



Clinical trial results:

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Idelalisib in Combination with Bendamustine and Rituximab for Previously Untreated Chronic Lymphocytic Leukemia

Summary

| | |
|--------------------------|----------------------|
| EudraCT number | 2013-003313-17 |
| Trial protocol | CZ BE HU IT ES PL HR |
| Global end of trial date | 16 June 2016 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 |
| This version publication date | 15 April 2017 |
| First version publication date | 15 April 2017 |

Trial information

Trial identification

| | |
|-----------------------|----------------|
| Sponsor protocol code | GS-US-312-0123 |
|-----------------------|----------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01980888 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Gilead Sciences |
| Sponsor organisation address | 333 Lakeside Drive, Foster City, CA, United States, 94404 |
| Public contact | Clinical Trial Mailbox, Gilead Sciences International Ltd, ClinicalTrialDisclosures@gilead.com |
| Scientific contact | Clinical Trial Mailbox, Gilead Sciences International Ltd, ClinicalTrialDisclosures@gilead.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 | 16 June 2016 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 16 June 2016 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the progression-free survival in participants with previously untreated chronic lymphocytic leukemia (CLL) who would otherwise be suitable for bendamustine and rituximab treatment as standard of care.

Protection of trial subjects:

The protocol and consent/assent forms were submitted by each investigator to a duly constituted Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for review and approval before study initiation. All revisions to the consent/assent forms (if applicable) after initial IEC/IRB approval were submitted by the investigator to the IEC/IRB for review and approval before implementation in accordance with regulatory requirements.

This study was conducted in accordance with recognized international scientific and ethical standards, including but not limited to the International Conference on Harmonization guideline for Good Clinical Practice (ICH GCP) and the original principles embodied in the Declaration of Helsinki.

Background therapy:

Bendamustine and rituximab

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 05 February 2014 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Poland: 33 |
| Country: Number of subjects enrolled | Romania: 5 |
| Country: Number of subjects enrolled | Spain: 34 |
| Country: Number of subjects enrolled | United Kingdom: 20 |
| Country: Number of subjects enrolled | Croatia: 11 |
| Country: Number of subjects enrolled | Belgium: 6 |
| Country: Number of subjects enrolled | Czech Republic: 27 |
| Country: Number of subjects enrolled | France: 9 |
| Country: Number of subjects enrolled | Hungary: 45 |
| Country: Number of subjects enrolled | Italy: 8 |
| Country: Number of subjects enrolled | United States: 60 |
| Country: Number of subjects enrolled | Canada: 19 |
| Country: Number of subjects enrolled | Australia: 34 |

| | |
|------------------------------------|-----|
| Worldwide total number of subjects | 311 |
| EEA total number of subjects | 198 |

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) | 153 |
| From 65 to 84 years | 158 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study sites in the North America, Australia, and Europe. The first participant was screened on 05 February 2014. The last study visit occurred on 16 June 2016.

Pre-assignment

Screening details:

392 participants were screened.

Period 1

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

Arms

| | |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

| | |
|------------------|-----------------------------------|
| Arm title | Idelalisib+Bendamustine+Rituximab |
|------------------|-----------------------------------|

Arm description:

Idelalisib + bendamustine + rituximab

| | |
|--|----------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Idelalisib |
| Investigational medicinal product code | |
| Other name | Zydelig®, GS-1101, CAL-101 |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

150 mg administered twice daily

| | |
|--|--|
| Investigational medicinal product name | Bendamustine |
| Investigational medicinal product code | |
| Other name | Levact |
| Pharmaceutical forms | Powder for concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Administered at a starting dose of 90 mg/m² for up to 6 total cycles

| | |
|--|---------------------------------------|
| Investigational medicinal product name | Rituximab |
| Investigational medicinal product code | |
| Other name | Rituxan, MabThera |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Single-use vials administered weekly starting at 375 mg/m² on Day 1 (Week 0) and 500 mg/m² thereafter for a total of 6 cycles

| | |
|------------------|--------------------------------|
| Arm title | Placebo+Bendamustine+Rituximab |
|------------------|--------------------------------|

Arm description:

Placebo + bendamustine + rituximab

| | |
|----------|---------|
| Arm type | Placebo |
|----------|---------|

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

Dosage and administration details:

Administered twice daily

| | |
|--|--|
| Investigational medicinal product name | Bendamustine |
| Investigational medicinal product code | |
| Other name | Levact |
| Pharmaceutical forms | Powder for concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Administered at a starting dose of 90 mg/m² for up to 6 total cycles

| | |
|--|---------------------------------------|
| Investigational medicinal product name | Rituximab |
| Investigational medicinal product code | |
| Other name | Rituxan, MabThera |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Single-use vials administered weekly starting at 375 mg/m² on Day 1 (Week 0) and 500 mg/m² thereafter for a total of 6 cycles

| Number of subjects in period 1 | Idelalisib+Bendamustine+Rituximab | Placebo+Bendamustine+Rituximab |
|---------------------------------------|--|---------------------------------------|
| Started | 157 | 154 |
| Completed | 13 | 21 |
| Not completed | 144 | 133 |
| Withdrew Consent | 17 | 6 |
| Non- Compliance with Study Drug | 3 | 2 |
| Investigator's Discretion | 8 | 3 |
| Study Terminated by Sponsor | 116 | 122 |

Baseline characteristics

Reporting groups

| | |
|---|-----------------------------------|
| Reporting group title | Idelalisib+Bendamustine+Rituximab |
| Reporting group description: Idelalisib + bendamustine + rituximab | |
| Reporting group title | Placebo+Bendamustine+Rituximab |
| Reporting group description: Placebo + bendamustine + rituximab | |

| Reporting group values | Idelalisib+Bendamustine+Rituximab | Placebo+Bendamustine+Rituximab | Total |
|------------------------------------|-----------------------------------|--------------------------------|-------|
| Number of subjects | 157 | 154 | 311 |
| Age categorical Units: Subjects | | | |

| | | | |
|--|-------------|------------|-----|
| Age continuous Units: years arithmetic mean standard deviation | 64 ± 8.7 | 63 ± 10 | - |
| Gender categorical Units: Subjects | | | |
| Female | 57 | 48 | 105 |
| Male | 100 | 106 | 206 |
| Race Units: Subjects | | | |
| Asian | 1 | 0 | 1 |
| Black or African American | 1 | 1 | 2 |
| White | 152 | 150 | 302 |
| Other | 3 | 1 | 4 |
| Not Permitted | 0 | 2 | 2 |
| Ethnicity Units: Subjects | | | |
| Hispanic or Latino | 11 | 2 | 13 |
| Not Hispanic or Latino | 146 | 149 | 295 |
| Not Permitted | 0 | 3 | 3 |
| Rai Stage at Screening | | | |
| Rai staging is a way to categorize the disease progression of chronic lymphocytic leukemia (CLL) with higher stages reflecting increasing severity. Rai Stage 0: Lymphocytosis only, Rai Stage I: Lymphocytosis with lymphadenopathy, Rai Stage II: Lymphocytosis with hepatomegaly or splenomegaly, Rai Stage III: Lymphocytosis with anemia, Rai Stage IV: Lymphocytosis with thrombocytopenia. | | | |
| Units: Subjects | | | |
| Stage I | 28 | 30 | 58 |
| Stage II | 66 | 58 | 124 |
| Stage III | 25 | 32 | 57 |
| Stage IV | 38 | 34 | 72 |
| IgHV Mutation | | | |
| The mutation status of the unique immunoglobulin gene (IgHV) rearrangement in the monoclonal proliferation of B-cells in CLL can be used to predict aggressiveness of the disease. Participants | | | |

with a mutated IgHV gene usually have a less aggressive and more indolent disease, with longer overall survival. Participants with an unmutated IgHV gene usually have a more aggressive disease and shorter overall survival.

| | | | |
|-----------------|-----|-----|-----|
| Units: Subjects | | | |
| Mutated | 54 | 54 | 108 |
| Unmutated | 102 | 100 | 202 |
| Missing | 1 | 0 | 1 |

| | | | |
|---------------------------|--|--|--|
| 17p Deletion in CLL Cells | | | |
|---------------------------|--|--|--|

Participants with CLL who have a 17p deletion lack a portion of the chromosome that acts to suppress cancer growth and is a recognized negative prognostic risk factor.

| | | | |
|-----------------|-----|-----|-----|
| Units: Subjects | | | |
| Absent | 146 | 145 | 291 |
| Present | 10 | 9 | 19 |
| Missing | 1 | 0 | 1 |

End points

End points reporting groups

| | |
|---------------------------------------|-----------------------------------|
| Reporting group title | Idelalisib+Bendamustine+Rituximab |
| Reporting group description: | |
| Idelalisib + bendamustine + rituximab | |
| Reporting group title | Placebo+Bendamustine+Rituximab |
| Reporting group description: | |
| Placebo + bendamustine + rituximab | |

Primary: Progression-Free Survival

| | |
|---|--|
| End point title | Progression-Free Survival ^[1] |
| End point description: | |
| Progression-free survival (PFS) is defined as the interval from randomization to the first documentation of definitive disease progression or death from any cause. Definitive disease progression is CLL progression based on standard criteria, excluding lymphocytosis alone. PFS was to be assessed by an independent review committee (IRC). | |
| Due to the early termination of the study, efficacy data were not available for all subjects, and therefore the prespecified analyses were not conducted. | |
| End point type | Primary |
| End point timeframe: | |
| Not applicable | |

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: Due to the early termination of the study, efficacy data were not available for all participants, and therefore the prespecified analyses were not conducted.

| End point values | Idelalisib+Bendamustine+Rituximab | Placebo+Bendamustine+Rituximab | | |
|-----------------------------|-----------------------------------|--------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[2] | 0 ^[3] | | |
| Units: Not applicable | | | | |

Notes:

[2] - Analysis was not performed due to early study termination.

[3] - Analysis was not performed due to early study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate

| | |
|--|-----------------------|
| End point title | Overall Response Rate |
| End point description: | |
| Overall response rate (ORR) is defined as the proportion of participants who achieve a confirmed complete or partial response. ORR was to be assessed by an IRC. | |
| Due to the early termination of the study, efficacy data were not available for all participants, and therefore the prespecified analyses were not conducted. | |
| End point type | Secondary |

End point timeframe:

Not applicable

| End point values | Idelalisib+Bendamustine+Rituximab | Placebo+Bendamustine+Rituximab | | |
|-----------------------------|-----------------------------------|--------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[4] | 0 ^[5] | | |
| Units: Not applicable | | | | |

Notes:

[4] - Analysis was not performed due to early study termination.

[5] - Analysis was not performed due to early study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Nodal Response Rate

| | |
|-----------------|---------------------|
| End point title | Nodal Response Rate |
|-----------------|---------------------|

End point description:

Nodal response rate is defined as the proportion of participants who achieve a 50% decrease from baseline in the sum of the products of the greatest perpendicular diameters of index lesions. Nodal response rate was to be assessed by an IRC.

Due to the early termination of the study, efficacy data were not available for all participants, and therefore the prespecified analyses were not conducted.

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

End point timeframe:

Not applicable

| End point values | Idelalisib+Bendamustine+Rituximab | Placebo+Bendamustine+Rituximab | | |
|-----------------------------|-----------------------------------|--------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[6] | 0 ^[7] | | |
| Units: Not applicable | | | | |

Notes:

[6] - Analysis was not performed due to early study termination.

[7] - Analysis was not performed due to early study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Complete Response Rate

| | |
|-----------------|------------------------|
| End point title | Complete Response Rate |
|-----------------|------------------------|

End point description:

Complete response rate is defined as the proportion of participants who achieve a confirmed complete response. Complete response rate was to be assessed by an IRC.

Due to the early termination of the study, efficacy data were not available for all participants, and therefore the prespecified analyses were not conducted.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Not applicable | |

| | | | | |
|-----------------------------|-----------------------------------|--------------------------------|--|--|
| End point values | Idelalisib+Bendamustine+Rituximab | Placebo+Bendamustine+Rituximab | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[8] | 0 ^[9] | | |
| Units: Not applicable | | | | |

Notes:

[8] - Analysis was not performed due to early study termination.

[9] - Analysis was not performed due to early study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

| | |
|--|------------------|
| End point title | Overall Survival |
| End point description: | |
| Overall survival is defined as the interval from randomization to death from any cause. | |
| Due to the early termination of the study, efficacy data were not mature for all participants, and therefore the prespecified analyses were not conducted. | |
| End point type | Secondary |
| End point timeframe: | |
| Not applicable | |

| | | | | |
|-----------------------------|-----------------------------------|--------------------------------|--|--|
| End point values | Idelalisib+Bendamustine+Rituximab | Placebo+Bendamustine+Rituximab | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[10] | 0 ^[11] | | |
| Units: Not applicable | | | | |

Notes:

[10] - Analysis was not performed due to early study termination.

[11] - Analysis was not performed due to early study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Minimal Residual Disease Negativity Rate at Week 36

| | |
|--|---|
| End point title | Minimal Residual Disease Negativity Rate at Week 36 |
| End point description: | |
| Minimal residual disease (MRD) negativity rate is defined as the proportion of participants with MRD < | |

10⁻⁴ assessed by flow cytometry in bone marrow at Week 36 after therapy initiation or at least 12 weeks after the last dose of rituximab or bendamustine (whichever is later) for participants receiving the final dose of rituximab after the original scheduled date. MRD negativity rate was to be assessed by an IRC.

Due to the early termination of the study, efficacy data were not available for all participants, and therefore the prespecified analyses were not conducted.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Not applicable | |

| End point values | Idelalisib+Bendamustine+Rituximab | Placebo+Bendamustine+Rituximab | | |
|-----------------------------|-----------------------------------|--------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[12] | 0 ^[13] | | |
| Units: Not applicable | | | | |

Notes:

[12] - Analysis was not performed due to early study termination.

[13] - Analysis was not performed due to early study termination.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 22 months plus 30 days

Adverse event reporting additional description:

Safety Analysis Set: participants who received at least 1 dose of study treatment, with treatment assignments designated according to the actual treatment received.

NOTE: Serious adverse events and deaths causally related to "treatment" refers to events deemed related to idelalisib/placebo/rituximab treatment per investigator assessment.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 19.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-----------------------------------|
| Reporting group title | Idelalisib+Bendamustine+Rituximab |
|-----------------------|-----------------------------------|

Reporting group description:

Idelalisib + bendamustine + rituximab

| | |
|-----------------------|--------------------------------|
| Reporting group title | Placebo+Bendamustine+Rituximab |
|-----------------------|--------------------------------|

Reporting group description:

Placebo + bendamustine + rituximab

| Serious adverse events | Idelalisib+Bendamustine+Rituximab | Placebo+Bendamustine+Rituximab | |
|---|-----------------------------------|--------------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 113 / 156 (72.44%) | 68 / 154 (44.16%) | |
| number of deaths (all causes) | 13 | 5 | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Malignant ascites | | | |
| subjects affected / exposed | 0 / 156 (0.00%) | 1 / 154 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malignant melanoma | | | |
| subjects affected / exposed | 1 / 156 (0.64%) | 0 / 154 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malignant pleural effusion | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 156 (0.00%) | 1 / 154 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Meningioma | | | |
| subjects affected / exposed | 1 / 156 (0.64%) | 0 / 154 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastatic squamous cell carcinoma | | | |
| subjects affected / exposed | 1 / 156 (0.64%) | 0 / 154 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin cancer | | | |
| subjects affected / exposed | 1 / 156 (0.64%) | 0 / 154 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Squamous cell carcinoma | | | |
| subjects affected / exposed | 1 / 156 (0.64%) | 0 / 154 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Squamous cell carcinoma of lung | | | |
| subjects affected / exposed | 0 / 156 (0.00%) | 1 / 154 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Aortitis | | | |
| subjects affected / exposed | 1 / 156 (0.64%) | 0 / 154 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Embolism | | | |
| subjects affected / exposed | 1 / 156 (0.64%) | 0 / 154 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematoma | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 156 (0.64%) | 0 / 154 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral embolism | | | |
| subjects affected / exposed | 1 / 156 (0.64%) | 0 / 154 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombophlebitis | | | |
| subjects affected / exposed | 0 / 156 (0.00%) | 1 / 154 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombophlebitis superficial | | | |
| subjects affected / exposed | 0 / 156 (0.00%) | 1 / 154 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombosis | | | |
| subjects affected / exposed | 1 / 156 (0.64%) | 0 / 154 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 1 / 156 (0.64%) | 0 / 154 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 156 (0.00%) | 1 / 154 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Influenza like illness | | | |
| subjects affected / exposed | 1 / 156 (0.64%) | 0 / 154 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mucosal inflammation | | | |

| | | | |
|---|-------------------|-------------------|--|
| subjects affected / exposed | 1 / 156 (0.64%) | 0 / 154 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 1 / 156 (0.64%) | 0 / 154 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 26 / 156 (16.67%) | 19 / 154 (12.34%) | |
| occurrences causally related to treatment / all | 24 / 35 | 18 / 23 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Systemic inflammatory response syndrome | | | |
| subjects affected / exposed | 0 / 156 (0.00%) | 1 / 154 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Unevaluable event | | | |
| subjects affected / exposed | 0 / 156 (0.00%) | 1 / 154 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Immune system disorders | | | |
| Anaphylactic reaction | | | |
| subjects affected / exposed | 2 / 156 (1.28%) | 0 / 154 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 0 / 156 (0.00%) | 3 / 154 (1.95%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypersensitivity | | | |
| subjects affected / exposed | 0 / 156 (0.00%) | 1 / 154 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Serum sickness | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 156 (0.64%) | 0 / 154 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 1 / 156 (0.64%) | 0 / 154 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 156 (0.00%) | 1 / 154 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 156 (0.64%) | 0 / 154 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonitis | | | |
| subjects affected / exposed | 5 / 156 (3.21%) | 3 / 154 (1.95%) | |
| occurrences causally related to treatment / all | 6 / 6 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Procedural pneumothorax | | | |
| subjects affected / exposed | 0 / 156 (0.00%) | 1 / 154 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 1 / 156 (0.64%) | 0 / 154 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Confusional state | | | |
| subjects affected / exposed | 1 / 156 (0.64%) | 0 / 154 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Depression | | | |
| subjects affected / exposed | 1 / 156 (0.64%) | 0 / 154 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hallucination, auditory | | | |
| subjects affected / exposed | 1 / 156 (0.64%) | 0 / 154 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mental status changes | | | |
| subjects affected / exposed | 1 / 156 (0.64%) | 0 / 154 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 2 / 156 (1.28%) | 0 / 154 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 2 / 156 (1.28%) | 0 / 154 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General physical condition abnormal | | | |
| subjects affected / exposed | 1 / 156 (0.64%) | 0 / 154 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transaminases increased | | | |
| subjects affected / exposed | 2 / 156 (1.28%) | 0 / 154 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 156 (0.00%) | 1 / 154 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hip fracture | | | |
| subjects affected / exposed | 0 / 156 (0.00%) | 1 / 154 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infusion related reaction | | | |
| subjects affected / exposed | 3 / 156 (1.92%) | 1 / 154 (0.65%) | |
| occurrences causally related to treatment / all | 4 / 4 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Procedural complication | | | |
| subjects affected / exposed | 0 / 156 (0.00%) | 1 / 154 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 156 (0.00%) | 2 / 154 (1.30%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arrhythmia | | | |
| subjects affected / exposed | 0 / 156 (0.00%) | 1 / 154 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 4 / 156 (2.56%) | 3 / 154 (1.95%) | |
| occurrences causally related to treatment / all | 2 / 5 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure | | | |
| subjects affected / exposed | 1 / 156 (0.64%) | 2 / 154 (1.30%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cardiac failure chronic | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 156 (0.00%) | 1 / 154 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 1 / 156 (0.64%) | 0 / 154 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiopulmonary failure | | | |
| subjects affected / exposed | 1 / 156 (0.64%) | 1 / 154 (0.65%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Coronary artery disease | | | |
| subjects affected / exposed | 1 / 156 (0.64%) | 0 / 154 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 0 / 156 (0.00%) | 1 / 154 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Supraventricular extrasystoles | | | |
| subjects affected / exposed | 0 / 156 (0.00%) | 1 / 154 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular extrasystoles | | | |
| subjects affected / exposed | 0 / 156 (0.00%) | 1 / 154 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Dysarthria | | | |
| subjects affected / exposed | 0 / 156 (0.00%) | 1 / 154 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Encephalopathy | | | |

| | | | |
|---|-------------------|-------------------|--|
| subjects affected / exposed | 1 / 156 (0.64%) | 0 / 154 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Facial paralysis | | | |
| subjects affected / exposed | 0 / 156 (0.00%) | 1 / 154 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ischaemic stroke | | | |
| subjects affected / exposed | 0 / 156 (0.00%) | 1 / 154 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 2 / 156 (1.28%) | 0 / 154 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 2 / 156 (1.28%) | 0 / 154 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 8 / 156 (5.13%) | 2 / 154 (1.30%) | |
| occurrences causally related to treatment / all | 11 / 11 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bone marrow failure | | | |
| subjects affected / exposed | 1 / 156 (0.64%) | 0 / 154 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 29 / 156 (18.59%) | 16 / 154 (10.39%) | |
| occurrences causally related to treatment / all | 29 / 33 | 19 / 20 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemolytic anaemia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 156 (0.64%) | 0 / 154 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lymphadenopathy mediastinal | | | |
| subjects affected / exposed | 0 / 156 (0.00%) | 1 / 154 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenia | | | |
| subjects affected / exposed | 7 / 156 (4.49%) | 1 / 154 (0.65%) | |
| occurrences causally related to treatment / all | 8 / 8 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 2 / 156 (1.28%) | 1 / 154 (0.65%) | |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Blindness | | | |
| subjects affected / exposed | 1 / 156 (0.64%) | 0 / 154 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 156 (0.64%) | 0 / 154 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colitis ulcerative | | | |
| subjects affected / exposed | 1 / 156 (0.64%) | 0 / 154 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 6 / 156 (3.85%) | 1 / 154 (0.65%) | |
| occurrences causally related to treatment / all | 4 / 6 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enterocolitis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 156 (1.28%) | 0 / 154 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Gastritis | | | |
| subjects affected / exposed | 0 / 156 (0.00%) | 1 / 154 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematochezia | | | |
| subjects affected / exposed | 0 / 156 (0.00%) | 1 / 154 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophagitis | | | |
| subjects affected / exposed | 1 / 156 (0.64%) | 0 / 154 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis | | | |
| subjects affected / exposed | 0 / 156 (0.00%) | 1 / 154 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis acute | | | |
| subjects affected / exposed | 0 / 156 (0.00%) | 1 / 154 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 1 / 156 (0.64%) | 0 / 154 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 156 (0.64%) | 1 / 154 (0.65%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholecystitis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 156 (0.64%) | 0 / 154 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 0 / 156 (0.00%) | 1 / 154 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatitis | | | |
| subjects affected / exposed | 1 / 156 (0.64%) | 0 / 154 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis allergic | | | |
| subjects affected / exposed | 0 / 156 (0.00%) | 1 / 154 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Drug eruption | | | |
| subjects affected / exposed | 1 / 156 (0.64%) | 0 / 154 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Generalised erythema | | | |
| subjects affected / exposed | 2 / 156 (1.28%) | 1 / 154 (0.65%) | |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Photosensitivity reaction | | | |
| subjects affected / exposed | 0 / 156 (0.00%) | 1 / 154 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rash | | | |
| subjects affected / exposed | 4 / 156 (2.56%) | 1 / 154 (0.65%) | |
| occurrences causally related to treatment / all | 4 / 4 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rash generalised | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 156 (0.64%) | 1 / 154 (0.65%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rash maculo-papular | | | |
| subjects affected / exposed | 2 / 156 (1.28%) | 0 / 154 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 2 / 156 (1.28%) | 0 / 154 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Prerenal failure | | | |
| subjects affected / exposed | 1 / 156 (0.64%) | 0 / 154 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal tubular acidosis | | | |
| subjects affected / exposed | 1 / 156 (0.64%) | 0 / 154 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocrine disorders | | | |
| Glucocorticoid deficiency | | | |
| subjects affected / exposed | 0 / 156 (0.00%) | 1 / 154 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Compartment syndrome | | | |
| subjects affected / exposed | 1 / 156 (0.64%) | 0 / 154 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetic amyotrophy | | | |
| subjects affected / exposed | 0 / 156 (0.00%) | 1 / 154 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 0 / 156 (0.00%) | 1 / 154 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal column stenosis | | | |
| subjects affected / exposed | 0 / 156 (0.00%) | 1 / 154 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 156 (0.64%) | 0 / 154 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 156 (0.64%) | 0 / 154 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 156 (0.64%) | 1 / 154 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cytomegalovirus gastritis | | | |
| subjects affected / exposed | 1 / 156 (0.64%) | 0 / 154 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cytomegalovirus infection | | | |
| subjects affected / exposed | 3 / 156 (1.92%) | 0 / 154 (0.00%) | |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Cytomegalovirus viraemia | | | |
| subjects affected / exposed | 1 / 156 (0.64%) | 0 / 154 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device related infection | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 156 (1.28%) | 0 / 154 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 156 (0.64%) | 0 / 154 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal bacterial infection | | | |
| subjects affected / exposed | 1 / 156 (0.64%) | 0 / 154 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Herpes simplex | | | |
| subjects affected / exposed | 1 / 156 (0.64%) | 0 / 154 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Herpes zoster | | | |
| subjects affected / exposed | 1 / 156 (0.64%) | 0 / 154 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infective exacerbation of chronic obstructive airways disease | | | |
| subjects affected / exposed | 0 / 156 (0.00%) | 1 / 154 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Influenza | | | |
| subjects affected / exposed | 2 / 156 (1.28%) | 0 / 154 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 2 / 156 (1.28%) | 1 / 154 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocarditis infectious | | | |

| | | | |
|---|------------------|-----------------|--|
| subjects affected / exposed | 1 / 156 (0.64%) | 0 / 154 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenic sepsis | | | |
| subjects affected / exposed | 5 / 156 (3.21%) | 1 / 154 (0.65%) | |
| occurrences causally related to treatment / all | 4 / 5 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Pneumocystis jirovecii pneumonia | | | |
| subjects affected / exposed | 1 / 156 (0.64%) | 0 / 154 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 11 / 156 (7.05%) | 6 / 154 (3.90%) | |
| occurrences causally related to treatment / all | 4 / 11 | 4 / 9 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Pneumonia fungal | | | |
| subjects affected / exposed | 1 / 156 (0.64%) | 0 / 154 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 3 / 156 (1.92%) | 1 / 154 (0.65%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 9 / 156 (5.77%) | 2 / 154 (1.30%) | |
| occurrences causally related to treatment / all | 3 / 9 | 1 / 2 | |
| deaths causally related to treatment / all | 1 / 4 | 0 / 0 | |
| Septic shock | | | |
| subjects affected / exposed | 1 / 156 (0.64%) | 0 / 154 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Staphylococcal sepsis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 156 (0.64%) | 0 / 154 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Strongyloidiasis | | | |
| subjects affected / exposed | 0 / 156 (0.00%) | 1 / 154 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Tonsillitis | | | |
| subjects affected / exposed | 0 / 156 (0.00%) | 1 / 154 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 156 (0.64%) | 1 / 154 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 4 / 156 (2.56%) | 1 / 154 (0.65%) | |
| occurrences causally related to treatment / all | 3 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Varicella zoster virus infection | | | |
| subjects affected / exposed | 1 / 156 (0.64%) | 0 / 154 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Viral infection | | | |
| subjects affected / exposed | 0 / 156 (0.00%) | 1 / 154 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 1 / 156 (0.64%) | 0 / 154 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dehydration | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 3 / 156 (1.92%) | 1 / 154 (0.65%) | |
| occurrences causally related to treatment / all | 3 / 3 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 156 (0.00%) | 1 / 154 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malnutrition | | | |
| subjects affected / exposed | 1 / 156 (0.64%) | 0 / 154 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tumour lysis syndrome | | | |
| subjects affected / exposed | 5 / 156 (3.21%) | 4 / 154 (2.60%) | |
| occurrences causally related to treatment / all | 5 / 5 | 3 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Idelalisib+Bendamustine+Rituximab | Placebo+Bendamustine+Rituximab | |
|---|--|---------------------------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 154 / 156 (98.72%) | 150 / 154 (97.40%) | |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 11 / 156 (7.05%) | 10 / 154 (6.49%) | |
| occurrences (all) | 13 | 11 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 21 / 156 (13.46%) | 9 / 154 (5.84%) | |
| occurrences (all) | 25 | 10 | |
| Chills | | | |
| subjects affected / exposed | 21 / 156 (13.46%) | 14 / 154 (9.09%) | |
| occurrences (all) | 28 | 14 | |
| Fatigue | | | |

| | | | |
|--|--------------------------|-------------------------|--|
| subjects affected / exposed occurrences (all) | 43 / 156 (27.56%) 52 | 44 / 154 (28.57%) 60 | |
| Mucosal inflammation subjects affected / exposed occurrences (all) | 14 / 156 (8.97%) 15 | 1 / 154 (0.65%) 2 | |
| Oedema peripheral subjects affected / exposed occurrences (all) | 19 / 156 (12.18%) 21 | 16 / 154 (10.39%) 19 | |
| Pyrexia subjects affected / exposed occurrences (all) | 71 / 156 (45.51%) 116 | 38 / 154 (24.68%) 61 | |
| Immune system disorders Drug hypersensitivity subjects affected / exposed occurrences (all) | 8 / 156 (5.13%) 10 | 2 / 154 (1.30%) 2 | |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 34 / 156 (21.79%) 47 | 29 / 154 (18.83%) 36 | |
| Dyspnoea subjects affected / exposed occurrences (all) | 24 / 156 (15.38%) 33 | 12 / 154 (7.79%) 12 | |
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 8 / 156 (5.13%) 10 | 9 / 154 (5.84%) 10 | |
| Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) | 11 / 156 (7.05%) 12 | 9 / 154 (5.84%) 9 | |
| Depression subjects affected / exposed occurrences (all) | 8 / 156 (5.13%) 8 | 2 / 154 (1.30%) 3 | |
| Insomnia subjects affected / exposed occurrences (all) | 17 / 156 (10.90%) 21 | 12 / 154 (7.79%) 18 | |
| Investigations | | | |

| | | | |
|---|-------------------------|-------------------------|--|
| Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 22 / 156 (14.10%) 33 | 3 / 154 (1.95%) 4 | |
| Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 18 / 156 (11.54%) 27 | 2 / 154 (1.30%) 2 | |
| Neutrophil count decreased subjects affected / exposed occurrences (all) | 8 / 156 (5.13%) 17 | 2 / 154 (1.30%) 3 | |
| Weight decreased subjects affected / exposed occurrences (all) | 19 / 156 (12.18%) 22 | 4 / 154 (2.60%) 4 | |
| Injury, poisoning and procedural complications Infusion related reaction subjects affected / exposed occurrences (all) | 21 / 156 (13.46%) 24 | 33 / 154 (21.43%) 41 | |
| Cardiac disorders Atrial fibrillation subjects affected / exposed occurrences (all) | 8 / 156 (5.13%) 9 | 3 / 154 (1.95%) 4 | |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) | 13 / 156 (8.33%) 13 | 13 / 154 (8.44%) 15 | |
| Dysgeusia subjects affected / exposed occurrences (all) | 10 / 156 (6.41%) 11 | 11 / 154 (7.14%) 12 | |
| Headache subjects affected / exposed occurrences (all) | 16 / 156 (10.26%) 22 | 25 / 154 (16.23%) 28 | |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) | 40 / 156 (25.64%) 52 | 29 / 154 (18.83%) 42 | |
| Neutropenia | | | |

| | | | |
|--|-------------------|-------------------|--|
| subjects affected / exposed | 84 / 156 (53.85%) | 90 / 154 (58.44%) | |
| occurrences (all) | 179 | 180 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 19 / 156 (12.18%) | 16 / 154 (10.39%) | |
| occurrences (all) | 26 | 20 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 14 / 156 (8.97%) | 14 / 154 (9.09%) | |
| occurrences (all) | 17 | 17 | |
| Constipation | | | |
| subjects affected / exposed | 26 / 156 (16.67%) | 34 / 154 (22.08%) | |
| occurrences (all) | 33 | 45 | |
| Diarrhoea | | | |
| subjects affected / exposed | 63 / 156 (40.38%) | 46 / 154 (29.87%) | |
| occurrences (all) | 111 | 72 | |
| Dry mouth | | | |
| subjects affected / exposed | 11 / 156 (7.05%) | 4 / 154 (2.60%) | |
| occurrences (all) | 11 | 4 | |
| Dyspepsia | | | |
| subjects affected / exposed | 15 / 156 (9.62%) | 12 / 154 (7.79%) | |
| occurrences (all) | 16 | 17 | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 9 / 156 (5.77%) | 4 / 154 (2.60%) | |
| occurrences (all) | 9 | 4 | |
| Nausea | | | |
| subjects affected / exposed | 61 / 156 (39.10%) | 63 / 154 (40.91%) | |
| occurrences (all) | 102 | 95 | |
| Stomatitis | | | |
| subjects affected / exposed | 10 / 156 (6.41%) | 4 / 154 (2.60%) | |
| occurrences (all) | 12 | 4 | |
| Vomiting | | | |
| subjects affected / exposed | 37 / 156 (23.72%) | 23 / 154 (14.94%) | |
| occurrences (all) | 61 | 31 | |
| Skin and subcutaneous tissue disorders | | | |
| Dry skin | | | |

| | | | |
|---|-------------------------|-------------------------|--|
| subjects affected / exposed occurrences (all) | 14 / 156 (8.97%) 16 | 4 / 154 (2.60%) 5 | |
| Erythema subjects affected / exposed occurrences (all) | 12 / 156 (7.69%) 17 | 8 / 154 (5.19%) 10 | |
| Pruritus subjects affected / exposed occurrences (all) | 24 / 156 (15.38%) 27 | 32 / 154 (20.78%) 36 | |
| Rash subjects affected / exposed occurrences (all) | 63 / 156 (40.38%) 87 | 34 / 154 (22.08%) 53 | |
| Rash macular subjects affected / exposed occurrences (all) | 8 / 156 (5.13%) 8 | 2 / 154 (1.30%) 2 | |
| Rash maculo-papular subjects affected / exposed occurrences (all) | 29 / 156 (18.59%) 40 | 12 / 154 (7.79%) 14 | |
| Renal and urinary disorders Dysuria subjects affected / exposed occurrences (all) | 9 / 156 (5.77%) 9 | 3 / 154 (1.95%) 3 | |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 16 / 156 (10.26%) 18 | 12 / 154 (7.79%) 13 | |
| Back pain subjects affected / exposed occurrences (all) | 11 / 156 (7.05%) 12 | 18 / 154 (11.69%) 18 | |
| Infections and infestations Bronchitis subjects affected / exposed occurrences (all) | 5 / 156 (3.21%) 5 | 8 / 154 (5.19%) 8 | |
| Influenza subjects affected / exposed occurrences (all) | 6 / 156 (3.85%) 6 | 8 / 154 (5.19%) 9 | |
| Nasopharyngitis | | | |

| | | | |
|------------------------------------|-------------------|-------------------|--|
| subjects affected / exposed | 8 / 156 (5.13%) | 14 / 154 (9.09%) | |
| occurrences (all) | 8 | 21 | |
| Oral candidiasis | | | |
| subjects affected / exposed | 8 / 156 (5.13%) | 4 / 154 (2.60%) | |
| occurrences (all) | 8 | 4 | |
| Oral herpes | | | |
| subjects affected / exposed | 5 / 156 (3.21%) | 8 / 154 (5.19%) | |
| occurrences (all) | 7 | 9 | |
| Pneumonia | | | |
| subjects affected / exposed | 10 / 156 (6.41%) | 3 / 154 (1.95%) | |
| occurrences (all) | 11 | 3 | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 9 / 156 (5.77%) | 4 / 154 (2.60%) | |
| occurrences (all) | 14 | 4 | |
| Sinusitis | | | |
| subjects affected / exposed | 9 / 156 (5.77%) | 4 / 154 (2.60%) | |
| occurrences (all) | 9 | 4 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 25 / 156 (16.03%) | 21 / 154 (13.64%) | |
| occurrences (all) | 32 | 29 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 15 / 156 (9.62%) | 6 / 154 (3.90%) | |
| occurrences (all) | 15 | 8 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 26 / 156 (16.67%) | 21 / 154 (13.64%) | |
| occurrences (all) | 32 | 26 | |
| Dehydration | | | |
| subjects affected / exposed | 12 / 156 (7.69%) | 2 / 154 (1.30%) | |
| occurrences (all) | 17 | 3 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 25 / 156 (16.03%) | 4 / 154 (2.60%) | |
| occurrences (all) | 33 | 5 | |
| Hypophosphataemia | | | |
| subjects affected / exposed | 9 / 156 (5.77%) | 0 / 154 (0.00%) | |
| occurrences (all) | 10 | 0 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 19 February 2014 | The following changes were to align with the bendamustine and rituximab Summary of Product Characteristics (SmPC): <ul style="list-style-type: none">• To align the protocol with the male contraceptive requirements in the SmPC for bendamustine• To exclude subjects with known hypersensitivity or intolerance to any of the active substances or excipients in the formulations for idelalisib, bendamustine, or rituximab• To exclude subjects who received yellow fever vaccine within 30 days prior to randomization• To exclude subjects who have undergone major surgery within 30 days prior to randomization• To include information regarding the use of live vaccines• To refer investigators to local prescribing guidelines for each specific concomitant medicine with potential for safety considerations and discuss any questions with the Gilead Medical Monitor before initiation of such treatments |
| 06 November 2014 | To change MRD from a primary to a secondary endpoint, update to the guidance to investigators for evaluation, intervention, and drug interruption/discontinuation for specific adverse events, and revisions to the information regarding the interaction of idelalisib and CYP3A inhibitors, inducers, and substrates. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|---------------|--|--------------|
| 11 March 2016 | An increased rate of deaths and serious adverse events (SAEs) among participants with front-line CLL and early-line indolent non-Hodgkin lymphoma (iNHL) treated with idelalisib in combination with standard therapies was observed by the independent data monitoring committee (DMC) during regular review of 3 Gilead Phase 3 studies. Gilead reviewed the unblinded data and terminated this study in agreement with the DMC recommendation and in consultation with the US Food and Drug Administration (FDA). | - |

Notes:

Limitations and caveats

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

Due to the early termination of the study, efficacy data were not available for all participants, and therefore the prespecified analyses were not conducted.

Notes: