



Clinical trial results:

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Idelalisib (GS-1101) in Combination with Rituximab for Previously Treated Indolent Non-Hodgkin Lymphomas

Summary

| | |
|--------------------------|-------------------------|
| EudraCT number | 2012-004013-13 |
| Trial protocol | DE GB SE ES HU CZ IT PT |
| Global end of trial date | 18 May 2016 |

Results information

| | |
|--------------------------------|--|
| Result version number | v2 (current) |
| This version publication date | 18 May 2019 |
| First version publication date | 15 April 2017 |
| Version creation reason | <ul style="list-style-type: none">• Correction of full data setAdding text to "Limitations and Caveats" section |

Trial information

Trial identification

| | |
|-----------------------|----------------|
| Sponsor protocol code | GS-US-313-0124 |
|-----------------------|----------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01732913 |
| 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 Trials Mailbox, Gilead Sciences International Ltd, ClinicalTrialDisclosures@gilead.com |
| Scientific contact | Clinical Trials 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 | 18 May 2016 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 18 May 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 effect of the addition of idelalisib to rituximab on progression-free survival (PFS) in adults with previously treated indolent non-Hodgkin lymphoma (iNHL).

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: -

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 16 January 2013 |
| 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: 12 |
| Country: Number of subjects enrolled | Portugal: 4 |
| Country: Number of subjects enrolled | Romania: 1 |
| Country: Number of subjects enrolled | Spain: 6 |
| Country: Number of subjects enrolled | Sweden: 8 |
| Country: Number of subjects enrolled | United Kingdom: 4 |
| Country: Number of subjects enrolled | Czech Republic: 2 |
| Country: Number of subjects enrolled | France: 42 |
| Country: Number of subjects enrolled | Germany: 2 |
| Country: Number of subjects enrolled | Hungary: 30 |
| Country: Number of subjects enrolled | Italy: 11 |
| Country: Number of subjects enrolled | Russian Federation: 9 |
| Country: Number of subjects enrolled | Singapore: 9 |
| Country: Number of subjects enrolled | United States: 99 |
| Country: Number of subjects enrolled | Japan: 32 |

| | |
|--------------------------------------|-----------------------|
| Country: Number of subjects enrolled | Taiwan: 2 |
| Country: Number of subjects enrolled | Australia: 13 |
| Country: Number of subjects enrolled | Israel: 3 |
| Country: Number of subjects enrolled | Korea, Republic of: 6 |
| Worldwide total number of subjects | 295 |
| EEA total number of subjects | 122 |

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) | 129 |
| From 65 to 84 years | 156 |
| 85 years and over | 10 |

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study sites in the North America, Europe, and Asia Pacific. The first participant was screened on 16 January 2013. The last study visit occurred on 18 May 2016.

Pre-assignment

Screening details:

385 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, Carer |

Arms

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

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

Arm description:

Idelalisib (Zydelig®) 150 mg tablet orally twice daily + rituximab 375 mg/m² intravenously starting on Day 1 for a total of 8 infusions

| | |
|--|----------------------------|
| 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 | 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 at a dose of 375 mg/m² starting on Day 1 for a total of 8 infusions.

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

Arm description:

Placebo tablet orally twice daily + rituximab 375 mg/m² intravenously starting on Day 1 for a total of 8 infusions

| | |
|--|--------------------|
| Arm type | Experimental |
| 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 | 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 at a dose of 375 mg/m² starting on Day 1 for a total of 8 infusions.

| Number of subjects in period 1 | Idelalisib + Rituximab | Placebo + Rituximab |
|--|---------------------------|---------------------|
| Started | 198 | 97 |
| Completed | 42 | 28 |
| Not completed | 156 | 69 |
| Physician decision | 14 | 7 |
| Initiation of Other Anti-Cancer Therapy | 3 | 2 |
| Other Reason | 7 | 1 |
| Withdrawal by Subject | 27 | 4 |
| Study Terminated by Sponsor | 105 | 55 |

Baseline characteristics

Reporting groups

| | |
|---|------------------------|
| Reporting group title | Idelalisib + Rituximab |
| Reporting group description: Idelalisib (Zydelig®) 150 mg tablet orally twice daily + rituximab 375 mg/m ² intravenously starting on Day 1 for a total of 8 infusions | |
| Reporting group title | Placebo + Rituximab |
| Reporting group description: Placebo tablet orally twice daily + rituximab 375 mg/m ² intravenously starting on Day 1 for a total of 8 infusions | |

| Reporting group values | Idelalisib + Rituximab | Placebo + Rituximab | Total |
|------------------------|------------------------|---------------------|-------|
| Number of subjects | 198 | 97 | 295 |
| Age categorical | | | |
| Units: Subjects | | | |

| | | | |
|---------------------------|--------|--------|-----|
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 64 | 67 | |
| standard deviation | ± 11.4 | ± 11.4 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 99 | 48 | 147 |
| Male | 99 | 49 | 148 |
| Race | | | |
| Units: Subjects | | | |
| Asian | 35 | 17 | 52 |
| Black or African American | 5 | 4 | 9 |
| White | 123 | 54 | 177 |
| Other | 3 | 3 | 6 |
| Not Permitted | 32 | 19 | 51 |
| Ethnicity | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 12 | 3 | 15 |
| Not Hispanic or Latino | 150 | 75 | 225 |
| Unknown or Not Reported | 36 | 19 | 55 |

End points

End points reporting groups

| | |
|---|------------------------|
| Reporting group title | Idelalisib + Rituximab |
| Reporting group description: | |
| Idelalisib (Zydelig®) 150 mg tablet orally twice daily + rituximab 375 mg/m ² intravenously starting on Day 1 for a total of 8 infusions | |
| Reporting group title | Placebo + Rituximab |
| Reporting group description: | |
| Placebo tablet orally twice daily + rituximab 375 mg/m ² intravenously starting on Day 1 for a total of 8 infusions | |

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 earlier of the first documentation of definitive iNHL disease progression or death from any cause. 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 participants, 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 + Rituximab | Placebo + 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 complete response or partial response (or very good partial response or minor response for participants with Waldenström's). 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 + Rituximab | Placebo + 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: Lymph Node Response Rate

| | |
|--|--------------------------|
| End point title | Lymph Node Response Rate |
| End point description: | |
| Lymph node response rate is defined as the proportion of participants who achieve $\geq 50\%$ decrease from baseline in the sum of the products of the greatest perpendicular diameters of index lesions. Lymph node 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 + Rituximab | Placebo + 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 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 + Rituximab | Placebo + 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 + Rituximab | Placebo + 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

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 27 months plus 30 days

Adverse event reporting additional description:

Safety Analysis Set included all participants who took at least 1 dose of study drug.

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 + rituximab |
|-----------------------|------------------------|

Reporting group description:

Idelalisib 150 mg tablet orally twice daily + rituximab 375 mg/m² intravenously starting on Day 1 for a total of 8 infusions

| | |
|-----------------------|---------------------|
| Reporting group title | Placebo + rituximab |
|-----------------------|---------------------|

Reporting group description:

Placebo tablet orally twice daily + rituximab 375 mg/m² intravenously starting on Day 1 for a total of 8 infusions

| Serious adverse events | Idelalisib + rituximab | Placebo + rituximab | |
|---|------------------------|---------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 103 / 198 (52.02%) | 11 / 95 (11.58%) | |
| number of deaths (all causes) | 11 | 2 | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Breast cancer recurrent | | | |
| subjects affected / exposed | 0 / 198 (0.00%) | 1 / 95 (1.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Glioblastoma | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 2 / 198 (1.01%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Death | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Fatigue | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 1 / 95 (1.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gait disturbance | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oedema | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 9 / 198 (4.55%) | 1 / 95 (1.05%) | |
| occurrences causally related to treatment / all | 2 / 9 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| Hypersensitivity | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 95 (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 | | | |
| Bronchitis chronic | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|----------------|--|
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 2 / 198 (1.01%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cough | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 95 (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 | 3 / 198 (1.52%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoxia | | | |
| subjects affected / exposed | 2 / 198 (1.01%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Interstitial lung disease | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung disorder | | | |
| subjects affected / exposed | 2 / 198 (1.01%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonitis | | | |
| subjects affected / exposed | 8 / 198 (4.04%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 7 / 8 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |

| | | | |
|---|------------------|----------------|--|
| subjects affected / exposed | 3 / 198 (1.52%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Major depression | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 95 (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 | 2 / 198 (1.01%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Suicidal ideation | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 95 (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 | 11 / 198 (5.56%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 11 / 11 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 10 / 198 (5.05%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 10 / 10 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|----------------|--|
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 0 / 198 (0.00%) | 1 / 95 (1.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood lactate dehydrogenase increased | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transaminases increased | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Clavicle fracture | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fall | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infusion related reaction | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 2 / 95 (2.11%) | |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Laceration | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|----------------|--|
| Rib fracture | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal compression fracture | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subdural haematoma | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subdural haemorrhage | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper limb fracture | | | |
| subjects affected / exposed | 0 / 198 (0.00%) | 1 / 95 (1.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bradycardia | | | |
| subjects affected / exposed | 0 / 198 (0.00%) | 1 / 95 (1.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac arrest | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 2 / 95 (2.11%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pericarditis | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tachycardia | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 2 / 198 (1.01%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dizziness | | | |
| subjects affected / exposed | 2 / 198 (1.01%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 3 / 198 (1.52%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 3 / 198 (1.52%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |

| | | | |
|---|-----------------|----------------|--|
| Anaemia | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 95 (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 | 7 / 198 (3.54%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 5 / 7 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Leukopenia | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenia | | | |
| subjects affected / exposed | 3 / 198 (1.52%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 3 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 1 / 95 (1.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colitis | | | |
| subjects affected / exposed | 8 / 198 (4.04%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 8 / 9 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colitis ulcerative | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Constipation | | | |

| | | | |
|---|------------------|----------------|--|
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 18 / 198 (9.09%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 21 / 23 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enteritis | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enterocolitis | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Incarcerated inguinal hernia | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal obstruction | | | |
| subjects affected / exposed | 0 / 198 (0.00%) | 1 / 95 (1.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 95 (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 | 1 / 198 (0.51%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Salivary gland disorder | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 0 / 198 (0.00%) | 1 / 95 (1.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Stomatitis | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 3 / 198 (1.52%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Salivary gland enlargement | | | |
| subjects affected / exposed | 0 / 198 (0.00%) | 1 / 95 (1.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Drug-induced liver injury | | | |
| subjects affected / exposed | 3 / 198 (1.52%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 5 / 5 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic failure | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Hepatic function abnormal | | | |
| subjects affected / exposed | 2 / 198 (1.01%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Jaundice | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 2 / 198 (1.01%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Psoriasis | | | |
| subjects affected / exposed | 2 / 198 (1.01%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rash | | | |
| subjects affected / exposed | 4 / 198 (2.02%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 3 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 5 / 198 (2.53%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 5 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary retention | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Bronchitis | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 95 (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 | 2 / 198 (1.01%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eczema herpeticum | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fungaemia | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Herpes zoster meningomyelitis | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infection | | | |

| | | | |
|---|------------------|----------------|--|
| subjects affected / exposed | 1 / 198 (0.51%) | 1 / 95 (1.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infective exacerbation of chronic obstructive airways disease | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 95 (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 | 0 / 198 (0.00%) | 1 / 95 (1.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metapneumovirus infection | | | |
| subjects affected / exposed | 0 / 198 (0.00%) | 1 / 95 (1.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenic sepsis | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Otitis externa | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumocystis jirovecii pneumonia | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 95 (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 | 19 / 198 (9.60%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 10 / 22 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Sepsis | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 5 / 198 (2.53%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 5 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Septic shock | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin bacterial infection | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Staphylococcal bacteraemia | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 2 / 198 (1.01%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 4 / 198 (2.02%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Cachexia | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Dehydration | | | |
| subjects affected / exposed | 4 / 198 (2.02%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 3 / 5 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypercalcaemia | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 2 / 198 (1.01%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 2 / 198 (1.01%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Idelalisib + rituximab | Placebo + rituximab | |
|---|------------------------|---------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 189 / 198 (95.45%) | 83 / 95 (87.37%) | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 12 / 198 (6.06%) | 2 / 95 (2.11%) | |
| occurrences (all) | 14 | 2 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 15 / 198 (7.58%) | 9 / 95 (9.47%) | |
| occurrences (all) | 17 | 11 | |
| Chills | | | |

| | | | |
|---|-------------------|------------------|--|
| subjects affected / exposed | 11 / 198 (5.56%) | 4 / 95 (4.21%) | |
| occurrences (all) | 16 | 4 | |
| Fatigue | | | |
| subjects affected / exposed | 41 / 198 (20.71%) | 20 / 95 (21.05%) | |
| occurrences (all) | 47 | 21 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 14 / 198 (7.07%) | 5 / 95 (5.26%) | |
| occurrences (all) | 15 | 5 | |
| Pyrexia | | | |
| subjects affected / exposed | 50 / 198 (25.25%) | 11 / 95 (11.58%) | |
| occurrences (all) | 67 | 12 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 28 / 198 (14.14%) | 14 / 95 (14.74%) | |
| occurrences (all) | 29 | 16 | |
| Dyspnoea | | | |
| subjects affected / exposed | 12 / 198 (6.06%) | 2 / 95 (2.11%) | |
| occurrences (all) | 13 | 2 | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 12 / 198 (6.06%) | 3 / 95 (3.16%) | |
| occurrences (all) | 15 | 3 | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 10 / 198 (5.05%) | 3 / 95 (3.16%) | |
| occurrences (all) | 10 | 3 | |
| Insomnia | | | |
| subjects affected / exposed | 21 / 198 (10.61%) | 11 / 95 (11.58%) | |
| occurrences (all) | 25 | 12 | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 65 / 198 (32.83%) | 0 / 95 (0.00%) | |
| occurrences (all) | 90 | 0 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 56 / 198 (28.28%) | 0 / 95 (0.00%) | |
| occurrences (all) | 72 | 0 | |
| Gamma-glutamyltransferase | | | |

| | | | |
|--|-------------------|------------------|--|
| increased | | | |
| subjects affected / exposed | 11 / 198 (5.56%) | 1 / 95 (1.05%) | |
| occurrences (all) | 11 | 1 | |
| Transaminases increased | | | |
| subjects affected / exposed | 12 / 198 (6.06%) | 1 / 95 (1.05%) | |
| occurrences (all) | 17 | 1 | |
| Weight decreased | | | |
| subjects affected / exposed | 20 / 198 (10.10%) | 1 / 95 (1.05%) | |
| occurrences (all) | 20 | 2 | |
| Injury, poisoning and procedural complications | | | |
| Infusion related reaction | | | |
| subjects affected / exposed | 36 / 198 (18.18%) | 20 / 95 (21.05%) | |
| occurrences (all) | 42 | 27 | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 12 / 198 (6.06%) | 6 / 95 (6.32%) | |
| occurrences (all) | 15 | 6 | |
| Headache | | | |
| subjects affected / exposed | 30 / 198 (15.15%) | 12 / 95 (12.63%) | |
| occurrences (all) | 42 | 15 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 12 / 198 (6.06%) | 6 / 95 (6.32%) | |
| occurrences (all) | 14 | 12 | |
| Neutropenia | | | |
| subjects affected / exposed | 25 / 198 (12.63%) | 5 / 95 (5.26%) | |
| occurrences (all) | 49 | 7 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 20 / 198 (10.10%) | 4 / 95 (4.21%) | |
| occurrences (all) | 24 | 5 | |
| Constipation | | | |
| subjects affected / exposed | 28 / 198 (14.14%) | 13 / 95 (13.68%) | |
| occurrences (all) | 30 | 14 | |
| Diarrhoea | | | |

| | | | |
|---|-------------------|------------------|--|
| subjects affected / exposed | 88 / 198 (44.44%) | 18 / 95 (18.95%) | |
| occurrences (all) | 133 | 26 | |
| Gastroesophageal reflux disease | | | |
| subjects affected / exposed | 10 / 198 (5.05%) | 3 / 95 (3.16%) | |
| occurrences (all) | 10 | 3 | |
| Nausea | | | |
| subjects affected / exposed | 50 / 198 (25.25%) | 12 / 95 (12.63%) | |
| occurrences (all) | 65 | 14 | |
| Vomiting | | | |
| subjects affected / exposed | 29 / 198 (14.65%) | 7 / 95 (7.37%) | |
| occurrences (all) | 33 | 10 | |
| Skin and subcutaneous tissue disorders | | | |
| Pruritus | | | |
| subjects affected / exposed | 25 / 198 (12.63%) | 4 / 95 (4.21%) | |
| occurrences (all) | 29 | 4 | |
| Rash | | | |
| subjects affected / exposed | 38 / 198 (19.19%) | 12 / 95 (12.63%) | |
| occurrences (all) | 42 | 16 | |
| Rash maculo-papular | | | |
| subjects affected / exposed | 16 / 198 (8.08%) | 2 / 95 (2.11%) | |
| occurrences (all) | 19 | 3 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 9 / 198 (4.55%) | 6 / 95 (6.32%) | |
| occurrences (all) | 12 | 6 | |
| Back pain | | | |
| subjects affected / exposed | 9 / 198 (4.55%) | 6 / 95 (6.32%) | |
| occurrences (all) | 10 | 7 | |
| Pain in extremity | | | |
| subjects affected / exposed | 16 / 198 (8.08%) | 3 / 95 (3.16%) | |
| occurrences (all) | 17 | 3 | |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 9 / 198 (4.55%) | 6 / 95 (6.32%) | |
| occurrences (all) | 10 | 8 | |
| Nasopharyngitis | | | |

| | | | |
|------------------------------------|-------------------|----------------|--|
| subjects affected / exposed | 10 / 198 (5.05%) | 6 / 95 (6.32%) | |
| occurrences (all) | 12 | 9 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 23 / 198 (11.62%) | 8 / 95 (8.42%) | |
| occurrences (all) | 30 | 9 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 13 / 198 (6.57%) | 3 / 95 (3.16%) | |
| occurrences (all) | 15 | 4 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 26 / 198 (13.13%) | 2 / 95 (2.11%) | |
| occurrences (all) | 27 | 2 | |
| Dehydration | | | |
| subjects affected / exposed | 11 / 198 (5.56%) | 0 / 95 (0.00%) | |
| occurrences (all) | 12 | 0 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 21 / 198 (10.61%) | 4 / 95 (4.21%) | |
| occurrences (all) | 22 | 4 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|---|
| 18 January 2013 | <ul style="list-style-type: none">• Updated information regarding secondary and tertiary endpoints• Updated inclusion criteria relating to contraception to comply with the European Union (EU) health authority• Clarified that the IRC findings were primary for analyses of PFS and other tumor control endpoints• Updated plan to control Type I error rate for secondary endpoints• Increased washout period for previous cancer therapies from 3 to 6 weeks• Provided clarification on phototoxicity risk• Clarified duration of therapy for each study treatment group• Clarified that subjects in Groups A and B who prematurely discontinued 1 study drug could continue other study drug• Updated safety and clinical information in alignment with Version 7 of the Investigator's Brochure (IB)• Added new section to differentiate discontinuation from study versus discontinuation of study drug• Clarified language around dose modifications that are made for adverse events (AEs) or laboratory abnormalities that the investigator considered related to study drug• Changed the criteria for splenomegaly with a splenic longest vertical dimension from 10 cm to 12 cm based on expert radiology recommendations |
| 17 September 2013 | Revised text to add 1 additional formal interim efficacy analysis after ~50% of the expected number of PFS events have occurred and changed the 2nd interim analysis from 66% of the planned events occurring to 75% |
| 22 October 2013 | Added monitoring guidelines for Hep B reactivation |
| 29 July 2014 | Added a double-blind extension to allow eligible subjects to receive idelalisib monotherapy at the time of iNHL disease progression |
| 31 October 2014 | <ul style="list-style-type: none">• Updated the following information to align with investigator's brochure Edition 11.<ul style="list-style-type: none">- Guidance to investigators for evaluation, intervention, and drug interruption/discontinuation for specific adverse events.- Information regarding the interaction of idelalisib with CYP3A inhibitors, inducers, and substrates. |
| 31 July 2015 | Added an open-label extension to permit subjects randomized to Group B (Placebo + Rituximab) the opportunity to receive open-label IDL150 mg twice daily |

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 chronic lymphocytic leukemia (CLL) and early-line 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). 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:

Limitations and caveats

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

An unplanned review of unblinded clinical trial data was performed in this study that was not prospectively specified in the protocol. There was no impact on the overall integrity or conclusions of the study.

Notes: