/= 50% increase in the absolute number of circulating lymphocytes to at least 5*10^9/L, 2) Appearance of new palpable lymph nodes (> 15 mm in longest diameter) or any new extra-nodal lesion; 3) >/= 50% increase in the longest diameter of any previous site of lymphadenopathy; 4) >/= 50% increase in the enlargement of the liver and/or spleen; 5) Transformation to a more aggressive histology. ITT population was defined as all randomised subjects. Here, 9999 indicates that the data for the specific time point were not evaluable due to insufficient number of subjects with events.

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

End point timeframe:

Baseline until disease progression or death up to approximately 3.75 years

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Efficacy data were analysed only for the randomised arms in the main study.

| **End point values** | Obinutuzumab + Chlorambucil | Obinutuzumab + Venetoclax | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 216 | 216 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 9999 (31.1 to 9999) | 9999 (9999 to 9999) | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects With an Overall Response (OR) at Completion of Treatment, as Determined by the Investigator According to IWCLL Criteria

| End point title | Percentage of Subjects With an Overall Response (OR) at Completion of Treatment, as Determined by the Investigator According to IWCLL Criteria[3] |
|---|---|

End point description:

OR: complete response (CR), CR with incomplete bone marrow recovery (CRi), or partial response (PR) according to IWCLL 2008 criteria. CR requires all of the following: peripheral blood lymphocytes below 4x10^9/L, absence of lymphadenopathy by physical examination and computed tomography (CT) scan, no hepatomegaly or splenomegaly, absence of disease or constitutional symptoms, blood counts of neutrophils >1.5*10^9/L, platelets >100*10^9/L and hemoglobin >110 g/L, bone marrow normocellular for age without clonal infiltrate (except for Cri). PR: two of the following for at least 2 months: >/= 50% decrease in peripheral blood lymphocyte count from the pretreatment value, >/=50% reduction in lymphadenopathy, >/=50% reduction of liver and/or spleen enlargement, and at least one of the following counts: neutrophils >1.5*10^9/L, platelets >100*10^9/L and hemoglobin >110 g/L. ITT population: all randomised subjects. 9999: data not evaluable due to insufficient number of events.

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

End point timeframe:

At the completion of treatment assessment 3 months after treatment completion (at approximately 15 months)

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Efficacy data were analysed only for the randomised arms in the main study.

| **End point values** | Obinutuzumab + Chlorambucil | Obinutuzumab + Venetoclax | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 216 | 216 | | |
| Units: percentage of subjects | | | | |
| number (confidence interval 95%) | 71.3 (64.77 to 77.23) | 84.7 (79.22 to 89.24) | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects With a Complete Response Rate (CRR) at the Completion of Treatment Assessment as Determined by the Investigator According to IWCLL Criteria

| End point title | Percentage of Subjects With a Complete Response Rate (CRR) at the Completion of Treatment Assessment as Determined by the Investigator According to IWCLL Criteria[4] |
|---|---|

End point description:

CRR was defined as the rate of a clinical response of CR or CRi according to IWCLL 2008 criteria. CR requires all of the following: peripheral blood lymphocytes below 4x10^9/L, absence of lymphadenopathy by physical examination and CT scan, no hepatomegaly or splenomegaly, absence of disease or constitutional symptoms, blood counts of neutrophils >1.5*10^9/L, platelets >100*10^9/L and hemoglobin >110 g/L, bone marrow at least normocellular for age without clonal infiltrate (except for Cri). ITT population was defined as all randomised subjects.

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

End point timeframe:

At the completion of treatment assessment 3 months after treatment completion (at approximately 15 months)

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Efficacy data were analysed only for the randomised arms in the main study.

| End point values | Obinutuzumab + Chlorambucil | Obinutuzumab + Venetoclax | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 216 | 216 | | |
| Units: percentage of subjects | | | | |
| number (confidence interval 95%) | 23.1 (17.70 to 29.35) | 49.5 (42.68 to 56.40) | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects With Minimal Residual Disease (MRD) Negativity in Peripheral Blood as Measured by Allele-Specific Oligonucleotide Polymerase Chain Reaction (ASO-PCR) at Completion of Treatment

| End point title | Percentage of Subjects With Minimal Residual Disease (MRD) Negativity in Peripheral Blood as Measured by Allele-Specific Oligonucleotide Polymerase Chain Reaction (ASO-PCR) at Completion of Treatment[5] |
|---|---|

End point description:

MRD negativity was defined as having < 1 CLL cell per 10,000 leucocytes in peripheral blood. ITT population was defined as all randomised subjects.

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

End point timeframe:

At the completion of treatment assessment 3 months after treatment completion (at approximately 15 months)

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Efficacy data were analysed only for the randomised arms in the main study.

| End point values | Obinutuzumab + Chlorambucil | Obinutuzumab + Venetoclax | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 216 | 216 | | |
| Units: percentage of subjects | | | | |
| number (confidence interval 95%) | 35.2 (28.83 to 41.95) | 75.5 (69.17 to 81.05) | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects With MRD Negativity in Bone marrow as Measured by ASO-PCR at Completion of Treatment

| End point title | Percentage of Subjects With MRD Negativity in Bone marrow as Measured by ASO-PCR at Completion of Treatment[6] |
|---|---|

End point description:

MRD negativity was defined as having < 1 CLL cell per 10,000 leucocytes in bone marrow. ITT population was defined as all randomised subjects.

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

End point timeframe:

At the completion of treatment assessment 3 months after treatment completion (at approximately 15 months)

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Efficacy data were analysed only for the randomised arms in the main study.

| **End point values** | Obinutuzumab + Chlorambucil | Obinutuzumab + Venetoclax | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 216 | 216 | | |
| Units: percentage of subjects | | | | |
| number (confidence interval 95%) | 17.1 (12.36 to 22.83) | 56.9 (50.05 to 63.64) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Overall Survival (OS)

| End point title | Overall Survival (OS)[7] |
|---|---|

End point description:

OS was defined as the time between the date of randomization and the date of death due to any cause. ITT population was defined as all randomised subjects.

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

End point timeframe:

Baseline until death, up to approximately 5.75 years

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data will be analysed only for the randomised arms in the main study once data collection is complete.

| **End point values** | Obinutuzumab + Chlorambucil | Obinutuzumab + Venetoclax | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0[8] | 0[9] | | |
| Units: months | | | | |
| median (confidence interval 95%) | ( to ) | ( to ) | | |

Notes:

[8] - Data to be reported upon study completion.

[9] - Data to be reported upon study completion.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects With MRD Negativity in Peripheral Blood as Measured by ASO-PCR at Completion of Combination Treatment Assessment

| End point title | Percentage of Subjects With MRD Negativity in Peripheral Blood as Measured by ASO-PCR at Completion of Combination Treatment Assessment[10] |
|---|---|

End point description:

MRD negativity was defined as having < 1 CLL cell per 10,000 leucocytes in peripheral blood. ITT population was defined as all randomised subjects.

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

End point timeframe:

Day 1 Cycle 9 or 3 months after last IV infusion, approximately 9 months

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Efficacy data were analysed only for the randomised arms in the main study.

| **End point values** | Obinutuzumab + Chlorambucil | Obinutuzumab + Venetoclax | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 216 | 216 | | |
| Units: percentage of subjects | | | | |
| number (confidence interval 95%) | 38.4 (31.91 to 45.27) | 71.3 (64.77 to 77.23) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects With MRD Negativity in Bone Marrow as Measured by ASO-PCR at Completion of Combination Treatment Assessment

| End point title | Percentage of Subjects With MRD Negativity in Bone Marrow as Measured by ASO-PCR at Completion of Combination Treatment Assessment[11] |
|---|---|

End point description:

MRD negativity was defined as having < 1 CLL cell per 10,000 leucocytes in bone marrow. ITT population was defined as all randomised subjects.

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

End point timeframe:

Day 1 Cycle 9 or 3 months after last IV infusion at approximately 9 months

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Efficacy data were analysed only for the randomised arms in the main study.

| **End point values** | Obinutuzumab + Chlorambucil | Obinutuzumab + Venetoclax | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 216 | 216 | | |
| Units: percentage of subjects | | | | |
| number (confidence interval 95%) | 13.0 (8.79 to 18.19) | 51.4 (44.51 to 58.23) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects With OR at Completion of Combination Treatment Response Assessment

| End point title | Percentage of Subjects With OR at Completion of Combination Treatment Response Assessment[12] |
|---|---|

End point description:

OR was defined as CR, CRi or PR according to IWCLL 2008 criteria. CR required all of the following: peripheral blood lymphocytes below 4x10^9/L, absence of lymphadenopathy by physical examination, no hepatomegaly or splenomegaly, Absence of disease or constitutional symptoms, blood counts of neutrophils >1.5*10^9/L, platelets >100*10^9/L and hemoglobin >110 g/L. PR: two of the following features for at least 2 months: >/= 50% decrease in peripheral blood lymphocyte count from the pretreatment value, >/=50% reduction in lymphadenopathy, >/=50% reduction of liver and/or spleen enlargement, and at least one of the following blood counts: neutrophils >1.5*10^9/L, platelets >100*10^9/L and hemoglobin >110 g/L. ITT population was defined as all randomised subjects.

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

End point timeframe:

Day 1 Cycle 7 or 28 days after last IV infusion, approximately 6 months

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Efficacy data were analysed only for the randomised arms in the main study.

| **End point values** | Obinutuzumab + Chlorambucil | Obinutuzumab + Venetoclax | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 216 | 216 | | |
| Units: percentage of subjects | | | | |
| number (confidence interval 95%) | 86.6 (81.29 to 90.82) | 88.4 (83.39 to 92.37) | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Duration of Objective Response (DOR)

| End point title | Duration of Objective Response (DOR)[13] |
|---|---|

End point description:

PD was defined as lymphadenopathy, >=50% increase in liver or spleen size, >=50% increase in lymphocyte count, transformation to a more aggressive histology or occurrence of cytopenia. ITT population was defined as all randomised subjects.

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

End point timeframe:

Time from the first occurrence of a documented objective response to the time of PD as determined by the investigator or death from any cause, up to approximately 5.75 years

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data will be analysed only for the randomised arms in the main study once data collection is complete.

| End point values | Obinutuzumab + Chlorambucil | Obinutuzumab + Venetoclax | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0[14] | 0[15] | | |
| Units: months | | | | |
| median (confidence interval 95%) | ( to ) | ( to ) | | |

Notes:

[14] - Data to be reported upon study completion.

[15] - Data to be reported upon study completion.

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects By Best Response Achieved (CR, CRi, PR, Stable Disease (SD), or PD)

| End point title | Percentage of Subjects By Best Response Achieved (CR, CRi, PR, Stable Disease (SD), or PD)[16] |
|---|---|

End point description:

CR: Peripheral blood lymphocytes below 4x10^9/L, absence of lymphadenopathy by physical examination and CT scan, no hepatomegaly or splenomegaly, absence of disease or constitutional symptoms, blood counts of neutrophils >1.5*10^9/L, platelets >100*10^9/L and hemoglobin >110 g/L, bone marrow normocellular for age without clonal infiltrate (except for Cri). PR: any 2 for at least 2 months: >/= 50% decrease in peripheral blood lymphocyte count from the pretreatment value, >/=50% reduction in lymphadenopathy, >/=50% reduction of liver and/or spleen enlargement, and at least one of the following: neutrophils >1.5*10^9/L, platelets >100*10^9/L and hemoglobin >110 g/L. PD: lymphadenopathy, >=50% increase in liver or spleen size, >=50% increase in lymphocyte count, transformation to a more aggressive histology or occurrence of cytopenia. SD: non-response used to characterize subjects who did not achieve a CR or a PR, and who have not exhibited PD. ITT population: all randomised subjects.

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

End point timeframe:

Baseline up to the completion of treatment assessment 3 months after treatment completion (up to approximately 15 months)

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Efficacy data were analysed only for the randomised arms in the main study.

| End point values | Obinutuzumab + Chlorambucil | Obinutuzumab + Venetoclax | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 216 | 216 | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |
| CR | 56.0 | 70.4 | | |
| CRi | 5.6 | 7.9 | | |
| PR | 29.2 | 13.4 | | |
| SD | 1.9 | 0.5 | | |
| PD | 0.5 | 0.5 | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Event-Free Survival

| End point title | Event-Free Survival[17] |
|---|---|

End point description:

ITT population was defined as all randomised subjects.

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

End point timeframe:

Time between date of randomisation and the date of disease progression/relapse on the basis of investigator-assessment, death, or start of a new anti-leukemic therapy, up to 5.75 years

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data will be analysed only for the randomised arms in the main study once data collection is complete.

| End point values | Obinutuzumab + Chlorambucil | Obinutuzumab + Venetoclax | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0[18] | 0[19] | | |
| Units: months | | | | |
| median (confidence interval 95%) | ( to ) | ( to ) | | |

Notes:

[18] - Data to be reported upon study completion.

[19] - Data to be reported upon study completion.

### Statistical analyses

No statistical analyses for this end point

## Secondary: Time to Next Anti-Leukemic Treatment

| End point title | Time to Next Anti-Leukemic Treatment[20] |
|---|---|

End point description:

ITT population was defined as all randomised subjects.

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

End point timeframe:

Time between the date of randomization and the date of first intake of new anti-leukemic therapy, up to 5.75 years

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data will be analysed only for the randomised arms in the main study once data collection is complete.

| End point values | Obinutuzumab + Chlorambucil | Obinutuzumab + Venetoclax | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0[21] | 0[22] | | |
| Units: months | | | | |
| median (confidence interval 95%) | ( to ) | ( to ) | | |

Notes:

[21] - Data to be reported upon study completion.

[22] - Data to be reported upon study completion.

### Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Subjects With Adverse Events (AEs)

| End point title | Number of Subjects With Adverse Events (AEs)[23] |
|---|---|

End point description:

An AE is any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a pharmaceutical product, whether or not considered related to the pharmaceutical product. Preexisting conditions which worsen during a study are also considered as AEs. Safety population was defined as all subjects who received at least one dose of any study medication (i.e., obinutuzumab, venetoclax, or chlorambucil).

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

End point timeframe:

Up to approximately 5.75 years

Notes:

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data will be analysed only for the randomised arms in the main study once data collection is complete.

| End point values | Obinutuzumab + Chlorambucil | Obinutuzumab + Venetoclax | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0[24] | 0[25] | | |
| Units: subjects | | | | |

Notes:

[24] - Data to be reported upon study completion.

[25] - Data to be reported upon study completion.

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects With CD19 + /CD5+ B Cells or CD14+ monocytes

| End point title | Percentage of Subjects With CD19 + /CD5+ B Cells or CD14+ monocytes |
|---|---|

End point description:

ITT population was defined as all randomised subjects.

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

End point timeframe:

Baseline up to approximately 5.75 years

| End point values | Obinutuzumab + Chlorambucil | Obinutuzumab + Venetoclax | Safety Run-in Obinutuzumab + Venetoclax | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 0[26] | 0[27] | 0[28] | |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |

Notes:

[26] - Data to be reported upon study completion.

[27] - Data to be reported upon study completion.

[28] - Data to be reported upon study completion.

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects With Human-Anti-Human Antibodies

| End point title | Percentage of Subjects With Human-Anti-Human Antibodies |
|---|---|

End point description:

ITT population was defined as all randomised subjects.

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

End point timeframe:

Baseline up to approximately 5.75 years

| End point values | Obinutuzumab + Chlorambucil | Obinutuzumab + Venetoclax | Safety Run-in Obinutuzumab + Venetoclax | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 0[29] | 0[30] | 0[31] | |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |

Notes:

[29] - Data to be reported upon study completion.

[30] - Data to be reported upon study completion.

[31] - Data to be reported upon study completion.

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects Recorded as Premature Study Withdrawals

| End point title | Percentage of Subjects Recorded as Premature Study Withdrawals |
|---|---|

End point description:

ITT population was defined as all randomised subjects.

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

End point timeframe:

Up to approximately 5.75 years

| End point values | Obinutuzumab + Chlorambucil | Obinutuzumab + Venetoclax | Safety Run-in Obinutuzumab + Venetoclax | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 0[32] | 0[33] | 0[34] | |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |

Notes:

[32] - Data to be reported upon study completion.

[33] - Data to be reported upon study completion.

[34] - Data to be reported upon study completion.

### Statistical analyses

No statistical analyses for this end point

## Secondary: Plasma Concentrations of Venetoclax

| End point title | Plasma Concentrations of Venetoclax[35] |
|---|---|

End point description:

Analysis population consisted of those subjects from whom one or more plasma samples were collected and who had received at least one dose of venetoclax treatment.

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

End point timeframe:

Pre-venetoclax dose (0 hour) and 4 hours post- venetoclax dose on Day 1 Cycle 4

Notes:

[35] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Samples were only collected for the obinutuzumab + venetoclax arm in the study.

| End point values | Obinutuzumab + Venetoclax | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 201 | | | |
| Units: µg/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Pre-Dose (n=129)<br><br>4 hours Post-Dose (n=142) | 0.578 (± 0.533)<br><br>1.21 (± 0.765) | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Serum Concentrations of Obinutuzumab

| End point title | Serum Concentrations of Obinutuzumab[36] |
|---|---|

End point description:

Analysis population consisted of subjects from whom one or more serum samples were collected and

who had received at least one dose of obinutuzumab treatment.

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

End point timeframe:

Pre-obinutuzumab infusion (0 hour) and end of obinutuzumab infusion on Day 1 Cycle 4

Notes:

[36] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Samples were only collected for the obinutuzumab + venetoclax arm in the study.

| **End point values** | Obinutuzumab + Venetoclax | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 201 | | | |
| Units: µg/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Pre-Dose (n=133) | 258 (± 140) | | | |
| 4 hours Post-Dose (n=133) | 568 (± 187) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in M.D. Anderson Symptom Inventory-CLL (MDASI-CLL) score

| End point title | Change From Baseline in M.D. Anderson Symptom Inventory-CLL (MDASI-CLL) score[37] |
|---|---|

End point description:

MDASI-CLL: questionnaire of 25 items related to CLL specific symptoms that a subject may have experienced in the past 24 hours. Subjects were asked to rate the severity of 13 symptoms called mean core symptom severity (i.e., pain, fatigue, nausea, disturbed sleep, distressed, shortness of breath, remembering things, lack of appetite, drowsy, dry mouth, sadness, vomiting, numbness or tingling), 6 disease-specific symptoms called mean module symptom severity (night sweats, fevers and chills, lymph node swelling, diarrhea, easy bruising or bleeding, constipation) and 6 mean interference on life questions (i.e., general activity, walking, work, mood, relations with other people, enjoyment of life) on a scale from 0 to 10 with 0 indicating that the symptom is "not present"/"did not interfere" with the subject's activities and 10 indicating "as bad as you can imagine"/"interfered completely". Scores were averaged (range 0 to 10) for each part.

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

End point timeframe:

Baseline up to approximately 5.75 years

Notes:

[37] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data will be analysed only for the randomised arms in the main study once data collection is complete.

| End point values | Obinutuzumab + Chlorambucil | Obinutuzumab + Venetoclax | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0[38] | 0[39] | | |
| Units: score on a scale | | | | |
| arithmetic mean (standard deviation) | () | () | | |

Notes:

[38] - Data to be reported upon study completion.

[39] - Data to be reported upon study completion.

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQC30)

| End point title | Change From Baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQC30) |
|---|---|

End point description:

The EORTC QLQ-C30 is a validated and reliable self-report measure consisting of 30 questions incorporated into five functional scales (physical, role, cognitive, emotional, and social scales), three symptom scales (fatigue, pain, nausea, and vomiting scales), and a global health status/global quality−of−life scale. The remaining single items (dyspnea, appetite loss, sleep disturbance, constipation, and diarrhea) assess the additional symptoms experienced by patients with cancer and the perceived financial burden of treatment. The 28 function and symptom items were scored on a 4-point scale that ranged from "not at all" to "very much," and the 2 global health status/global quality-of-life items were scored on a 7-point scale that ranged from "very poor" to "excellent." Raw average scale scores were linearly transformed to range 0-100 with higher scores indicating higher response levels (i.e., higher functioning, higher symptom severity).

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

End point timeframe:

Baseline up to approximately 5.75 years

| End point values | Obinutuzumab + Chlorambucil | Obinutuzumab + Venetoclax | Safety Run-in Obinutuzumab + Venetoclax | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 0[40] | 0[41] | 0[42] | |
| Units: score on a scale | | | | |
| arithmetic mean (standard deviation) | () | () | () | |

Notes:

[40] - Data to be reported upon study completion.

[41] - Data to be reported upon study completion.

[42] - Data to be reported upon study completion.

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in EuroQol 5 Dimension Questionnaire (EQ-5D-3L)

| End point title | Change From Baseline in EuroQol 5 Dimension Questionnaire (EQ-5D-3L)[43] |
|---|---|

End point description:

The EQ-5D-3L questionnaire is a generic, preference based health utility measure that assesses 5 health states (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and is used to build a composite of the patient's health status. The EQ-5D-3L was employed in this study to calculate health utilities for economic modeling, which ranged 0-1. The EQ-5D-3L also contained a visual analog scale (VAS) to assess the participant's overall health, which ranged from 0-100 with a higher score indicating a worse health status.

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

End point timeframe:

Baseline up to approximately 5.75 years

Notes:

[43] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data will be analysed only for the randomised arms in the main study once data collection is complete.

| **End point values** | Obinutuzumab + Chlorambucil | Obinutuzumab + Venetoclax | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0[44] | 0[45] | | |
| Units: score on a scale | | | | |
| arithmetic mean (standard deviation) | () | () | | |

Notes:

[44] - Data to be reported upon study completion.

[45] - Data to be reported upon study completion.

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All AEs: up to 1 year, Grade 3-4 AEs: up to 1.5 years, Grade 3-4 major infections: up to 3 years (causality only if subject received leukemic treatment). SAEs: before PD up to 3.75 years, after PD only related SAEs and second primary malignancies.

Adverse event reporting additional description:

Safety population was defined as all subjects who received at least one dose of any study medication (i.e., obinutuzumab, venetoclax, or chlorambucil).

| | |
|---|---|
| Assessment type | Systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 21.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Obinutuzumab + Chlorambucil |

Reporting group description:

Subjects received obinutuzumab for 6 cycles and chlorambucil for 12 cycles. Cycles comprised of 28 days.

| | |
|---|---|
| Reporting group title | Obinutuzumab + Venetoclax |

Reporting group description:

Subjects received obinutuzumab for 6 cycles and venetoclax for 12 cycles. Cycles comprised of 28 days.

| | |
|---|---|
| Reporting group title | Safety Run-in Obinutuzumab + Venetoclax |

Reporting group description:

Subjects received obinutuzumab for 6 cycles and venetoclax for 12 cycles. Cycles comprised of 28 days.

| Serious adverse events | Obinutuzumab + Chlorambucil | Obinutuzumab + Venetoclax | Safety Run-in Obinutuzumab + Venetoclax |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 90 / 214 (42.06%) | 104 / 212 (49.06%) | 10 / 13 (76.92%) |
| number of deaths (all causes) | 9 | 16 | 2 |
| number of deaths resulting from adverse events | 1 | 5 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Acute myeloid leukaemia | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 0 / 212 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Anal squamous cell carcinoma | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 0 / 212 (0.00%) | 0 / 13 (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 |
| Basal cell carcinoma | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 214 (0.47%) | 0 / 212 (0.00%) | 0 / 13 (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 |
| Bladder cancer | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Bladder cancer recurrent | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (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 |
| Bladder neoplasm | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 0 / 212 (0.00%) | 0 / 13 (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 |
| Invasive breast carcinoma | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (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 |
| Invasive ductal breast carcinoma | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung adenocarcinoma | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 0 / 212 (0.00%) | 0 / 13 (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 |
| Lung adenocarcinoma stage IV | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (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 |
| Malignant melanoma | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 214 (0.47%) | 1 / 212 (0.47%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metastatic malignant melanoma | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Myelodysplastic syndrome | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (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 |
| Pancreatic carcinoma metastatic | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 0 / 212 (0.00%) | 0 / 13 (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 |
| Penile cancer | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (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 |
| Prostate cancer | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 2 / 212 (0.94%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Prostate cancer metastatic | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (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 |
| Salivary gland adenoma | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 0 / 212 (0.00%) | 0 / 13 (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 |
| Sarcoma of skin | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 214 (0.47%) | 0 / 212 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Skin squamous cell carcinoma metastatic | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 0 / 212 (0.00%) | 0 / 13 (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 of skin | | | |
| subjects affected / exposed | 3 / 214 (1.40%) | 2 / 212 (0.94%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| T-cell lymphoma | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (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 stenosis | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 2 / 212 (0.94%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (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 |
| Hypertension | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypotension | | | |
| subjects affected / exposed | 2 / 214 (0.93%) | 0 / 212 (0.00%) | 0 / 13 (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 |
| Peripheral arterial occlusive disease | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 214 (0.47%) | 0 / 212 (0.00%) | 0 / 13 (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 |
| Thrombophlebitis superficial | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (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 |
| **Surgical and medical procedures** | | | |
| Aortic valve replacement | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (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 |
| Medical device removal | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 0 / 212 (0.00%) | 0 / 13 (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 |
| **General disorders and administration site conditions** | | | |
| Adverse drug reaction | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (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 |
| Asthenia | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 0 / 212 (0.00%) | 1 / 13 (7.69%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chest pain | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (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 |
| Chills | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 0 / 212 (0.00%) | 1 / 13 (7.69%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Device related thrombosis | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 1 / 212 (0.47%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fatigue | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 1 / 212 (0.47%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General physical health deterioration | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 1 / 13 (7.69%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Pyrexia | | | |
| subjects affected / exposed | 7 / 214 (3.27%) | 8 / 212 (3.77%) | 2 / 13 (15.38%) |
| occurrences causally related to treatment / all | 5 / 8 | 3 / 8 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| Anaphylactic reaction | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (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 | | | |
| Cystocele | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (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 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute pulmonary oedema | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (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 |
| Bronchitis chronic | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 214 (0.47%) | 0 / 212 (0.00%) | 0 / 13 (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 |
| Bronchopneumopathy | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (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 |
| Bronchospasm | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (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 |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 2 / 214 (0.93%) | 3 / 212 (1.42%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 10 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cough | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 1 / 212 (0.47%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 2 / 212 (0.94%) | 0 / 13 (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 |
| Hypoxia | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung disorder | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 1 / 212 (0.47%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleural effusion | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 214 (0.93%) | 1 / 212 (0.47%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 0 / 212 (0.00%) | 1 / 13 (7.69%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonitis | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 0 / 212 (0.00%) | 0 / 13 (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 embolism | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Pulmonary oedema | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 0 / 212 (0.00%) | 0 / 13 (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 | | | |
| Confusional state | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (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 |
| Delirium | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (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 |
| Depression | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 0 / 212 (0.00%) | 0 / 13 (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 |
| Investigations | | | |

| | | | |
|---|---|---|---|
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 3 / 214 (1.40%) | 0 / 212 (0.00%) | 0 / 13 (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 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 4 / 214 (1.87%) | 0 / 212 (0.00%) | 0 / 13 (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 |
| Blood urea increased | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (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 enzyme increased | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (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 |
| Prothrombin time prolonged | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (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 |
| Transaminases increased | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 1 / 13 (7.69%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| White blood cell count decreased | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (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 |
| Injury, poisoning and procedural complications | | | |
| Chillblains | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 0 / 212 (0.00%) | 0 / 13 (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 |

| | | | |
|---|---|---|---|
| Clavicle fracture | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (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 |
| Femoral neck fracture | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (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 |
| Femur fracture | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (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 |
| Head injury | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 0 / 212 (0.00%) | 0 / 13 (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 |
| Infusion related reaction | | | |
| subjects affected / exposed | 13 / 214 (6.07%) | 9 / 212 (4.25%) | 1 / 13 (7.69%) |
| occurrences causally related to treatment / all | 12 / 13 | 9 / 9 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Limb injury | | | |
| subjects affected / exposed | 2 / 214 (0.93%) | 0 / 212 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lumbar vertebral fracture | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (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 |
| Overdose | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 0 / 212 (0.00%) | 0 / 13 (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 |
| Pelvic fracture | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 214 (0.47%) | 0 / 212 (0.00%) | 0 / 13 (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 |
| Rib fracture | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (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 |
| Subcutaneous haematoma | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 0 / 212 (0.00%) | 0 / 13 (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 |
| Subdural haematoma | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (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 |
| Thoracic vertebral fracture | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (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 |
| Toxicity to various agents | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (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 |
| Transfusion reaction | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 0 / 212 (0.00%) | 0 / 13 (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 |
| Traumatic haemothorax | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (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 |
| Vasoplegia syndrome | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 214 (0.47%) | 0 / 212 (0.00%) | 0 / 13 (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 |
| Wound evisceration | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (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 |
| Congenital, familial and genetic disorders | | | |
| Gilbert's syndrome | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 0 / 212 (0.00%) | 0 / 13 (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 myocardial infarction | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 2 / 212 (0.94%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 3 / 214 (1.40%) | 1 / 212 (0.47%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 1 / 3 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial flutter | | | |
| subjects affected / exposed | 2 / 214 (0.93%) | 0 / 212 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bradycardia | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 0 / 212 (0.00%) | 1 / 13 (7.69%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac arrest | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 1 / 212 (0.47%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |

| | | | |
|---|---|---|---|
| Cardiac failure | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 3 / 212 (1.42%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Mitral valve incompetence | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (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 |
| Myocardial infarction | | | |
| subjects affected / exposed | 3 / 214 (1.40%) | 1 / 212 (0.47%) | 1 / 13 (7.69%) |
| occurrences causally related to treatment / all | 1 / 4 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 0 / 212 (0.00%) | 0 / 13 (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 |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 2 / 214 (0.93%) | 0 / 212 (0.00%) | 0 / 13 (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 |
| Tachycardia | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 0 / 212 (0.00%) | 0 / 13 (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 fibrillation | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 0 / 212 (0.00%) | 0 / 13 (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 |
| Nervous system disorders | | | |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (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 |
| Cerebral infarction | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 214 (0.47%) | 0 / 212 (0.00%) | 0 / 13 (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 |
| Cerebral ischaemia | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Generalised tonic-clonic seizure | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 0 / 212 (0.00%) | 1 / 13 (7.69%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Headache | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (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 |
| Ischaemic stroke | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (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 |
| Presyncope | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 1 / 13 (7.69%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Radiculopathy | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (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 |
| Seizure | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 214 (0.47%) | 0 / 212 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |
| subjects affected / exposed | 2 / 214 (0.93%) | 1 / 212 (0.47%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 1 / 212 (0.47%) | 1 / 13 (7.69%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vertebrobasilar insufficiency | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 0 / 212 (0.00%) | 0 / 13 (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 |
| **Blood and lymphatic system disorders** | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 2 / 212 (0.94%) | 0 / 13 (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 |
| Autoimmune haemolytic anaemia | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (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 |
| Coombs negative haemolytic anaemia | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 0 / 212 (0.00%) | 0 / 13 (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 |
| Disseminated intravascular coagulation | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (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 |
| Febrile neutropenia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 8 / 214 (3.74%) | 11 / 212 (5.19%) | 3 / 13 (23.08%) |
| occurrences causally related to treatment / all | 9 / 10 | 11 / 12 | 2 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune thrombocytopenic purpura | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 0 / 212 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Neutropenia | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 3 / 212 (1.42%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancytopenia | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (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 |
| Splenic infarction | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 0 / 212 (0.00%) | 0 / 13 (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 |
| Splenomegaly | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (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 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 5 / 214 (2.34%) | 2 / 212 (0.94%) | 1 / 13 (7.69%) |
| occurrences causally related to treatment / all | 5 / 5 | 2 / 2 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 2 / 212 (0.94%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |

| | | | |
|---|---|---|---|
| Amaurosis fugax | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (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 |
| Eye inflammation | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 0 / 212 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Keratitis | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 0 / 212 (0.00%) | 0 / 13 (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 |
| Gastrointestinal disorders | | | |
| Colitis | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (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 | 0 / 214 (0.00%) | 2 / 212 (0.94%) | 1 / 13 (7.69%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Duodenal ulcer haemorrhage | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (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 |
| Enteritis | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (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 |
| Faecaloma | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 0 / 212 (0.00%) | 0 / 13 (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 |
| Gastric ulcer perforation | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 214 (0.47%) | 0 / 212 (0.00%) | 0 / 13 (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 |
| Inguinal hernia | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 2 / 212 (0.94%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Large intestine polyp | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (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 |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 0 / 212 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 0 / 212 (0.00%) | 0 / 13 (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 |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (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 |
| Skin and subcutaneous tissue disorders | | | |
| Blister | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 0 / 212 (0.00%) | 0 / 13 (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 |
| Diabetic foot | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 0 / 212 (0.00%) | 0 / 13 (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 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 214 (0.47%) | 0 / 212 (0.00%) | 0 / 13 (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 |
| Urticaria | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 0 / 212 (0.00%) | 0 / 13 (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 |
| Renal and urinary disorders | | | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (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 |
| Musculoskeletal and connective tissue disorders | | | |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 2 / 214 (0.93%) | 0 / 212 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lumbar spinal stenosis | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (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 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 0 / 212 (0.00%) | 0 / 13 (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 |
| Spondylitis | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 0 / 212 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Atypical pneumonia | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 1 / 212 (0.47%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Bronchiolitis | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 0 / 212 (0.00%) | 0 / 13 (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 | 2 / 214 (0.93%) | 2 / 212 (0.94%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchopulmonary aspergillosis | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 0 / 212 (0.00%) | 0 / 13 (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 |
| Candida infection | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (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 |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 3 / 212 (1.42%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis infective | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 0 / 212 (0.00%) | 1 / 13 (7.69%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chronic sinusitis | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 0 / 212 (0.00%) | 0 / 13 (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 |
| Cytomegalovirus infection | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (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 |
| Device related infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 214 (0.00%) | 2 / 212 (0.94%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eczema infected | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 0 / 212 (0.00%) | 0 / 13 (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 |
| Endocarditis | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (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 |
| Erysipelas | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (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 |
| Gastroenteritis | | | |
| subjects affected / exposed | 2 / 214 (0.93%) | 0 / 212 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (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 |
| Gastrointestinal infection | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (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 |
| Hepatitis E | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (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 |
| Herpes zoster | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 214 (0.47%) | 0 / 212 (0.00%) | 0 / 13 (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 |
| Infection | | | |
| subjects affected / exposed | 2 / 214 (0.93%) | 2 / 212 (0.94%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 2 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| Infectious pleural effusion | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 1 / 212 (0.47%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infective exacerbation of chronic obstructive airways disease | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 0 / 212 (0.00%) | 0 / 13 (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 |
| Influenza | | | |
| subjects affected / exposed | 2 / 214 (0.93%) | 1 / 212 (0.47%) | 1 / 13 (7.69%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Listeriosis | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (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 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung infection | | | |
| subjects affected / exposed | 2 / 214 (0.93%) | 0 / 212 (0.00%) | 0 / 13 (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 |
| Muscle abscess | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (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 |
| Neutropenic infection | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 0 / 212 (0.00%) | 0 / 13 (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 |
| Ophthalmic herpes zoster | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (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 |
| Pneumocystis jirovecii pneumonia | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 1 / 212 (0.47%) | 1 / 13 (7.69%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 9 / 214 (4.21%) | 10 / 212 (4.72%) | 1 / 13 (7.69%) |
| occurrences causally related to treatment / all | 6 / 11 | 3 / 10 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Pneumonia fungal | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (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 |
| Pneumonia haemophilus | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 0 / 212 (0.00%) | 0 / 13 (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 respiratory syncytial viral | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 0 / 212 (0.00%) | 0 / 13 (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 |
| Pseudomembranous colitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (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 |
| Pyelonephritis | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 1 / 212 (0.47%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 2 / 212 (0.94%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 2 / 214 (0.93%) | 6 / 212 (2.83%) | 1 / 13 (7.69%) |
| occurrences causally related to treatment / all | 1 / 2 | 3 / 7 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 1 | 2 / 5 | 0 / 1 |
| Septic shock | | | |
| subjects affected / exposed | 2 / 214 (0.93%) | 1 / 212 (0.47%) | 1 / 13 (7.69%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Sinusitis aspergillus | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (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 |
| Soft tissue infection | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (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 |
| Staphylococcal infection | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 0 / 212 (0.00%) | 0 / 13 (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 |
| Urinary tract infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 214 (0.47%) | 1 / 212 (0.47%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urosepsis | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 2 / 212 (0.94%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Varicella zoster virus infection | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (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 |
| Wound infection fungal | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 0 / 212 (0.00%) | 0 / 13 (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 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (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 |
| Dehydration | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (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 |
| Hypercalcaemia | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (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 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 2 / 214 (0.93%) | 1 / 212 (0.47%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperkalaemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 0 / 13 (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 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 0 / 212 (0.00%) | 0 / 13 (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 |
| Hyponatraemia | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 1 / 212 (0.47%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tumour lysis syndrome | | | |
| subjects affected / exposed | 4 / 214 (1.87%) | 1 / 212 (0.47%) | 0 / 13 (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 |

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

| **Non-serious adverse events** | Obinutuzumab + Chlorambucil | Obinutuzumab + Venetoclax | Safety Run-in Obinutuzumab + Venetoclax |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 205 / 214 (95.79%) | 193 / 212 (91.04%) | 12 / 13 (92.31%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 5 / 214 (2.34%) | 6 / 212 (2.83%) | 1 / 13 (7.69%) |
| occurrences (all) | 6 | 6 | 1 |
| Benign breast neoplasm | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 0 / 212 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| Seborrhoeic keratosis | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 2 / 212 (0.94%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 2 | 1 |
| Skin papilloma | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 1 | 1 |
| Vascular disorders | | | |
| Flushing | | | |
| subjects affected / exposed | 3 / 214 (1.40%) | 2 / 212 (0.94%) | 2 / 13 (15.38%) |
| occurrences (all) | 3 | 2 | 2 |
| Hypertension | | | |
| subjects affected / exposed | 11 / 214 (5.14%) | 12 / 212 (5.66%) | 0 / 13 (0.00%) |
| occurrences (all) | 12 | 17 | 0 |
| Hypotension | | | |
| subjects affected / exposed | 8 / 214 (3.74%) | 11 / 212 (5.19%) | 2 / 13 (15.38%) |
| occurrences (all) | 10 | 15 | 2 |
| Thrombophlebitis | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 0 / 212 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| General disorders and administration site conditions | | | |
| Adverse drug reaction | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 0 / 212 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| Asthenia | | | |
| subjects affected / exposed | 17 / 214 (7.94%) | 14 / 212 (6.60%) | 0 / 13 (0.00%) |
| occurrences (all) | 20 | 20 | 0 |
| Chills | | | |
| subjects affected / exposed | 10 / 214 (4.67%) | 12 / 212 (5.66%) | 1 / 13 (7.69%) |
| occurrences (all) | 13 | 14 | 1 |
| Extravasation | | | |
| subjects affected / exposed | 2 / 214 (0.93%) | 0 / 212 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 2 | 0 | 1 |
| Fatigue | | | |
| subjects affected / exposed | 29 / 214 (13.55%) | 32 / 212 (15.09%) | 3 / 13 (23.08%) |
| occurrences (all) | 36 | 40 | 6 |
| Influenza like illness | | | |
| subjects affected / exposed | 3 / 214 (1.40%) | 4 / 212 (1.89%) | 1 / 13 (7.69%) |
| occurrences (all) | 3 | 4 | 1 |
| Oedema | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 7 / 214 (3.27%) | 3 / 212 (1.42%) | 1 / 13 (7.69%) |
| occurrences (all) | 7 | 3 | 1 |
| Oedema peripheral | | | |
| subjects affected / exposed | 16 / 214 (7.48%) | 17 / 212 (8.02%) | 1 / 13 (7.69%) |
| occurrences (all) | 18 | 20 | 2 |
| Pyrexia | | | |
| subjects affected / exposed | 26 / 214 (12.15%) | 40 / 212 (18.87%) | 3 / 13 (23.08%) |
| occurrences (all) | 28 | 53 | 4 |
| Sensation of foreign body | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 0 / 212 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 24 / 214 (11.21%) | 33 / 212 (15.57%) | 6 / 13 (46.15%) |
| occurrences (all) | 27 | 37 | 6 |
| Dyspnoea | | | |
| subjects affected / exposed | 11 / 214 (5.14%) | 11 / 212 (5.19%) | 1 / 13 (7.69%) |
| occurrences (all) | 12 | 12 | 2 |
| Epistaxis | | | |
| subjects affected / exposed | 4 / 214 (1.87%) | 3 / 212 (1.42%) | 1 / 13 (7.69%) |
| occurrences (all) | 5 | 3 | 1 |
| Pharyngeal paraesthesia | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 0 / 212 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| Productive cough | | | |
| subjects affected / exposed | 3 / 214 (1.40%) | 6 / 212 (2.83%) | 1 / 13 (7.69%) |
| occurrences (all) | 3 | 6 | 2 |
| Rhinorrhoea | | | |
| subjects affected / exposed | 3 / 214 (1.40%) | 3 / 212 (1.42%) | 1 / 13 (7.69%) |
| occurrences (all) | 3 | 3 | 1 |
| Throat irritation | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 0 / 212 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| Psychiatric disorders | | | |

| | | | |
|---|---|---|---|
| Depression | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 8 / 212 (3.77%) | 1 / 13 (7.69%) |
| occurrences (all) | 1 | 8 | 1 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 13 / 214 (6.07%) | 11 / 212 (5.19%) | 0 / 13 (0.00%) |
| occurrences (all) | 15 | 15 | 0 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 17 / 214 (7.94%) | 12 / 212 (5.66%) | 0 / 13 (0.00%) |
| occurrences (all) | 20 | 14 | 0 |
| Blood albumin decreased | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 0 / 212 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 6 / 214 (2.80%) | 7 / 212 (3.30%) | 1 / 13 (7.69%) |
| occurrences (all) | 6 | 9 | 2 |
| Blood glucose increased | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 1 / 212 (0.47%) | 1 / 13 (7.69%) |
| occurrences (all) | 1 | 1 | 1 |
| Blood lactate dehydrogenase increased | | | |
| subjects affected / exposed | 2 / 214 (0.93%) | 2 / 212 (0.94%) | 2 / 13 (15.38%) |
| occurrences (all) | 2 | 2 | 2 |
| Blood magnesium decreased | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 1 | 1 |
| Blood phosphorus increased | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 2 / 212 (0.94%) | 1 / 13 (7.69%) |
| occurrences (all) | 1 | 4 | 1 |
| C-reactive protein increased | | | |
| subjects affected / exposed | 2 / 214 (0.93%) | 4 / 212 (1.89%) | 1 / 13 (7.69%) |
| occurrences (all) | 2 | 4 | 1 |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 11 / 214 (5.14%) | 10 / 212 (4.72%) | 0 / 13 (0.00%) |
| occurrences (all) | 32 | 27 | 0 |
| Procalcitonin increased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 214 (0.00%) | 0 / 212 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| Protein total decreased | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 0 / 212 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| Transaminases increased | | | |
| subjects affected / exposed | 2 / 214 (0.93%) | 0 / 212 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 2 | 0 | 1 |
| Weight decreased | | | |
| subjects affected / exposed | 5 / 214 (2.34%) | 5 / 212 (2.36%) | 1 / 13 (7.69%) |
| occurrences (all) | 5 | 5 | 1 |
| Injury, poisoning and procedural complications | | | |
| Arthropod bite | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 1 | 1 |
| Eye contusion | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 1 | 1 |
| Fall | | | |
| subjects affected / exposed | 8 / 214 (3.74%) | 5 / 212 (2.36%) | 1 / 13 (7.69%) |
| occurrences (all) | 11 | 7 | 1 |
| Head injury | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 0 / 212 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| Infusion related reaction | | | |
| subjects affected / exposed | 103 / 214 (48.13%) | 89 / 212 (41.98%) | 9 / 13 (69.23%) |
| occurrences (all) | 131 | 122 | 10 |
| Limb injury | | | |
| subjects affected / exposed | 4 / 214 (1.87%) | 0 / 212 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 4 | 0 | 1 |
| Skin abrasion | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 2 / 212 (0.94%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 2 | 1 |
| Cardiac disorders | | | |

| | | | |
|---|---|---|---|
| Coronary artery disease | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 0 / 212 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| Tachycardia | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 5 / 212 (2.36%) | 1 / 13 (7.69%) |
| occurrences (all) | 1 | 5 | 1 |
| Ventricular extrasystoles | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 1 / 212 (0.47%) | 1 / 13 (7.69%) |
| occurrences (all) | 1 | 1 | 1 |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 17 / 214 (7.94%) | 16 / 212 (7.55%) | 4 / 13 (30.77%) |
| occurrences (all) | 20 | 18 | 5 |
| Headache | | | |
| subjects affected / exposed | 21 / 214 (9.81%) | 23 / 212 (10.85%) | 3 / 13 (23.08%) |
| occurrences (all) | 24 | 29 | 3 |
| Paraesthesia | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 4 / 212 (1.89%) | 1 / 13 (7.69%) |
| occurrences (all) | 1 | 4 | 1 |
| Presyncope | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 1 / 212 (0.47%) | 2 / 13 (15.38%) |
| occurrences (all) | 1 | 1 | 3 |
| Somnolence | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 1 | 1 |
| Syncope | | | |
| subjects affected / exposed | 4 / 214 (1.87%) | 5 / 212 (2.36%) | 2 / 13 (15.38%) |
| occurrences (all) | 4 | 5 | 2 |
| Tremor | | | |
| subjects affected / exposed | 3 / 214 (1.40%) | 6 / 212 (2.83%) | 1 / 13 (7.69%) |
| occurrences (all) | 4 | 6 | 1 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 39 / 214 (18.22%) | 33 / 212 (15.57%) | 2 / 13 (15.38%) |
| occurrences (all) | 55 | 53 | 2 |
| Leukopenia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 13 / 214 (6.07%) | 12 / 212 (5.66%) | 1 / 13 (7.69%) |
| occurrences (all) | 19 | 23 | 1 |
| Neutropenia | | | |
| subjects affected / exposed | 122 / 214 (57.01%) | 121 / 212 (57.08%) | 8 / 13 (61.54%) |
| occurrences (all) | 294 | 370 | 12 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 49 / 214 (22.90%) | 49 / 212 (23.11%) | 2 / 13 (15.38%) |
| occurrences (all) | 76 | 86 | 5 |
| Ear and labyrinth disorders | | | |
| Excessive cerumen production | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 1 / 212 (0.47%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 1 | 1 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 10 / 214 (4.67%) | 11 / 212 (5.19%) | 2 / 13 (15.38%) |
| occurrences (all) | 11 | 15 | 2 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 4 / 214 (1.87%) | 7 / 212 (3.30%) | 1 / 13 (7.69%) |
| occurrences (all) | 4 | 7 | 1 |
| Constipation | | | |
| subjects affected / exposed | 19 / 214 (8.88%) | 28 / 212 (13.21%) | 5 / 13 (38.46%) |
| occurrences (all) | 23 | 32 | 6 |
| Diarrhoea | | | |
| subjects affected / exposed | 32 / 214 (14.95%) | 59 / 212 (27.83%) | 5 / 13 (38.46%) |
| occurrences (all) | 42 | 99 | 8 |
| Dry mouth | | | |
| subjects affected / exposed | 4 / 214 (1.87%) | 0 / 212 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 4 | 0 | 1 |
| Dyspepsia | | | |
| subjects affected / exposed | 3 / 214 (1.40%) | 7 / 212 (3.30%) | 1 / 13 (7.69%) |
| occurrences (all) | 3 | 7 | 1 |
| Epigastric discomfort | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 0 / 212 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| Haemorrhoids | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 214 (0.00%) | 2 / 212 (0.94%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 2 | 1 |
| Nausea | | | |
| subjects affected / exposed | 46 / 214 (21.50%) | 40 / 212 (18.87%) | 4 / 13 (30.77%) |
| occurrences (all) | 62 | 61 | 7 |
| Stomatitis | | | |
| subjects affected / exposed | 2 / 214 (0.93%) | 1 / 212 (0.47%) | 1 / 13 (7.69%) |
| occurrences (all) | 2 | 1 | 2 |
| Vomiting | | | |
| subjects affected / exposed | 18 / 214 (8.41%) | 21 / 212 (9.91%) | 3 / 13 (23.08%) |
| occurrences (all) | 22 | 27 | 3 |
| Skin and subcutaneous tissue disorders | | | |
| Dry skin | | | |
| subjects affected / exposed | 6 / 214 (2.80%) | 4 / 212 (1.89%) | 2 / 13 (15.38%) |
| occurrences (all) | 7 | 4 | 2 |
| Erythema | | | |
| subjects affected / exposed | 4 / 214 (1.87%) | 2 / 212 (0.94%) | 2 / 13 (15.38%) |
| occurrences (all) | 4 | 2 | 2 |
| Pruritus | | | |
| subjects affected / exposed | 9 / 214 (4.21%) | 18 / 212 (8.49%) | 6 / 13 (46.15%) |
| occurrences (all) | 9 | 20 | 6 |
| Rash | | | |
| subjects affected / exposed | 12 / 214 (5.61%) | 12 / 212 (5.66%) | 2 / 13 (15.38%) |
| occurrences (all) | 13 | 12 | 3 |
| Urticaria | | | |
| subjects affected / exposed | 5 / 214 (2.34%) | 0 / 212 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 5 | 0 | 1 |
| Renal and urinary disorders | | | |
| Dysuria | | | |
| subjects affected / exposed | 2 / 214 (0.93%) | 1 / 212 (0.47%) | 1 / 13 (7.69%) |
| occurrences (all) | 2 | 1 | 1 |
| Renal failure | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 1 / 212 (0.47%) | 1 / 13 (7.69%) |
| occurrences (all) | 1 | 1 | 3 |
| Renal impairment | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 214 (0.00%) | 2 / 212 (0.94%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 2 | 1 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 18 / 214 (8.41%) | 16 / 212 (7.55%) | 1 / 13 (7.69%) |
| occurrences (all) | 23 | 19 | 1 |
| Back pain | | | |
| subjects affected / exposed | 20 / 214 (9.35%) | 21 / 212 (9.91%) | 2 / 13 (15.38%) |
| occurrences (all) | 21 | 24 | 2 |
| Groin pain | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 0 / 212 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 0 / 212 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| Muscle spasms | | | |
| subjects affected / exposed | 11 / 214 (5.14%) | 10 / 212 (4.72%) | 1 / 13 (7.69%) |
| occurrences (all) | 11 | 11 | 1 |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 2 / 212 (0.94%) | 2 / 13 (15.38%) |
| occurrences (all) | 0 | 4 | 2 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 4 / 214 (1.87%) | 7 / 212 (3.30%) | 1 / 13 (7.69%) |
| occurrences (all) | 4 | 8 | 2 |
| Pain in extremity | | | |
| subjects affected / exposed | 13 / 214 (6.07%) | 10 / 212 (4.72%) | 1 / 13 (7.69%) |
| occurrences (all) | 14 | 11 | 1 |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 5 / 214 (2.34%) | 11 / 212 (5.19%) | 1 / 13 (7.69%) |
| occurrences (all) | 6 | 14 | 2 |
| Cystitis | | | |
| subjects affected / exposed | 2 / 214 (0.93%) | 1 / 212 (0.47%) | 1 / 13 (7.69%) |
| occurrences (all) | 2 | 1 | 1 |
| Ear infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 214 (0.00%) | 2 / 212 (0.94%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 2 | 1 |
| Eye infection | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 0 / 212 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 1 | 0 | 3 |
| Herpes zoster | | | |
| subjects affected / exposed | 6 / 214 (2.80%) | 9 / 212 (4.25%) | 1 / 13 (7.69%) |
| occurrences (all) | 7 | 9 | 1 |
| Influenza | | | |
| subjects affected / exposed | 4 / 214 (1.87%) | 3 / 212 (1.42%) | 1 / 13 (7.69%) |
| occurrences (all) | 4 | 3 | 1 |
| Localised infection | | | |
| subjects affected / exposed | 3 / 214 (1.40%) | 1 / 212 (0.47%) | 1 / 13 (7.69%) |
| occurrences (all) | 3 | 1 | 1 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 14 / 214 (6.54%) | 16 / 212 (7.55%) | 0 / 13 (0.00%) |
| occurrences (all) | 16 | 16 | 0 |
| Oral herpes | | | |
| subjects affected / exposed | 4 / 214 (1.87%) | 5 / 212 (2.36%) | 1 / 13 (7.69%) |
| occurrences (all) | 5 | 7 | 4 |
| Paronychia | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 0 / 212 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| Pneumonia | | | |
| subjects affected / exposed | 3 / 214 (1.40%) | 6 / 212 (2.83%) | 1 / 13 (7.69%) |
| occurrences (all) | 3 | 9 | 1 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 6 / 214 (2.80%) | 10 / 212 (4.72%) | 1 / 13 (7.69%) |
| occurrences (all) | 7 | 14 | 3 |
| Rhinitis | | | |
| subjects affected / exposed | 5 / 214 (2.34%) | 2 / 212 (0.94%) | 1 / 13 (7.69%) |
| occurrences (all) | 6 | 3 | 1 |
| Sinusitis | | | |
| subjects affected / exposed | 6 / 214 (2.80%) | 8 / 212 (3.77%) | 1 / 13 (7.69%) |
| occurrences (all) | 6 | 8 | 1 |
| Upper respiratory tract infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 15 / 214 (7.01%) | 16 / 212 (7.55%) | 2 / 13 (15.38%) |
| occurrences (all) | 17 | 19 | 4 |
| Urinary tract infection | | | |
| subjects affected / exposed | 9 / 214 (4.21%) | 10 / 212 (4.72%) | 1 / 13 (7.69%) |
| occurrences (all) | 10 | 13 | 1 |
| Viral skin infection | | | |
| subjects affected / exposed | 0 / 214 (0.00%) | 0 / 212 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 6 / 214 (2.80%) | 10 / 212 (4.72%) | 1 / 13 (7.69%) |
| occurrences (all) | 8 | 10 | 1 |
| Gout | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 3 / 212 (1.42%) | 1 / 13 (7.69%) |
| occurrences (all) | 2 | 4 | 1 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 7 / 214 (3.27%) | 14 / 212 (6.60%) | 2 / 13 (15.38%) |
| occurrences (all) | 7 | 16 | 4 |
| Hyperkalaemia | | | |
| subjects affected / exposed | 5 / 214 (2.34%) | 4 / 212 (1.89%) | 5 / 13 (38.46%) |
| occurrences (all) | 6 | 13 | 7 |
| Hyperphosphataemia | | | |
| subjects affected / exposed | 3 / 214 (1.40%) | 4 / 212 (1.89%) | 1 / 13 (7.69%) |
| occurrences (all) | 3 | 5 | 1 |
| Tumour lysis syndrome | | | |
| subjects affected / exposed | 1 / 214 (0.47%) | 2 / 212 (0.94%) | 2 / 13 (15.38%) |
| occurrences (all) | 1 | 2 | 2 |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 21 October 2014 | Correction of inclusion criterion and clarification of adverse event (AE) reporting. |
| 07 November 2014 | Alignment of contraceptive requirements with product information for obinutuzumab in the inclusion criteria. |
| 21 May 2015 | Modification/correction of tumor lysis syndrome (TLS) laboratory assessments. Correction/modification of inclusion and exclusion criteria regarding infection and timing of CYP3A inhibitors/inducers relative to venetoclax dosing. Reporting of AEs and serious adverse events (SAEs) during follow-up period was modified in accordance with German Ethics Committee Chairman recommendation. Contraception and pregnancy testing requirements were updated to comply with International Conference for Harmonization (ICH) and health authority guidance. |
| 02 November 2015 | Inclusion of new safety data for obinutuzumab relating to subjects with previous history of gastrointestinal bleeding. Cytogenetic sample moved to screening visit so that results are available prior to randomization of the subject into the trial, allowing investigators to decide whether alternative treatment should be considered, particularly for subjects with 17p deletion and/or TP53 mutation. Clarification of eligibility of subjects with previous infections and timing of CYP3A inhibitors/inducers relative to venetoclax dosing, and clarification that subjects with previous deep vein thrombosis or pulmonary embolism could continue treatment if they did not revert to > Grade 1. |
| 29 March 2017 | Modification of timing of the interim analysis for efficacy to introduce a date-based stopping rule for PFS. Amendment of PFS analysis assumptions. Clarification that all response assessments to be made according to iwCLL criteria. In addition, clarification of response criteria for stable disease. Removal of requirement for first meal of day to be a low-fat meal. |
| 12 February 2018 | Addition of the option to add an additional earlier interim efficacy analysis to mitigate the potential for an undue delay in delivery of the study read-out. Prolongation of blood sample collection to characterize MRD kinetics in subjects responding longer than originally expected. Addition of complete response as a stand-alone secondary endpoint. Clarification of time windows for assessment of blood sampling for B-cell recovery and removal of an inconsistency in reporting instructions for unrelated SAEs. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported