# Clinical trial results:
# Open-Label, Single Arm, Phase 3b, Multi-Center Study Evaluating the Efficacy of Venetoclax (ABT 199) in Relapsed/Refractory Subjects With Chronic Lymphocytic Leukemia (CLL)

## Summary

| | |
|---|---|
| EudraCT number | 2015-003667-11 |
| Trial protocol | GR SE BE NL DE AT IE PT FI DK ES FR IT |
| Global end of trial date | 17 March 2022 |

### Results information

| | |
|---|---|
| Result version number | v2 (current) |
| This version publication date | 28 April 2023 |
| First version publication date | 09 March 2023 |
| Version creation reason | • Correction of full data set<br>Clarifications made to endpoint type. |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | M15-550 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02756611 |
| WHO universal trial number (UTN) | - |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | AbbVie Deutschland GmbH & Co. KG |
| Sponsor organisation address | AbbVie House, Vanwall Business Park, Vanwall Road, Maidenhead, Berkshire, United Kingdom, SL6 4UB |
| Public contact | Global Medical Services, AbbVie, 001 8006339110, abbvieclinicaltrials@abbvie.com |
| Scientific contact | Global Medical Services, AbbVie, 001 8006339110, abbvieclinicaltrials@abbvie.com |

Notes:

### Paediatric regulatory details

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

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 17 March 2022 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 17 March 2022 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The purpose of this study is to evaluate the efficacy of venetoclax monotherapy in participants with relapsed/refractory CLL with or without the 17p deletion or TP53 mutation, including those who have received prior treatment with a B-cell receptor inhibitor (BCRi).

Protection of trial subjects:

All subjects entering the study had to sign an informed consent that was explained to them and questions encouraged.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 22 June 2016 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Efficacy |
| Long term follow-up duration | 2 Years |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Austria: 3 |
| Country: Number of subjects enrolled | Belgium: 10 |
| Country: Number of subjects enrolled | Canada: 15 |
| Country: Number of subjects enrolled | Denmark: 12 |
| Country: Number of subjects enrolled | Finland: 7 |
| Country: Number of subjects enrolled | France: 13 |
| Country: Number of subjects enrolled | Germany: 4 |
| Country: Number of subjects enrolled | Greece: 29 |
| Country: Number of subjects enrolled | Ireland: 13 |
| Country: Number of subjects enrolled | Israel: 14 |
| Country: Number of subjects enrolled | Italy: 12 |
| Country: Number of subjects enrolled | Netherlands: 8 |
| Country: Number of subjects enrolled | Portugal: 3 |
| Country: Number of subjects enrolled | Puerto Rico: 5 |
| Country: Number of subjects enrolled | Spain: 10 |
| Country: Number of subjects enrolled | Sweden: 12 |
| Country: Number of subjects enrolled | Switzerland: 9 |
| Country: Number of subjects enrolled | Turkey: 50 |

| | |
|---|---|
| Country: Number of subjects enrolled | United Kingdom: 16 |
| Country: Number of subjects enrolled | United States: 13 |
| Worldwide total number of subjects | 258 |
| EEA total number of subjects | 136 |

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) | 94 |
| From 65 to 84 years | 157 |
| 85 years and over | 7 |

## Subject disposition

### Recruitment

Recruitment details:

Participants were enrolled at 59 sites in 19 countries. The primary analysis of results occurred after all participants completed the Week 48 disease assessment, with a data cut-off date of 30 June 2019.

### Pre-assignment

Screening details:

Overall, 287 subjects were screened for this study, and 258 subjects were enrolled (29 subjects were screening failures due to inclusion/exclusion criteria, withdrawal of consent, or other reason), including 191 subjects who were B-cell receptor inhibitor (BCRi) naïve and 67 subjects who had been previously exposed to BCRi.

### Period 1

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

### Arms

| | |
|---|---|
| **Arm title** | Venetoclax |

Arm description:

Participants received venetoclax on a once daily (QD) dosing schedule for up to 108 weeks. The starting dose was 20 mg daily, increasing over a period of 5 weeks up to the daily dose of 400 mg.
In countries where venetoclax was not commercially available, participants who continued to derive benefit after 2 years of treatment could extend their treatment for up to two additional years plus one additional year until the venetoclax extension study was open.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Venetoclax |
| Investigational medicinal product code | ABT-199 |
| Other name | Venclexta®, Venclyxto® |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Tablets for oral administration

| **Number of subjects in period 1** | Venetoclax |
|---|---|
| Started | 258 |
| Completed | 124 |
| Not completed | 134 |
| Consent withdrawn by subject | 2 |
| Transitioned to long-term extension study M19-388 | 49 |
| Other | 10 |
| Death | 70 |
| Lost to follow-up | 3 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Venetoclax |
| Reporting group description: | |
| Participants received venetoclax on a once daily (QD) dosing schedule for up to 108 weeks. The starting dose was 20 mg daily, increasing over a period of 5 weeks up to the daily dose of 400 mg.<br>In countries where venetoclax was not commercially available, participants who continued to derive benefit after 2 years of treatment could extend their treatment for up to two additional years plus one additional year until the venetoclax extension study was open. | |

| Reporting group values | Venetoclax | Total | |
|---|---|---|---|
| Number of subjects | 258 | 258 | |
| Age categorical<br>Units: Subjects | | | |
| < 65 years | 94 | 94 | |
| >= 65 years | 164 | 164 | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 67.7 | | |
| standard deviation | ± 9.04 | - | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 78 | 78 | |
| Male | 180 | 180 | |
| Race<br>Units: Subjects | | | |
| White | 252 | 252 | |
| Black or African American | 3 | 3 | |
| Asian | 2 | 2 | |
| Missing | 1 | 1 | |
| Ethnicity<br>Units: Subjects | | | |
| Hispanic or Latino | 9 | 9 | |
| Not Hispanic or Latino | 248 | 248 | |
| Missing | 1 | 1 | |
| Geographic Region<br>Units: Subjects | | | |
| Europe | 161 | 161 | |
| North America | 28 | 28 | |
| Rest of the World | 69 | 69 | |
| Prior Treatment With B-cell Receptor Inhibitor (BCRi)<br>Units: Subjects | | | |
| BCRi-naive | 191 | 191 | |
| BCRi-exposed | 67 | 67 | |

## End points

### End points reporting groups

| Reporting group title | Venetoclax |
|---|---|

Reporting group description:

Participants received venetoclax on a once daily (QD) dosing schedule for up to 108 weeks. The starting dose was 20 mg daily, increasing over a period of 5 weeks up to the daily dose of 400 mg.
In countries where venetoclax was not commercially available, participants who continued to derive benefit after 2 years of treatment could extend their treatment for up to two additional years plus one additional year until the venetoclax extension study was open.

### Primary: Complete Remission Rate in Participants Not Previously Treated With BCRi Therapy - Primary Analysis

| End point title | Complete Remission Rate in Participants Not Previously Treated With BCRi Therapy - Primary Analysis[1] |
|---|---|

End point description:

Complete remission rate is defined as the percentage of participants achieving a best response of complete remission (CR) or complete remission with incomplete marrow recovery (CRi) assessed by the investigator based on 2008 Modified International Workshop for Chronic Lymphocytic Leukemia National Cancer Institute-Working Group (IWCLL NCI-WG) criteria.
CR required all of the following:
•Peripheral blood lymphocytes < 4000/µL;
•Absence of lymphadenopathy by physical examination and computed tomography scan;
•No hepatomegaly or splenomegaly by physical examination;
•Absence of disease or constitutional symptoms (unexplained fevers > 38°C, drenching night sweats, > 10% weight loss in last 6 months);
•Blood counts above the following: Neutrophils > 1500/µL, platelets > 100,000/µL, and hemoglobin > 110 g/L;
•Bone marrow at least normocellular for age, < 30% lymphocytes.
CRi was defined as for CR but with persistent cytopenia apparently unrelated to CLL but related to drug toxicity.

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

End point timeframe:

From first dose of study drug until the last participant completed Week 48 assessments (data cut-off date 30 June 2019); overall median time on follow-up was 23.2 months.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analyses cannot be entered for single-arm studies. Please see attachment.

| End point values | Venetoclax | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 191[2] | | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 35.1 (28.3 to 42.3) | | | |

Notes:

[2] - All treated participants who were BCRi treatment naive.

| Attachments (see zip file) | Complete Remission Rate in BCRi-naive Subjects/Complete |
|---|---|

### Statistical analyses

No statistical analyses for this end point

## Secondary: Complete Remission Rate in Participants Previously Treated With BCRi Therapy - Primary Analysis

| End point title | Complete Remission Rate in Participants Previously Treated With BCRi Therapy - Primary Analysis |
|---|---|

End point description:

Complete remission rate is defined as the percentage of participants achieving a best response of complete remission (CR) or complete remission with incomplete marrow recovery (CRi) assessed by the investigator based on 2008 Modified IWCLL NCI-WG criteria.
CR required all of the following:
• Peripheral blood lymphocytes < 4000/µL;
• Absence of lymphadenopathy by physical examination and computed tomography scan;
• No hepatomegaly or splenomegaly by physical examination;
• Absence of disease or constitutional symptoms (unexplained fevers > 38°C, drenching night sweats, > 10% weight loss in last 6 months);
• Blood counts above the following: Neutrophils > 1500/µL, platelets > 100,000/µL, and hemoglobin > 110 g/L;
• Bone marrow at least normocellular for age, < 30% lymphocytes.
CRi was defined as for CR but with persistent cytopenia apparently unrelated to CLL but related to drug toxicity.

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

End point timeframe:

From first dose of study drug until the last participant completed Week 48 assessments (data cut-off date 30 June 2019); overall median time on follow-up was 23.2 months.

| **End point values** | Venetoclax | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 67[3] | | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 25.4 (15.5 to 37.5) | | | |

Notes:

[3] - All treated participants who were previously treated with BCRi

### Statistical analyses

No statistical analyses for this end point

## Secondary: Overall Response Rate (ORR) - Primary Analysis

| End point title | Overall Response Rate (ORR) - Primary Analysis |
|---|---|

End point description:

Overall response rate was defined as the percentage of participants with an overall best response of CR, CRi, nodular partial remission (nPR), or confirmed partial remission (PR) based on the 2008 modified IWCLL NCI-WG criteria assessed by the investigator.
CR and CRi are defined above.
nPR is defined as for CR but bone marrow nodules could be identified histologically.
For PR at least 2 of the following must be met:
•≥ 50% decrease in peripheral blood lymphocyte count from the Baseline value;
•≥ 50% reduction in lymphadenopathy;
•≥ 50% reduction in the size of the liver and/or spleen (if abnormal prior to therapy);
In addition at least 1 of the following criteria must be met:
•Neutrophils > 1,500/µL or ≥ 50% improvement over Baseline;
•Platelets > 100,000/µL or ≥ 50% improvement over Baseline;
•Hemoglobin > 11.0 g/dL or ≥ 50% improvement over Baseline without transfusions or exogenous growth factors.

PR must have been confirmed at least 7 weeks later.

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

End point timeframe:

From first dose of study drug until the last participant completed Week 48 assessments (data cut-off date 30 June 2019); overall median time on follow-up was 23.2 months.

| **End point values** | Venetoclax | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 258[4] | | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 79.8 (74.4 to 84.6) | | | |

Notes:

[4] - All treated participants

### Statistical analyses

No statistical analyses for this end point

## Secondary: Duration of Overall Response (DOR) - Primary Analysis

| End point title | Duration of Overall Response (DOR) - Primary Analysis |
|---|---|

End point description:

Duration of response was defined as the time from the date of first response (CR, CRi, nPR, or PR) to the earliest date that progressive disease (PD) was objectively documented (radiographic or clinical) or death. Duration of response was analyzed by Kaplan-Meier (K-M) methodology. If a participant was still responding the data were censored at the date of the last available disease assessment prior to the data cutoff date.

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

End point timeframe:

From first dose of study drug until the last participant completed Week 48 assessments (data cut-off date 30 June 2019); overall median time on follow-up was 23.2 months.

| **End point values** | Venetoclax | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 205[5] | | | |
| Units: months | | | | |
| median (confidence interval 95%) | 25.2 (23.0 to 25.2) | | | |

Notes:

[5] - Participants who had an overall response of CR, CRi, nPR, or confirmed PR.

### Statistical analyses

No statistical analyses for this end point

## Secondary: Time to Progression (TTP) - Primary Analysis

| End point title | Time to Progression (TTP) - Primary Analysis |
|---|---|

End point description:

Time to progression was defined as the time from the date of first dose of venetoclax to the date of earliest PD (radiographic or clinical). Participants who did not experience disease progression were censored at the date of the last available disease assessment prior to the data cutoff date; participants with no post-baseline disease assessments were censored at the first dose date plus 1 day. Time to progression was estimated using Kaplan-Meier methodology.

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

End point timeframe:

From first dose of study drug until the last participant completed Week 48 assessments (data cut-off date 30 June 2019); overall median time on follow-up was 23.2 months.

| **End point values** | Venetoclax | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 258[6] | | | |
| Units: months | | | | |
| median (confidence interval 95%) | 30.5 (29.6 to 30.5) | | | |

Notes:

[6] - All treated participants

### Statistical analyses

No statistical analyses for this end point

## Secondary: Progression-Free Survival (PFS) - Primary Analysis

| End point title | Progression-Free Survival (PFS) - Primary Analysis |
|---|---|

End point description:

Progression-free survival (PFS) was defined as the time from the date of first dose of venetoclax to the date of earliest PD (radiographic or clinical) or death. Participants who did not experience disease progression or death were censored at the date of the last available disease assessment prior to the data cutoff date; participants with no post-baseline tumor assessment or clinical assessment for progression were censored at the date of first dose plus 1 day. Progression-free survival was analyzed by Kaplan-Meier methodology.

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

End point timeframe:

From first dose of study drug until the last participant completed Week 48 assessments (data cut-off date 30 June 2019); overall median time on follow-up was 23.2 months.

| **End point values** | Venetoclax | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 258[7] | | | |
| Units: months | | | | |
| number (confidence interval 95%) | 30.5 (28.6 to 30.5) | | | |

Notes:

[7] - All treated participants

### Statistical analyses

No statistical analyses for this end point

## Secondary: Overall Survival (OS) - Primary Analysis

| End point title | Overall Survival (OS) - Primary Analysis |
|---|---|

End point description:

Overall survival (time to death) was defined as the number of days from the first dose date of venetoclax to the date of death. If a participant had not died the data were censored at the date when they were last known to be alive prior to the cutoff date. Overall survival was analyzed using Kaplan-Meier methodology.
"99999" indicates data that could not be estimated due to the low number of events.

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

End point timeframe:

From first dose of study drug until the last participant completed Week 48 assessments (data cut-off date 30 June 2019); overall median time on follow-up was 23.2 months.

| **End point values** | Venetoclax | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 258[8] | | | |
| Units: months | | | | |
| median (confidence interval 95%) | 99999 (99999 to 99999) | | | |

Notes:

[8] - All treated participants

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Functional Assessment of Cancer Therapy – Leukemia Questionnaire (FACT-Leu)

| End point title | Change From Baseline in Functional Assessment of Cancer Therapy – Leukemia Questionnaire (FACT-Leu) |
|---|---|

End point description:

The FACT-Leu is a 44-item, leukemia-specific questionnaire designed to assess health-related quality of life (HRQoL) and leukemia-specific symptoms using a core set of questions (Functional Assessment of Cancer Therapy-General; FACT-G), and a leukemia-specific subscale. Questions are scored on a scale from 0 (not at all) to 4 (very much).
FACT-G consists of 27 general items divided into 4 primary HRQoL domains: Physical Well-being (PWB; 7 items; score range 0-28), Social/Family Well-being (SWB; 7 items; score range 0-28), Emotional Well-being (EWB; 6 items; score range 0-24), Functional Well-being (FWB; 7 items; score range 0-28). The leukemia subscale consists of 17 items (score range 0-68) that assess patient concerns relating to leukemia. Three summary scales were calculated: FACT-Trial Outcome Index (TOI) composed of the PWB, FWB, and leukemia subscale (score range 0-124); FACT-G (score range 0-108) and the FACT-Leu Total (range 0-176). Higher scores reflect better HRQoL.

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

End point timeframe:

Baseline and Weeks 48 and 108

| End point values | Venetoclax | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 205[9] | | | |
| Units: score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Physical well-being - Week 48 (N=205) | 1.2 (± 4.07) | | | |
| Physical well-being - Week 108 (N=153) | 0.9 (± 4.20) | | | |
| Social/family well-being - Week 48 (N=203) | 0.2 (± 5.14) | | | |
| Social/family well-being - Week 108 (N=151) | -0.4 (± 4.86) | | | |
| Emotional well-being - Week 48 (N=202) | 2.1 (± 3.52) | | | |
| Emotional well-being - Week 108 (N=154) | 1.7 (± 3.94) | | | |
| Functional well-being - Week 48 (N=202) | 1.8 (± 5.63) | | | |
| Functional well-being - Week 108 (N=153) | 1.4 (± 5.67) | | | |
| Leukemia subscale - Week 48 (N=202) | 6.8 (± 7.99) | | | |
| Leukemia subscale - Week 108 (N=153) | 6.0 (± 9.08) | | | |
| FACT-G total score - Week 48 (N=200) | 5.5 (± 12.34) | | | |
| FACT-G total score - Week 108 (N=148) | 3.6 (± 13.56) | | | |
| FACT-leukemia TOI - Week 48 (N=201) | 9.8 (± 14.23) | | | |
| FACT-leukemia TOI - Week 108 (N=150) | 8.2 (± 15.61) | | | |
| FACT-leukemia total score - Week 48 (N=199) | 12.3 (± 18.18) | | | |
| FACT-leukemia total score - Week 108 (N=147) | 9.5 (± 20.62) | | | |

Notes:

[9] - All treated participants with available data for each scale at each time point

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Functional Assessment of Chronic Illness Therapy – Fatigue Scale (FACIT-Fatigue)

| End point title | Change From Baseline in Functional Assessment of Chronic Illness Therapy – Fatigue Scale (FACIT-Fatigue) |
|---|---|

End point description:

The FACIT-Fatigue questionnaire measures fatigue and its effect on functioning and daily activities. The FACIT-Fatigue includes 13 items answered on a 5-point rating scale based on a 7-day recall period. Scores range from 0 to 52, with lower scores reflecting greater fatigue.

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

End point timeframe:

Baseline and Weeks 48 and 108

| End point values | Venetoclax | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 205[10] | | | |
| Units: score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 48 | 4.9 (± 9.43) | | | |
| Week 108 | 3.3 (± 9.96) | | | |

Notes:

[10] - Treated participants with available data at each timepoint. N=154 at Week 108.

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in EuroQoL 5 Dimension 5 Level Questionnaire (EQ-5D-5L) Health Index Score

| End point title | Change From Baseline in EuroQoL 5 Dimension 5 Level Questionnaire (EQ-5D-5L) Health Index Score |
|---|---|

End point description:

The EQ-5D-5L is a generic measure of health status consisting of two parts: a descriptive system consisting of 5 items and a visual analog scale (VAS).
The descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The participant is asked to rate each dimension on 5 levels of severity (1: no problems, 2: slight problems, 3: moderate problems, 4: severe problems, 5: extreme problems).
The scores for the 5 dimensions are used to compute a single health utility index score representing the general health status of the individual. The health index score ranges from zero (defined as a health state equivalent to being dead) to 1 (full health).

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

End point timeframe:

Baseline and Weeks 48 and 108

| End point values | Venetoclax | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 204[11] | | | |
| Units: score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 48 | 0.0 (± 0.14) | | | |
| Week 108 | 0.0 (± 0.15) | | | |

Notes:

[11] - All treated participants with available data at each time point. N=152 at Week 108.

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in EuroQoL 5 Dimension 5 Level Questionnaire (EQ-5D-5L) Visual Analog Scale Score

| End point title | Change From Baseline in EuroQoL 5 Dimension 5 Level Questionnaire (EQ-5D-5L) Visual Analog Scale Score |
|---|---|

End point description:

The EQ-5D-5L is a generic measure of health status consisting of two parts, a descriptive system consisting of 5 items and a visual analog scale (VAS).
The VAS assesses the participant's self-rated overall health on a scale from 0 (worst health imaginable) to 100 (best health imaginable).

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

End point timeframe:

Baseline and Weeks 48 and 108

| **End point values** | Venetoclax | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 204[12] | | | |
| Units: score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 48 | 8.5 (± 14.43) | | | |
| Week 108 | 7.1 (± 14.61) | | | |

Notes:

[12] - All treated participants with available data at each time point; N=156 at Week 108.

### Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Complete Remission Rate in Participants Not Previously Treated With BCRi Therapy - Final Analysis

| End point title | Complete Remission Rate in Participants Not Previously Treated With BCRi Therapy - Final Analysis |
|---|---|

End point description:

Complete remission rate is defined as the percentage of participants achieving a best response of complete remission (CR) or complete remission with incomplete marrow recovery (CRi) assessed by the investigator based on 2008 modified IWCLL NCI-WG criteria.
CR required all of the following:
• Peripheral blood lymphocytes < 4000/µL;
• Absence of lymphadenopathy by physical examination and computed tomography scan;
• No hepatomegaly or splenomegaly by physical examination;
• Absence of disease or constitutional symptoms (unexplained fevers > 38°C, drenching night sweats, > 10% weight loss in last 6 months);
• Blood counts above the following: Neutrophils > 1500/µL, platelets > 100,000/µL, and hemoglobin > 110 g/L;
• Bone marrow at least normocellular for age, < 30% lymphocytes.
CRi was defined as for CR but with persistent cytopenia apparently unrelated to CLL but related to drug toxicity.

| End point type | Other pre-specified |
|---|---|

End point timeframe:

From first dose of study drug until the end of study; overall median time on follow-up was 49.5 months.

| End point values | Venetoclax | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 191[13] | | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 34.6 (27.8 to 41.8) | | | |

Notes:

[13] - All treated participants who were BCRi treatment naive.

| Attachments (see zip file) | Complete Remission Rate in BCRi-naive Subjects/Complete |
|---|---|

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Complete Remission Rate in Participants Previously Treated With BCRi Therapy - Final Analysis

| End point title | Complete Remission Rate in Participants Previously Treated With BCRi Therapy - Final Analysis |
|---|---|

End point description:

Complete remission rate is defined as the percentage of participants achieving a best response of complete remission (CR) or complete remission with incomplete marrow recovery (CRi) assessed by the investigator based on 2008 modified IWCLL NCI-WG criteria.
CR required all of the following:
• Peripheral blood lymphocytes < 4000/µL;
• Absence of lymphadenopathy by physical examination and computed tomography scan;
• No hepatomegaly or splenomegaly by physical examination;
• Absence of disease or constitutional symptoms (unexplained fevers > 38°C, drenching night sweats, > 10% weight loss in last 6 months);
• Blood counts above the following: Neutrophils > 1500/µL, platelets > 100,000/µL, and hemoglobin > 110 g/L;
• Bone marrow at least normocellular for age, < 30% lymphocytes;
CRi was defined as for CR but with persistent cytopenia apparently unrelated to CLL but related to drug toxicity.

| End point type | Other pre-specified |
|---|---|

End point timeframe:

From first dose of study drug until the end of study; overall median time on follow-up was 49.5 months.

| End point values | Venetoclax | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 67[14] | | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 26.9 (16.8 to 39.1) | | | |

Notes:

[14] - All treated participants who were previously treated with BCRi

### Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Overall Response Rate (ORR) - Final Analysis

| End point title | Overall Response Rate (ORR) - Final Analysis |
|---|---|

End point description:

Overall response rate was defined as the percentage of participants with an overall best response of CR, CRi, nodular partial remission (nPR), or confirmed partial remission (PR) based on the 2008 modified IWCLL NCI-WG criteria assessed by the investigator.
CR and CRi are defined above. nPR is defined as for CR but bone marrow nodules could be identified histologically.
For PR at least 2 of the following must be met:
• 50% decrease in peripheral blood lymphocyte count from the Baseline value;
• 50% reduction in lymphadenopathy;
• 50% reduction in the size of the liver and/or spleen (if abnormal prior to therapy);
In addition at least 1 of the following criteria must be met:
• Neutrophils > 1,500/µL or ≥ 50% improvement over Baseline;
• Platelets > 100,000/µL or ≥ 50% improvement over Baseline;
• Hemoglobin > 11.0 g/dL or ≥ 50% improvement over Baseline without transfusions or exogenous growth factors.
PR must have been confirmed at least 7 weeks later.

| End point type | Other pre-specified |
|---|---|

End point timeframe:

From first dose of study drug until the end of study; overall median time on follow-up was 49.5 months.

| **End point values** | Venetoclax | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 258[15] | | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 79.8 (74.4 to 84.6) | | | |

Notes:

[15] - All treated participants

### Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Duration of Overall Response (DOR) - Final Analysis

| End point title | Duration of Overall Response (DOR) - Final Analysis |
|---|---|

End point description:

Duration of response was defined as the time from the date of first response (CR, CRi, nPR, or PR) to the earliest date that progressive disease (PD) was objectively documented (radiographic or clinical) or death. Duration of response was analyzed by Kaplan-Meier (K-M) methodology. If a participant was still responding the data were censored at the date of the last available disease assessment prior to the data cutoff date.

| End point type | Other pre-specified |
|---|---|

End point timeframe:

From first dose of study drug until the end of study; overall median time on follow-up was 49.5 months.

| End point values | Venetoclax | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 205[16] | | | |
| Units: months | | | | |
| median (confidence interval 95%) | 25.1 (19.4 to 28.6) | | | |

Notes:

[16] - Participants who had an overall response of CR, CRi, nPR, or confirmed PR.

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Time to Progression (TTP) - Final Analysis

| End point title | Time to Progression (TTP) - Final Analysis |
|---|---|

End point description:

Time to progression was defined as the time from the date of first dose of venetoclax to the date of earliest PD (radiographic or clinical). Participants who did not experience disease progression were censored at the date of the last available disease assessment prior to the data cutoff date; participants with no post-baseline disease assessments were censored at the first dose date plus 1 day. Time to progression was estimated using Kaplan-Meier methodology.

| End point type | Other pre-specified |
|---|---|

End point timeframe:

From first dose of study drug until the end of study; overall median time on follow-up was 49.5 months.

| End point values | Venetoclax | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 258[17] | | | |
| Units: months | | | | |
| median (confidence interval 95%) | 28.3 (23.4 to 32.6) | | | |

Notes:

[17] - All treated participants

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Progression-Free Survival (PFS) - Final Analysis

| End point title | Progression-Free Survival (PFS) - Final Analysis |
|---|---|

End point description:

Progression-free survival (PFS) was defined as the time from the date of first dose of venetoclax to the date of earliest PD (radiographic or clinical) or death. Participants who did not experience disease progression or death were censored at the date of the last available disease assessment prior to the data cutoff date; participants with no post-baseline tumor assessment or clinical assessment for progression were censored at the date of first dose plus 1 day. Progression-free survival was analyzed by Kaplan-Meier methodology.

| End point type | Other pre-specified |
|---|---|

End point timeframe:

From first dose of study drug until the end of study; overall median time on follow-up was 49.5 months.

| End point values | Venetoclax | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 258[18] | | | |
| Units: months | | | | |
| median (confidence interval 95%) | 28.3 (22.2 to 30.5) | | | |

Notes:

[18] - All treated participants

### Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Overall Survival (OS) - Final Analysis

| End point title | Overall Survival (OS) - Final Analysis |
|---|---|

End point description:

Overall survival (time to death) was defined as the time from the first dose date of venetoclax to the date of death. If a participant had not died the data were censored at the date when they were last known to be alive prior to the cutoff date. Overall survival was analyzed using Kaplan-Meier methodology. "99999" indicates data that could not be estimated due to the low number of events.

| End point type | Other pre-specified |
|---|---|

End point timeframe:

From first dose of study drug until the end of study; overall median time on follow-up was 49.5 months.

| End point values | Venetoclax | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 258[19] | | | |
| Units: months | | | | |
| median (confidence interval 95%) | 99999 (99999 to 99999) | | | |

Notes:

[19] - All treated participants

### Statistical analyses

No statistical analyses for this end point

## Post-hoc: Minimal Residual Disease (MRD) Negativity Rate - Primary Analysis

| End point title | Minimal Residual Disease (MRD) Negativity Rate - Primary Analysis |
|---|---|

End point description:

The MRD negativity rate is defined as the percentage of participants who had MRD negative status with less than one CLL cell per 10,000 leukocytes (< $10^4$) in peripheral blood and bone marrow. MRD was

evaluated using next-generation sequencing. Per protocol, peripheral blood MRD assessments were to be collected from all participants at Week 24 and Week 48 and at the time the bone marrow assessment for confirmation of CR/CRi, and bone marrow (BM) MRD assessments were to be collected for participants undergoing a bone marrow procedure for confirmation of CR/CRi. Participants with no blood or BM MRD assessments were included in the calculation of MRD negativity rate as not having MRD negative status.

| End point type | Post-hoc |
|---|---|

End point timeframe:

From first dose of study drug until the last participant completed Week 48 assessments (data cut-off date 30 June 2019); overall median time on follow-up was 23.2 months.

| **End point values** | Venetoclax | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 258[20] | | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| Peripheral blood | 39.9 (33.9 to 46.2) | | | |
| Bone marrow | 9.7 (6.4 to 14.0) | | | |

Notes:

[20] - All treated participants

### Statistical analyses

No statistical analyses for this end point

## Post-hoc: Minimal Residual Disease (MRD) Negativity Rate - Final Analysis

| End point title | Minimal Residual Disease (MRD) Negativity Rate - Final Analysis |
|---|---|

End point description:

The MRD negativity rate is defined as the percentage of participants who had MRD negative status with less than one CLL cell per 10,000 leukocytes ($< 10^4$) in peripheral blood and bone marrow. MRD was evaluated using next-generation sequencing. Per protocol, peripheral blood MRD assessments were to be collected from all participants at Week 24 and Week 48 and at the time the bone marrow assessment for confirmation of CR/CRi, and bone marrow MRD assessments were to be collected for participants undergoing a bone marrow procedure for confirmation of CR/CRi. Participants with no blood or BM MRD assessments were included in the calculation of MRD negativity rate as not having MRD negative status.

| End point type | Post-hoc |
|---|---|

End point timeframe:

From first dose of study drug until the end of study; overall median time on follow-up was 49.5 months.

| **End point values** | Venetoclax | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 258[21] | | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| Peripheral blood | 40.3 (34.3 to 46.6) | | | |

| | | | | |
|---|---|---|---|---|
| Bone marrow | 10.5 (7.0 to 14.9) | | | |

Notes:

[21] - All treated participants

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All-cause mortality is reported up to the end of the study; median time on study was 210 weeks. Adverse events are reported from the first dose of venetoclax up to 30 days after last dose; median (min, max) duration of treatment was 108 (0.1, 255) weeks.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 24.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Venetoclax |

Reporting group description:

Participants received venetoclax on a once daily dosing schedule for up to 108 weeks. The starting dose was 20 mg daily, increasing over a period of 5 weeks up to the daily dose of 400 mg. Participants who continued to derive benefit after 2 years of treatment may have continued venetoclax therapy for up to 3 additional years.

| **Serious adverse events** | Venetoclax | | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 136 / 258 (52.71%) | | |
| number of deaths (all causes) | 70 | | |
| number of deaths resulting from adverse events | 13 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| CENTRAL NERVOUS SYSTEM LYMPHOMA | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| BREAST CANCER | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| BLADDER CANCER | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| ADRENAL ADENOMA | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| ADENOMA BENIGN | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| INFECTED NEOPLASM | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| DIFFUSE LARGE B-CELL LYMPHOMA | | | | |
| subjects affected / exposed | 2 / 258 (0.78%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| CHRONIC LYMPHOCYTIC LEUKAEMIA TRANSFORMATION | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| LUNG ADENOCARCINOMA | | | | |
| subjects affected / exposed | 2 / 258 (0.78%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| MYELODYSPLASTIC SYNDROME | | | | |
| subjects affected / exposed | 4 / 258 (1.55%) | | | |
| occurrences causally related to treatment / all | 3 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| PROSTATE CANCER | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| SQUAMOUS CELL CARCINOMA | | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| SKIN NEOPLASM BLEEDING | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| RECTAL ADENOCARCINOMA | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| SQUAMOUS CELL CARCINOMA OF SKIN | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Vascular disorders | | | | |
| DEEP VEIN THROMBOSIS | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| AORTIC INTRAMURAL HAEMATOMA | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| ANEURYSM | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| HYPERTENSIVE CRISIS | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| General disorders and administration site conditions | | | | |

| | | | | |
|---|---|---|---|---|
| CHEST PAIN | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| FATIGUE | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| PYREXIA | | | | |
| subjects affected / exposed | 11 / 258 (4.26%) | | | |
| occurrences causally related to treatment / all | 6 / 12 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| MULTIPLE ORGAN DYSFUNCTION SYNDROME | | | | |
| subjects affected / exposed | 2 / 258 (0.78%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 2 | | | |
| MUCOSAL HAEMORRHAGE | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| MALAISE | | | | |
| subjects affected / exposed | 2 / 258 (0.78%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| GENERAL PHYSICAL HEALTH DETERIORATION | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Immune system disorders | | | | |
| DRUG HYPERSENSITIVITY | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |

| | | | | |
|---|---|---|---|---|
| HYPERSENSITIVITY | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Reproductive system and breast disorders | | | | |
| BENIGN PROSTATIC HYPERPLASIA | | | | |
| subjects affected / exposed | 3 / 258 (1.16%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| PROSTATIC PAIN | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Respiratory, thoracic and mediastinal disorders | | | | |
| ACUTE RESPIRATORY FAILURE | | | | |
| subjects affected / exposed | 2 / 258 (0.78%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| ASTHMA | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| ATELECTASIS | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| BRONCHIECTASIS | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| CHRONIC OBSTRUCTIVE PULMONARY DISEASE | | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| DYSPNOEA | | | | |
| subjects affected / exposed | 5 / 258 (1.94%) | | | |
| occurrences causally related to treatment / all | 0 / 5 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| COUGH | | | | |
| subjects affected / exposed | 3 / 258 (1.16%) | | | |
| occurrences causally related to treatment / all | 3 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| DYSPNOEA EXERTIONAL | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| PHARYNGEAL DISORDER | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| OROPHARYNGEAL PAIN | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| LUNG DISORDER | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| HAEMOPTYSIS | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| EPISTAXIS | | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| PHARYNGEAL SWELLING | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| PLEURAL EFFUSION | | | | |
| subjects affected / exposed | 3 / 258 (1.16%) | | | |
| occurrences causally related to treatment / all | 0 / 4 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| PNEUMONITIS | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| PULMONARY EMBOLISM | | | | |
| subjects affected / exposed | 2 / 258 (0.78%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| PULMONARY HYPERTENSION | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Psychiatric disorders | | | | |
| CONFUSIONAL STATE | | | | |
| subjects affected / exposed | 2 / 258 (0.78%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| DEPRESSION | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| MENTAL STATUS CHANGES | | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| READING DISORDER | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Investigations | | | | |
| ASPARTATE AMINOTRANSFERASE INCREASED | | | | |
| subjects affected / exposed | 3 / 258 (1.16%) | | | |
| occurrences causally related to treatment / all | 3 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| BLOOD BILIRUBIN INCREASED | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| WEIGHT DECREASED | | | | |
| subjects affected / exposed | 2 / 258 (0.78%) | | | |
| occurrences causally related to treatment / all | 1 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| BLOOD POTASSIUM INCREASED | | | | |
| subjects affected / exposed | 3 / 258 (1.16%) | | | |
| occurrences causally related to treatment / all | 3 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| GENERAL PHYSICAL CONDITION ABNORMAL | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| PLATELET COUNT DECREASED | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| BLOOD LACTATE DEHYDROGENASE | | | | |

| | | | | |
|---|---|---|---|---|
| INCREASED | | | | |
| subjects affected / exposed | 4 / 258 (1.55%) | | | |
| occurrences causally related to treatment / all | 4 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| BLOOD CREATININE INCREASED | | | | |
| subjects affected / exposed | 2 / 258 (0.78%) | | | |
| occurrences causally related to treatment / all | 1 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| BLOOD PHOSPHORUS INCREASED | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Injury, poisoning and procedural complications | | | | |
| CLAVICLE FRACTURE | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| CONTUSION | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| FALL | | | | |
| subjects affected / exposed | 2 / 258 (0.78%) | | | |
| occurrences causally related to treatment / all | 0 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| FEMORAL NECK FRACTURE | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| FRACTURE | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |

| | | | | |
|---|---|---|---|---|
| HIP FRACTURE | | | | |
| subjects affected / exposed | 2 / 258 (0.78%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| HEAD INJURY | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| HUMERUS FRACTURE | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| INFUSION RELATED REACTION | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| PELVIC FRACTURE | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Congenital, familial and genetic disorders | | | | |
| HYDROCELE | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cardiac disorders | | | | |
| AORTIC VALVE STENOSIS | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| ATRIAL FIBRILLATION | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |

| | | | | |
|---|---|---|---|---|
| ATRIOVENTRICULAR BLOCK | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| BRADYCARDIA | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| BIFASCICULAR BLOCK | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| CARDIAC ARREST | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| CARDIAC FAILURE | | | | |
| subjects affected / exposed | 2 / 258 (0.78%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| CARDIAC FAILURE CONGESTIVE | | | | |
| subjects affected / exposed | 2 / 258 (0.78%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| CORONARY ARTERY DISEASE | | | | |
| subjects affected / exposed | 2 / 258 (0.78%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| MYOCARDIAL INFARCTION | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Nervous system disorders | | | | |

| | | | |
|---|---|---|---|
| ATAXIA | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| DIZZINESS | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| DYSARTHRIA | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| SCIATICA | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| METABOLIC ENCEPHALOPATHY | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| ISCHAEMIC STROKE | | | |
| subjects affected / exposed | 2 / 258 (0.78%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| HAEMORRHAGE INTRACRANIAL | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| FACIAL PARALYSIS | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| SEIZURE | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| SUBARACHNOID HAEMORRHAGE | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| SOMNOLENCE | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| SYNCOPE | | | | |
| subjects affected / exposed | 2 / 258 (0.78%) | | | |
| occurrences causally related to treatment / all | 1 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Blood and lymphatic system disorders | | | | |
| ANAEMIA | | | | |
| subjects affected / exposed | 5 / 258 (1.94%) | | | |
| occurrences causally related to treatment / all | 2 / 5 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| AUTOIMMUNE HAEMOLYTIC ANAEMIA | | | | |
| subjects affected / exposed | 3 / 258 (1.16%) | | | |
| occurrences causally related to treatment / all | 3 / 6 | | | |
| deaths causally related to treatment / all | 1 / 1 | | | |
| APLASIA PURE RED CELL | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| FEBRILE NEUTROPENIA | | | | |
| subjects affected / exposed | 15 / 258 (5.81%) | | | |
| occurrences causally related to treatment / all | 13 / 18 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| GRANULOMATOUS LYMPHADENITIS | | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 258 (0.39%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| LEUKOCYTOSIS | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| INTRAVASCULAR HAEMOLYSIS | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 1 / 1 | | |
| HAEMOLYSIS | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| NEUTROPENIA | | | |
| subjects affected / exposed | 4 / 258 (1.55%) | | |
| occurrences causally related to treatment / all | 4 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| THROMBOCYTOPENIA | | | |
| subjects affected / exposed | 3 / 258 (1.16%) | | |
| occurrences causally related to treatment / all | 1 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| PANCYTOPENIA | | | |
| subjects affected / exposed | 2 / 258 (0.78%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ear and labyrinth disorders | | | |
| DEAFNESS NEUROSENSORY | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |

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|---|---|---|---|---|
| DIARRHOEA | | | | |
| subjects affected / exposed | 5 / 258 (1.94%) | | | |
| occurrences causally related to treatment / all | 2 / 5 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| ASCITES | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| ABDOMINAL PAIN | | | | |
| subjects affected / exposed | 3 / 258 (1.16%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| DIVERTICULUM INTESTINAL HAEMORRHAGIC | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| INGUINAL HERNIA | | | | |
| subjects affected / exposed | 2 / 258 (0.78%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| INTESTINAL OBSTRUCTION | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| RECTAL PERFORATION | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| VOMITING | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hepatobiliary disorders | | | | |

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|---|---|---|---|
| BILE DUCT STONE | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| BILIARY COLIC | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| CHOLELITHIASIS | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| CHOLANGITIS | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| GALLBLADDER NECROSIS | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| HEPATIC CIRRHOSIS | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| PARANEOPLASTIC PEMPHIGUS | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| SKIN ULCER | | | |
| subjects affected / exposed | 2 / 258 (0.78%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| RASH | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 258 (0.39%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| BLADDER MASS | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| ARTHRITIS | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| BACK PAIN | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| OSTEOPOROSIS | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| OSTEOARTHRITIS | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| HAEMATOMA MUSCLE | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| BONE PAIN | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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|---|---|---|---|---|
| PAIN IN EXTREMITY | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| SPINAL PAIN | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infections and infestations | | | | |
| ABSCESS LIMB | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| ARTHRITIS BACTERIAL | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| BRONCHITIS | | | | |
| subjects affected / exposed | 2 / 258 (0.78%) | | | |
| occurrences causally related to treatment / all | 1 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| BRONCHIOLITIS | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| CELLULITIS | | | | |
| subjects affected / exposed | 2 / 258 (0.78%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| ESCHERICHIA INFECTION | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 2 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| EPIDIDYMITIS | | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| ENDOPHTHALMITIS | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| DIVERTICULITIS | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| COVID-19 | | | | |
| subjects affected / exposed | 2 / 258 (0.78%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| INFLUENZA | | | | |
| subjects affected / exposed | 3 / 258 (1.16%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| HERPES ZOSTER | | | | |
| subjects affected / exposed | 2 / 258 (0.78%) | | | |
| occurrences causally related to treatment / all | 2 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| GASTROENTERITIS | | | | |
| subjects affected / exposed | 2 / 258 (0.78%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| LOCALISED INFECTION | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| LOWER RESPIRATORY TRACT INFECTION | | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 4 / 258 (1.55%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| NEUTROPENIC SEPSIS | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| RESPIRATORY TRACT INFECTION | | | |
| subjects affected / exposed | 2 / 258 (0.78%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| RESPIRATORY SYNCYTIAL VIRUS INFECTION | | | |
| subjects affected / exposed | 2 / 258 (0.78%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| PYELONEPHRITIS | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| PNEUMONIA BACTERIAL | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| PNEUMONIA | | | |
| subjects affected / exposed | 21 / 258 (8.14%) | | |
| occurrences causally related to treatment / all | 7 / 30 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| OSTEOMYELITIS | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| UROSEPSIS | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| UPPER RESPIRATORY TRACT INFECTION | | | | |
| subjects affected / exposed | 2 / 258 (0.78%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| TONSILLITIS BACTERIAL | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| STAPHYLOCOCCAL INFECTION | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| SKIN INFECTION | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| SEPTIC SHOCK | | | | |
| subjects affected / exposed | 2 / 258 (0.78%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 2 | | | |
| SEPSIS | | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Metabolism and nutrition disorders | | | | |
| DIABETES MELLITUS | | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 258 (0.39%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| CACHEXIA | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| FLUID RETENTION | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| HYPOGLYCAEMIA | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| HYPERPHOSPHATAEMIA | | | |
| subjects affected / exposed | 3 / 258 (1.16%) | | |
| occurrences causally related to treatment / all | 4 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| HYPERKALAEMIA | | | |
| subjects affected / exposed | 4 / 258 (1.55%) | | |
| occurrences causally related to treatment / all | 7 / 7 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| HYPERGLYCAEMIA | | | |
| subjects affected / exposed | 1 / 258 (0.39%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| TUMOUR LYSIS SYNDROME | | | |
| subjects affected / exposed | 2 / 258 (0.78%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| **Non-serious adverse events** | Venetoclax | | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 246 / 258 (95.35%) | | |
| Vascular disorders | | | |
| HYPERTENSION | | | |
| subjects affected / exposed | 29 / 258 (11.24%) | | |
| occurrences (all) | 34 | | |
| General disorders and administration site conditions | | | |
| ASTHENIA | | | |
| subjects affected / exposed | 32 / 258 (12.40%) | | |
| occurrences (all) | 41 | | |
| PYREXIA | | | |
| subjects affected / exposed | 43 / 258 (16.67%) | | |
| occurrences (all) | 56 | | |
| OEDEMA PERIPHERAL | | | |
| subjects affected / exposed | 13 / 258 (5.04%) | | |
| occurrences (all) | 17 | | |
| FATIGUE | | | |
| subjects affected / exposed | 45 / 258 (17.44%) | | |
| occurrences (all) | 56 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| DYSPNOEA | | | |
| subjects affected / exposed | 23 / 258 (8.91%) | | |
| occurrences (all) | 26 | | |
| OROPHARYNGEAL PAIN | | | |
| subjects affected / exposed | 14 / 258 (5.43%) | | |
| occurrences (all) | 15 | | |
| COUGH | | | |
| subjects affected / exposed | 52 / 258 (20.16%) | | |
| occurrences (all) | 63 | | |
| Psychiatric disorders | | | |
| INSOMNIA | | | |
| subjects affected / exposed | 25 / 258 (9.69%) | | |
| occurrences (all) | 27 | | |

| | | | |
|---|---|---|---|
| Investigations | | | |
| ALANINE AMINOTRANSFERASE INCREASED | | | |
| subjects affected / exposed | 13 / 258 (5.04%) | | |
| occurrences (all) | 15 | | |
| NEUTROPHIL COUNT DECREASED | | | |
| subjects affected / exposed | 28 / 258 (10.85%) | | |
| occurrences (all) | 47 | | |
| WEIGHT DECREASED | | | |
| subjects affected / exposed | 22 / 258 (8.53%) | | |
| occurrences (all) | 25 | | |
| PLATELET COUNT DECREASED | | | |
| subjects affected / exposed | 21 / 258 (8.14%) | | |
| occurrences (all) | 27 | | |
| Injury, poisoning and procedural complications | | | |
| FALL | | | |
| subjects affected / exposed | 13 / 258 (5.04%) | | |
| occurrences (all) | 13 | | |
| Nervous system disorders | | | |
| HEADACHE | | | |
| subjects affected / exposed | 27 / 258 (10.47%) | | |
| occurrences (all) | 29 | | |
| DIZZINESS | | | |
| subjects affected / exposed | 20 / 258 (7.75%) | | |
| occurrences (all) | 26 | | |
| Blood and lymphatic system disorders | | | |
| ANAEMIA | | | |
| subjects affected / exposed | 57 / 258 (22.09%) | | |
| occurrences (all) | 84 | | |
| NEUTROPENIA | | | |
| subjects affected / exposed | 108 / 258 (41.86%) | | |
| occurrences (all) | 251 | | |
| THROMBOCYTOPENIA | | | |
| subjects affected / exposed | 53 / 258 (20.54%) | | |
| occurrences (all) | 88 | | |
| Gastrointestinal disorders | | | |

| | | | |
|---|---|---|---|
| ABDOMINAL PAIN<br>subjects affected / exposed<br>occurrences (all) | 21 / 258 (8.14%)<br>23 | | |
| ABDOMINAL PAIN UPPER<br>subjects affected / exposed<br>occurrences (all) | 13 / 258 (5.04%)<br>17 | | |
| CONSTIPATION<br>subjects affected / exposed<br>occurrences (all) | 34 / 258 (13.18%)<br>42 | | |
| DIARRHOEA<br>subjects affected / exposed<br>occurrences (all) | 95 / 258 (36.82%)<br>170 | | |
| VOMITING<br>subjects affected / exposed<br>occurrences (all) | 20 / 258 (7.75%)<br>24 | | |
| NAUSEA<br>subjects affected / exposed<br>occurrences (all) | 69 / 258 (26.74%)<br>98 | | |
| DYSPEPSIA<br>subjects affected / exposed<br>occurrences (all) | 13 / 258 (5.04%)<br>13 | | |
| Skin and subcutaneous tissue disorders<br>DRY SKIN<br>subjects affected / exposed<br>occurrences (all) | 17 / 258 (6.59%)<br>22 | | |
| PRURITUS<br>subjects affected / exposed<br>occurrences (all) | 25 / 258 (9.69%)<br>29 | | |
| RASH<br>subjects affected / exposed<br>occurrences (all) | 20 / 258 (7.75%)<br>33 | | |
| Musculoskeletal and connective tissue disorders<br>PAIN IN EXTREMITY<br>subjects affected / exposed<br>occurrences (all) | 14 / 258 (5.43%)<br>17 | | |
| MUSCLE SPASMS | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 17 / 258 (6.59%) | | |
| occurrences (all) | 20 | | |
| BACK PAIN | | | |
| subjects affected / exposed | 34 / 258 (13.18%) | | |
| occurrences (all) | 36 | | |
| ARTHRALGIA | | | |
| subjects affected / exposed | 37 / 258 (14.34%) | | |
| occurrences (all) | 48 | | |
| Infections and infestations | | | |
| INFLUENZA | | | |
| subjects affected / exposed | 14 / 258 (5.43%) | | |
| occurrences (all) | 14 | | |
| HERPES ZOSTER | | | |
| subjects affected / exposed | 14 / 258 (5.43%) | | |
| occurrences (all) | 17 | | |
| URINARY TRACT INFECTION | | | |
| subjects affected / exposed | 25 / 258 (9.69%) | | |
| occurrences (all) | 39 | | |
| UPPER RESPIRATORY TRACT INFECTION | | | |
| subjects affected / exposed | 47 / 258 (18.22%) | | |
| occurrences (all) | 68 | | |
| PNEUMONIA | | | |
| subjects affected / exposed | 16 / 258 (6.20%) | | |
| occurrences (all) | 19 | | |
| NASOPHARYNGITIS | | | |
| subjects affected / exposed | 39 / 258 (15.12%) | | |
| occurrences (all) | 62 | | |
| Metabolism and nutrition disorders | | | |
| HYPERURICAEMIA | | | |
| subjects affected / exposed | 17 / 258 (6.59%) | | |
| occurrences (all) | 17 | | |
| HYPERPHOSPHATAEMIA | | | |
| subjects affected / exposed | 20 / 258 (7.75%) | | |
| occurrences (all) | 23 | | |
| HYPERKALAEMIA | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 21 / 258 (8.14%) | | |
| occurrences (all) | 31 | | |
| DECREASED APPETITE | | | |
| subjects affected / exposed | 24 / 258 (9.30%) | | |
| occurrences (all) | 29 | | |
| HYPOCALCAEMIA | | | |
| subjects affected / exposed | 15 / 258 (5.81%) | | |
| occurrences (all) | 19 | | |
| HYPOKALAEMIA | | | |
| subjects affected / exposed | 15 / 258 (5.81%) | | |
| occurrences (all) | 20 | | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 25 April 2016 | Updates included:<br>● Revised Inclusion Criteria to remove the double-barrier method as an acceptable form of contraception.<br>● Updated Safety Variables to include details about the safety monitoring to be performed throughout the study.<br>● Revised Suitability of Subject Population to remove the sentence related to treatment naïve subjects being included in this study population. |
| 22 May 2017 | Updates included:<br>● Revised the protocol title. Added the study name 'Venice I.' Added that the protocol will be conducted in compliance with the Declaration of Helsinki.<br>● Simplified language around the patient population included in the study.<br>● Updated the primary endpoint to exclude subjects previously treated with BCRi therapy in order to analyze BCRi treated subjects separately in the secondary endpoints.<br>● Added 6 sites to the study.<br>● Clarified that relapsed/refractory subjects with or without the 17p deletion or TP53 mutation status, including subjects with an unknown status, can be enrolled, as well as subjects who have been previously treated with BCRi therapy.<br>● Added INR as a reportable lab result for coagulation parameters.<br>● Updated contraception requirements.<br>● Updated Prior and Concomitant Therapy section.<br>● Updated Tumor Lysis Syndrome (TLS) prophylaxis and management, including pre-and post-dose laboratory requirements.<br>● Included a 30-day safety follow up visit after last dose of venetoclax.<br>● Implemented a Data Monitoring Committee.<br>● Clarified that any subject who has not experienced progressive disease at the time of study drug discontinuation will be followed up with phone calls until death, discontinuation from the study or upon study completion.<br>● Clarified that MRI should only be used in case a CT scan with contrast is medically contraindicated.<br>● Updated use of diaries from Week 20 to Week 24.<br>● Corrected details of 2008 Modified IWCLL NCI-WG Criteria for Tumor Response.<br>● Updated the relationship to study drug definitions used to assess adverse events.<br>● Updated Dose Modifications Based on Toxicities section.<br>● Specified that immunizations with live virus vaccines should not be administered prior to, during, or after treatment with venetoclax until B-cell recovery occurs.<br>● Updated NCI CTCAE version.<br>● Updates and corrections made to align with standard AbbVie template and Investigator’s brochure. |

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| 23 July 2018 | Updates included:<br>● Updated the Venetoclax Clinical Data section to align with the most recent Investigator's Brochure.<br>● Changed MRD level and the rate of MRD negativity from secondary endpoints to exploratory endpoints; clarified that MRD will be assessed in the peripheral blood and bone marrow (BM) by flow cytometry and PCR.<br>● Updated the number of sites to the study.<br>● Add a ± 2 day visit window as of Week 8.<br>● Clarified that BM examinations at screening are not required. BM samples will be collected for subjects with CR to confirm response. Subjects with PR at Week 48 may have a BM examination between Weeks 48-108 to confirm CR based on laboratory tests and physical exam.<br>● Removed requirement to evaluate lymph nodes except for screening and Weeks 24, 36 and 48.<br>● Clarified that subjects with ongoing AEs or unresolved clinically significant laboratory results 30 days after last dose of study drug will be followed-up until the AE has resolved to ≤ Grade 1 or baseline or the investigator judges that the event is unlikely to resolve.<br>● Added Extended Access Phase section to explain that in countries where venetoclax is not commercially available, subjects who continue to derive benefit after 2 years of treatment may be able to extend their treatment for up to 2 additional years.<br>● Clarified that subjects have the right to withdraw from the study and/or study treatment at any time.<br>● Updated pregnancy verbiage in line with AbbVie's latest standard language.<br>● Clarified that subjects will be followed for survival every 6 months even if they had an event of progression, required alternate therapy, etc.<br>● Added reference to DMC separate charter and details of DMC review.<br>● Added that Adverse Event/Concomitant medication assessment is to be done also at the following visits: within 72 hours of Week (W)2 Day (D)1, W3 D1, W4 D1 and W5 D1.<br>● Separated the study activities list for Extended Access Visits from the main study activities list. |
| 12 October 2020 | Updates included:<br>Updated to indicate that if a subject in the extended access phase of this study continues to derive benefit from Venetoclax after the 2-year extension, then per PI's assessment, subjects who are transferring to the venetoclax extension study, Study M19-388, may remain in Extended Access for up to additional 1 year or until the extension study is approved and initiated at the site, whichever is sooner. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported