# Clinical trial results:
# A Phase 3, Randomized, Open Label Study Investigating the Efficacy of the BiTE® Antibody Blinatumomab Versus Standard of Care Chemotherapy in Adult Subjects With Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia (ALL) (TOWER Study)

## Summary

| | |
|---|---|
| EudraCT number | 2013-000536-10 |
| Trial protocol | IT CZ DE BE IE AT GB ES FR GR PL BG |
| Global end of trial date | 14 March 2017 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 09 March 2018 |
| First version publication date | 09 March 2018 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | 00103311 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02013167 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Amgen Inc. |
| Sponsor organisation address | One Amgen Center Drive, Thousand Oaks, CA, United States, 91320 |
| Public contact | IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com |
| Scientific contact | IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.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 | 14 March 2017 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 14 March 2017 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of the study was to evaluate the effect of blinatumomab on overall survival when compared to standard of care (SOC) chemotherapy.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines. The regulations or guidelines were applicable to all regions where the study was conducted and in accordance with the ethical principles set forth in the Declaration of Helsinki. All study centers complied with local regulations.
The study and all amendments were reviewed by an independent ethics committee (IEC)/institutional review board (IRB) at each center.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 03 January 2014 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Efficacy |
| Long term follow-up duration | 12 Months |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Belgium: 15 |
| Country: Number of subjects enrolled | Bulgaria: 2 |
| Country: Number of subjects enrolled | Czech Republic: 10 |
| Country: Number of subjects enrolled | France: 31 |
| Country: Number of subjects enrolled | Germany: 41 |
| Country: Number of subjects enrolled | Greece: 11 |
| Country: Number of subjects enrolled | Italy: 45 |
| Country: Number of subjects enrolled | Poland: 12 |
| Country: Number of subjects enrolled | Russian Federation: 10 |
| Country: Number of subjects enrolled | Spain: 25 |
| Country: Number of subjects enrolled | Turkey: 28 |
| Country: Number of subjects enrolled | United Kingdom: 21 |
| Country: Number of subjects enrolled | Australia: 30 |
| Country: Number of subjects enrolled | Canada: 18 |
| Country: Number of subjects enrolled | Israel: 14 |
| Country: Number of subjects enrolled | Korea, Republic of: 15 |

| | |
|---|---|
| Country: Number of subjects enrolled | Mexico: 10 |
| Country: Number of subjects enrolled | Taiwan: 7 |
| Country: Number of subjects enrolled | Ireland: 7 |
| Country: Number of subjects enrolled | United States: 46 |
| Country: Number of subjects enrolled | Austria: 7 |
| Worldwide total number of subjects | 405 |
| EEA total number of subjects | 227 |

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) | 357 |
| From 65 to 84 years | 48 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

This study was conducted at 101 centers in 21 countries in Asia, Australia, Europe, and Latin and North America.
The first participant was enrolled on 03 January 2014 and was treated on 06 January 2014. The last participant enrolled on 25 September 2015.

### Pre-assignment

Screening details:

Participants were randomized in a 2:1 ratio to either blinatumomab or standard of care (SOC) chemotherapy regimens. Randomization was stratified by age (< 35 years vs ≥ 35 years), prior salvage therapy (yes vs no), and prior allogeneic hematopoietic stem cell transplantation (HSCT) (yes vs no) as assessed at the time of consent.

### Period 1

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

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Standard of Care Chemotherapy |

Arm description:

Participants received one of four prespecified, investigator-chosen chemotherapy regimens for 2 induction cycles. Participants who achieved a bone marrow response, CR/CRh*/CRi within 2 induction cycles of treatment could receive up to 3 additional consolidation cycles of SOC chemotherapy. Participants who received 2 induction and up to 3 consolidation cycles of therapy and continued to have a bone marrow response or CR/CRh*/CRi could continue to receive SOC therapy for an additional 12 months.

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Standard of Care Chemotherapy |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

• FLAG (fludarabine, cytarabine arabinoside, and granulocyte colony-stimulating factor) ± anthracycline-based regimen (e.g. idarubicin 10 mg/m² days 1 & 3; fludarabine 30 mg/m² days 1-5; cytarabine arabinoside 2 g/m² days 1-5). Patients > 60 years: Idarubicin 5 mg/m² day 1 & 3; fludarabine 20 mg/m² day 1-5; cytarabine arabinoside 1 g/m² day 1-5
• HiDAC (high-dose cytarabine arabinoside) - based regimen ≥1 g/m²/day ± anthracycline and/or in combination with other drugs such as native Escherichia coli asparaginase, polyethylene glycol linked to asparaginase (PEG-asparaginase), vinca alkaloids, steroids, etoposide or alkylating agents
• High-dose methotrexate-based regimen (HDMTX; 500 mg/m² to 3 g/m² infused up to 24 hours) in combination with native E. coli asparaginase, PEG-asparaginase, vinca alkaloids, steroids, etoposide or alkylating agents.
• Clofarabine as a single agent as recommended in the prescribing information or clofarabine-based regimens with 20 mg/m²/day for up to 5 days.

| | |
|---|---|
| **Arm title** | Blinatumomab |

Arm description:

Participants received blinatumomab by continuous intravenous infusion (CIVI) over 4 weeks followed by a 2 week treatment-free interval for 2 induction cycles. Participants who achieved a bone marrow response, complete remission, or complete remission with partial or incomplete hematologic recovery (CR/CRh*/CRi) within 2 induction cycles of treatment could receive up to 3 additional consolidation cycles of blinatumomab.
Participants who received 2 induction and up to 3 consolidation cycles of therapy and continued to have

a bone marrow response or CR/CRh*/CRi could continue to receive blinatumomab for an additional 12 months (4 cycles), where 1 cycle consisted of 4 weeks of CIVI followed by an 8-week treatment-free period.
The initial dose of blinatumomab was 9 µg/day for the first 7 days of treatment, increased to 28 µg/day starting on day 8 through day 29 and for all subsequent cycles.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Blinatumomab |
| Investigational medicinal product code | MT103 |
| Other name | Blincyto®<br>AMG 103<br>MT103 |
| Pharmaceutical forms | Powder for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Blinatumomab is administered as a continuous intravenous infusion (CIV).

| **Number of subjects in period 1** | Standard of Care Chemotherapy | Blinatumomab |
|---|---|---|
| Started | 134 | 271 |
| Received Treatment | 109 | 267 |
| Completed | 0 | 0 |
| Not completed | 134 | 271 |
| Consent withdrawn by subject | 15 | 15 |
| Death | 88 | 178 |
| Lost to follow-up | - | 1 |
| Decision by sponsor | 31 | 77 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Standard of Care Chemotherapy |

Reporting group description:

Participants received one of four prespecified, investigator-chosen chemotherapy regimens for 2 induction cycles. Participants who achieved a bone marrow response, CR/CRh*/CRi within 2 induction cycles of treatment could receive up to 3 additional consolidation cycles of SOC chemotherapy.
Participants who received 2 induction and up to 3 consolidation cycles of therapy and continued to have a bone marrow response or CR/CRh*/CRi could continue to receive SOC therapy for an additional 12 months.

| Reporting group title | Blinatumomab |
|---|---|

Reporting group description:

Participants received blinatumomab by continuous intravenous infusion (CIVI) over 4 weeks followed by a 2 week treatment-free interval for 2 induction cycles. Participants who achieved a bone marrow response, complete remission, or complete remission with partial or incomplete hematologic recovery (CR/CRh*/CRi) within 2 induction cycles of treatment could receive up to 3 additional consolidation cycles of blinatumomab.
Participants who received 2 induction and up to 3 consolidation cycles of therapy and continued to have a bone marrow response or CR/CRh*/CRi could continue to receive blinatumomab for an additional 12 months (4 cycles), where 1 cycle consisted of 4 weeks of CIVI followed by an 8-week treatment-free period.
The initial dose of blinatumomab was 9 µg/day for the first 7 days of treatment, increased to 28 µg/day starting on day 8 through day 29 and for all subsequent cycles.

| Reporting group values | Standard of Care Chemotherapy | Blinatumomab | Total |
|---|---|---|---|
| Number of subjects | 134 | 271 | 405 |
| Age Categorical<br>Units: Subjects | | | |
| < 35 years | 60 | 124 | 184 |
| 35 to 54 years | 33 | 80 | 113 |
| 55 to 64 years | 26 | 34 | 60 |
| ≥ 65 years | 15 | 33 | 48 |
| Age Continuous<br>Units: years | | | |
| arithmetic mean | 41.1 | 40.8 | |
| standard deviation | ± 17.3 | ± 17.1 | - |
| Gender Categorical<br>Units: Subjects | | | |
| Female | 57 | 109 | 166 |
| Male | 77 | 162 | 239 |
| Ethnicity<br>Units: Subjects | | | |
| Hispanic or Latino | 11 | 26 | 37 |
| Not Hispanic or Latino | 122 | 243 | 365 |
| Unknown | 1 | 2 | 3 |
| Race<br>Units: Subjects | | | |
| American Indian or Alaska Native | 1 | 4 | 5 |
| Asian | 9 | 19 | 28 |
| Native Hawaiian or Other Pacific Islander | 1 | 1 | 2 |
| Black or African American | 3 | 5 | 8 |

| | | | |
|---|---|---|---|
| White | 112 | 228 | 340 |
| Multiple | 0 | 2 | 2 |
| Other | 8 | 12 | 20 |
| Age Stratification at Randomization<br>Units: Subjects | | | |
| < 35 years | 60 | 123 | 183 |
| ≥ 35 years | 74 | 148 | 222 |
| Prior Salvage Therapy Stratification at Randomization<br>Units: Subjects | | | |
| Yes | 80 | 164 | 244 |
| No | 54 | 107 | 161 |
| Prior Allogeneic Hematopoietic Stem Cell Transplant (HCST)<br>Units: Subjects | | | |
| Yes | 46 | 94 | 140 |
| No | 88 | 177 | 265 |
| Standard of Care Chemotherapy Regimen Received | | | |
| FLAG = fludarabine, cytarabine arabinoside, and granulocyte colony-stimulating factor (filgrastim); HiDAC = high-dose cytarabine arabinoside | | | |
| Units: Subjects | | | |
| FLAG ± anthracycline | 56 | 0 | 56 |
| High-dose methotrexate | 30 | 0 | 30 |
| Clofarabine | 26 | 0 | 26 |
| HIDAC | 22 | 0 | 22 |
| Not applicable | 0 | 271 | 271 |

## End points

### End points reporting groups

| Reporting group title | Standard of Care Chemotherapy |
|---|---|

Reporting group description:

Participants received one of four prespecified, investigator-chosen chemotherapy regimens for 2 induction cycles. Participants who achieved a bone marrow response, CR/CRh*/CRi within 2 induction cycles of treatment could receive up to 3 additional consolidation cycles of SOC chemotherapy.
Participants who received 2 induction and up to 3 consolidation cycles of therapy and continued to have a bone marrow response or CR/CRh*/CRi could continue to receive SOC therapy for an additional 12 months.

| Reporting group title | Blinatumomab |
|---|---|

Reporting group description:

Participants received blinatumomab by continuous intravenous infusion (CIVI) over 4 weeks followed by a 2 week treatment-free interval for 2 induction cycles. Participants who achieved a bone marrow response, complete remission, or complete remission with partial or incomplete hematologic recovery (CR/CRh*/CRi) within 2 induction cycles of treatment could receive up to 3 additional consolidation cycles of blinatumomab.
Participants who received 2 induction and up to 3 consolidation cycles of therapy and continued to have a bone marrow response or CR/CRh*/CRi could continue to receive blinatumomab for an additional 12 months (4 cycles), where 1 cycle consisted of 4 weeks of CIVI followed by an 8-week treatment-free period.
The initial dose of blinatumomab was 9 µg/day for the first 7 days of treatment, increased to 28 µg/day starting on day 8 through day 29 and for all subsequent cycles.

### Primary: Overall survival

| End point title | Overall survival |
|---|---|

End point description:

Overall survival (OS) was calculated from time of randomization until death due to any cause. Participants still alive were censored at the date they were last known to be alive.

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

End point timeframe:

From randomization until end of study (14 March 2017); median observation time was 13.6 months in the SOC group and 15.7 months in the blinatumomab group.

| End point values | Standard of Care Chemotherapy | Blinatumomab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 134 | 271 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 4.0 (2.9 to 5.5) | 7.7 (5.6 to 9.6) | | |

### Statistical analyses

| Statistical analysis title | Primary Analysis of Overall Survival |
|---|---|

Statistical analysis description:

A 2-sided stratified log-rank test, stratified by the randomization factors, was used to determine if overall survival was superior in the blinatumomab arm compared to SOC chemotherapy arm. A hazard

ratio with a 95% CI was estimated from a stratified Cox proportional hazard model. A hazard ratio < 1.0 indicates a lower average event rate and longer survival time for blinatumomab relative to SOC chemotherapy.

| | |
|---|---|
| Comparison groups | Standard of Care Chemotherapy v Blinatumomab |
| Number of subjects included in analysis | 405 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.052 [1] |
| Method | Stratified Log Rank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.78 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.6 |
| upper limit | 1 |

Notes:

[1] - Stratified by age (< 35 years; ≥ 35 years), prior salvage therapy (yes vs. no), and prior allogeneic HSCT (yes vs. no).

## Secondary: Percentage of Participants With Complete Remission Within 12 Weeks of Treatment Initiation

| | |
|---|---|
| End point title | Percentage of Participants With Complete Remission Within 12 Weeks of Treatment Initiation |

End point description:

Participants were evaluated for efficacy at the end of each treatment cycle via a central bone marrow aspiration and local peripheral blood counts.
Complete Remission (CR) was defined as having ≤ 5% blasts in the bone marrow, no evidence of disease, and full recovery of peripheral blood counts: platelets > 100,000/µl, and absolute neutrophil count (ANC) > 1,000/µl. CR must have occurred within 12 weeks of the first dose of therapy.

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

End point timeframe:

12 weeks

| **End point values** | Standard of Care Chemotherapy | Blinatumomab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 134 | 271 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 15.7 (10.0 to 23.0) | 33.6 (28.0 to 39.5) | | |

## Statistical analyses

| **Statistical analysis title** | PrimaryAnalysis of Complete Remission |
|---|---|
| Comparison groups | Standard of Care Chemotherapy v Blinatumomab |

| | |
|---|---|
| Number of subjects included in analysis | 405 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 [2] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Treatment Difference |
| Point estimate | 17.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 9.6 |
| upper limit | 26.2 |

Notes:

[2] - Adjusted for the stratification factors: age (< 35 vs. ≥ 35), prior salvage therapy (yes vs. no), and prior allogeneic HSCT (yes vs. no).

## Secondary: Percentage of Participants With Complete Remission/Complete Remission With Partial Hematological Recovery/Complete Remission With Incomplete Hematological Recovery (CR/CRh*/CRi) Within 12 Weeks of Treatment Initiation

| | |
|---|---|
| End point title | Percentage of Participants With Complete Remission/Complete Remission With Partial Hematological Recovery/Complete Remission With Incomplete Hematological Recovery (CR/CRh*/CRi) Within 12 Weeks of Treatment Initiation |

End point description:

Participants were evaluated for efficacy at the end of each treatment cycle via a central bone marrow aspiration and local peripheral blood counts.
Complete remission was defined as having ≤ 5% blasts in the bone marrow, no evidence of disease, and full recovery of peripheral blood counts: platelets > 100,000/µl, and ANC > 1,000/µl.
Complete Remission with partial hematological recovery (CRh*) was defined as ≤ 5% blasts in the bone marrow, no evidence of disease and partial recovery of peripheral blood counts: platelets > 50,000/µl, and ANC > 500/µl.
Complete remission with incomplete hematological recovery (CRi) was defined as ≤ 5% blasts in the bone marrow, no evidence of disease and incomplete recovery of peripheral blood counts: platelets > 100,000/µl or ANC > 1000 (but not both).

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

End point timeframe:

12 weeks

| End point values | Standard of Care Chemotherapy | Blinatumomab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 134 | 271 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 24.6 (17.6 to 32.8) | 43.9 (37.9 to 50.0) | | |

## Statistical analyses

| Statistical analysis title | Primary Analysis of CR/CRh*/CRi |
|---|---|
| Comparison groups | Standard of Care Chemotherapy v Blinatumomab |
| Number of subjects included in analysis | 405 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 [3] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Treatment Difference |
| Point estimate | 19.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 9.9 |
| upper limit | 28.7 |

Notes:

[3] - Adjusted for the stratification factors: age (< 35 vs. ≥ 35), prior salvage therapy (yes vs. no), and prior allogeneic HSCT (yes vs. no).

## Secondary: Event Free Survival (EFS) Rate at 6 Months

| End point title | Event Free Survival (EFS) Rate at 6 Months |
|---|---|

End point description:

Event free survival was defined as the time from randomization until a documented relapse after achieving CR/CRh*/CRi or death, whichever occurred first. Participants who failed to achieve a CR/CRh*/CRi within 12 weeks of treatment initiation were considered as non-responders and assigned an EFS duration of 1 day. Participants still alive and relapse-free were censored on their last disease assessment date.
A relapse event was any one of the following:
• Hematological relapse: proportion of blasts in bone marrow >5% or blasts in peripheral blood after documented CR or CRh* or CRi
• Progressive disease: An increase from baseline of at least 25% of bone marrow blasts or an absolute increase of at least 5,000 cells/µL in the number of circulating leukemia cells
• Extramedullary relapse: extramedullary lesion that is new or increased by 50% from nadir as assessed by Cheson criteria.

The Kaplan-Meier estimate of EFS at 6 months is reported.

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

End point timeframe:

6 months

| End point values | Standard of Care Chemotherapy | Blinatumomab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 134 | 271 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 13.3 (8.0 to 19.9) | 31.4 (25.8 to 37.1) | | |

## Statistical analyses

| Statistical analysis title | Primary Analysis of Event-free Survival |
|---|---|

Statistical analysis description:

The hazard ratio estimates were obtained from the Cox Proportional Hazard Model. A hazard ratio < 1.0 indicates a lower average event rate and a longer survival for Blinatumomab relative to SOC Chemotherapy.

| | |
|---|---|
| Comparison groups | Standard of Care Chemotherapy v Blinatumomab |
| Number of subjects included in analysis | 405 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 [4] |
| Method | Stratified log-rank test |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.57 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.44 |
| upper limit | 0.73 |

Notes:

[4] - Stratified by age (< 35 years; ≥ 35 years), prior salvage therapy (yes vs. no), and prior allogeneic HSCT (yes vs. no).

## Secondary: Duration of Complete Remission

| End point title | Duration of Complete Remission |
|---|---|

End point description:

Duration of complete remission, calculated only for participants who achieved a CR, was calculated from the date a CR was first achieved until the earliest date of a disease assessment indicating a relapse event or death, whichever occurred first. Participants who did not have a relapse event were censored on their last disease assessment date.

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

End point timeframe:

Up to the end of study (14 March 2017); median observation time was 10.8 months in the SOC group and 15.3 months in the blinatumomab group.

| End point values | Standard of Care Chemotherapy | Blinatumomab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 21[5] | 91[6] | | |
| Units: months | | | | |
| median (confidence interval 95%) | 7.8 (2.2 to 19.0) | 8.9 (6.0 to 10.7) | | |

Notes:

[5] - Participants with a best response of complete remission within 12 weeks of treatment initiation.

[6] - Participants with a best response of complete remission within 12 weeks of treatment initiation.

### Statistical analyses

No statistical analyses for this end point

## Secondary: Duration of Complete Remission/Complete Remission With Partial Hematological Recovery/Complete Remission With Incomplete Hematological

## Recovery (CR/CRh*/CRi)

| End point title | Duration of Complete Remission/Complete Remission With Partial Hematological Recovery/Complete Remission With Incomplete Hematological Recovery (CR/CRh*/CRi) |
|---|---|

End point description:

Duration of CR/CRh*/CRi, calculated only for participants who achieved a CR/CRh*/CRi, was calculated from the date a CR/CRh*/CRi was first achieved until the earliest date of a disease assessment indicating a relapse event or death, whichever occurred first. Participants who did not have a relapse event were censored on their last disease assessment date.

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

End point timeframe:

Up to the end of study (14 March 2017); median observation time was 10.8 months in the SOC group and 15.3 months in the blinatumomab group.

| End point values | Standard of Care Chemotherapy | Blinatumomab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 33[7] | 119[8] | | |
| Units: months | | | | |
| median (confidence interval 95%) | 5.4 (1.8 to 19.0) | 8.8 (6.0 to 10.2) | | |

Notes:

[7] - Participants with a best response of CR/CRh*/CRi within 12 weeks of treatment initiation.

[8] - Participants with a best response of CR/CRh*/CRi within 12 weeks of treatment initiation.

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants With Minimal Residual Disease (MRD) Within 12 Weeks of Treatment Initiation

| End point title | Percentage of Participants With Minimal Residual Disease (MRD) Within 12 Weeks of Treatment Initiation |
|---|---|

End point description:

Bone marrow samples were evaluated for MRD remission by a central laboratory. MRD remission was defined as the occurrence of an MRD level below 10^-4 measured by quantitative reverse transcription polymerase chain reaction (PCR) or flow cytometry.

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

End point timeframe:

12 weeks

| End point values | Standard of Care Chemotherapy | Blinatumomab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 134 | 271 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 14.2 (8.8 to 21.3) | 29.9 (24.5 to 35.7) | | |

**Statistical analyses**

| **Statistical analysis title** | Primary Analysis of MRD Response |
|---|---|
| Comparison groups | Standard of Care Chemotherapy v Blinatumomab |
| Number of subjects included in analysis | 405 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 [9] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Treatment Difference |
| Point estimate | 15.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 7.7 |
| upper limit | 23.7 |

Notes:

[9] - Stratified by age (<35 vs. ≥ 35), prior salvage therapy (yes vs. no), and prior alloHSCT (yes vs. no)

**Secondary: Percentage of Participants Who Received an Allogeneic Hematopoietic Stem Cell Transplant (HSCT)**

| End point title | Percentage of Participants Who Received an Allogeneic Hematopoietic Stem Cell Transplant (HSCT) |
|---|---|

End point description:

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

End point timeframe:

Up to the end of study; maximum time on study was 26 months.

| **End point values** | Standard of Care Chemotherapy | Blinatumomab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 134 | 271 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 23.9 (16.9 to 32.0) | 24.7 (19.7 to 30.3) | | |

**Statistical analyses**

| Statistical analysis title | Analysis of Postbaseline alloHSCT |
|---|---|
| Comparison groups | Standard of Care Chemotherapy v Blinatumomab |
| Number of subjects included in analysis | 405 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.81 [10] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Treatment Difference |
| Point estimate | 0.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -8 |
| upper limit | 9.7 |

Notes:

[10] - Stratified by age (< 35 years; ≥ 35 years), prior salvage therapy (yes vs. no), and prior allogeneic HSCT (yes vs. no).

## Secondary: Number of Participants With Adverse Events

| End point title | Number of Participants With Adverse Events |
|---|---|

End point description:

Adverse events (AEs) were graded for severity according to the CTCAE version 4.0, where Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.
Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care activities of daily living.
Grade 4: Life-threatening consequences; urgent intervention indicated. Grade 5: Death related to AE.
Treatment-related adverse events (TRAEs) were those assessed by the investigator as possibly related to blinatumomab based on response to the question: Is there a reasonable possibility that the event may have been caused by blinatumomab or other protocol-specified therapies/procedures?

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

End point timeframe:

From first dose of protocol-specified therapy until 30 days after the last dose; median duration of treatment was 5 days in the SOC group and 70 days in the blinatumomab group.

| End point values | Standard of Care Chemotherapy | Blinatumomab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 109[11] | 267[12] | | |
| Units: participants | | | | |
| Any adverse event | 108 | 263 | | |
| AE grade ≥ 2 | 106 | 256 | | |
| AE grade ≥ 3 | 100 | 231 | | |
| AE grade ≥ 4 | 67 | 135 | | |
| Serious adverse events | 49 | 168 | | |
| AEs leading to interruption of study drug | 6 | 72 | | |
| AEs leading to discontinuation of study drug | 10 | 42 | | |
| Life-threatening adverse events | 27 | 56 | | |
| Fatal adverse events | 20 | 52 | | |

| | | | | |
|---|---|---|---|---|
| Treatment-related adverse events | 92 | 214 | | |
| Treatment-related AE grade ≥ 2 | 89 | 195 | | |
| Treatment-related AE grade ≥ 3 | 78 | 144 | | |
| Treatment-related AE grade ≥ 4 | 51 | 59 | | |
| Serious treatment-related adverse events | 34 | 76 | | |
| TRAEs leading to interruption of study drug | 6 | 55 | | |
| TRAEs leading to discontinuation of study drug | 8 | 23 | | |
| Treatment-related life-threatening adverse events | 17 | 21 | | |
| Treatment-related fatal adverse events | 8 | 8 | | |

Notes:

[11] - Partipants who received protocol-specified therapy

[12] - Partipants who received protocol-specified therapy

### Statistical analyses

No statistical analyses for this end point

## Secondary: 100-Day Mortality After Allogeneic Hematopoietic Stem Cell Transplant

| End point title | 100-Day Mortality After Allogeneic Hematopoietic Stem Cell Transplant |
|---|---|

End point description:

The analysis of 100-day mortality after allogeneic HSCT was assessed for participants who achieved a best response of CR/CRh*CTi within 12 weeks of treatment initiation, who received an allogeneic HSCT and did not receive any additional anticancer treatment before the transplant. 100-day mortality after allogeneic HSCT was calculated relative to the date of allogeneic HSCT.
The 100-day mortality rate after allogeneic HSCT was defined as the percentage of participants having died up to 100 days after allogeneic HSCT estimated using the estimated time to death in percent calculated by Kaplan-Meier methods. Participants alive were censored on the last documented visit date or the date of the last phone contact when the patient was last known to have been alive.
"99999" indicates data not estimable.

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

End point timeframe:

100 days, from the date of allogeneic HSCT until the end of study

| **End point values** | Standard of Care Chemotherapy | Blinatumomab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 12[13] | 42[14] | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 0.0 (-99999 to 99999) | 12.3 (5.3 to 27.1) | | |

Notes:

[13] - Subjects with CR/CRh*/CRi within 12 weeks of treatment & no other anticancer therapy before alloHSCT

[14] - Subjects with CR/CRh*/CRi within 12 weeks of treatment & no other anticancer therapy before alloHSCT

### Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants With Anti-blinatumomab Antibodies

| End point title | Number of Participants With Anti-blinatumomab Antibodies[15] |
|---|---|

End point description:

Anti-blinatumomab binding antibodies were evaluated using a validated electrochemiluminescence (ECL)-based assay (binding assay). Samples positive for binding were analyzed using a cell-based bioassay to determine if the detected antibodies had neutralizing properties (neutralizing assay).

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

End point timeframe:

Samples were collected on day 29 at the end of cycle 2 and 30 days after the last dose of blinatumomab (median duration of treatment was 70 days).

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Analysis was only conducted in participants who received blinatumomab.

| **End point values** | Blinatumomab | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 171[16] | | | |
| Units: participants | | | | |
| Binding antibody positive | 5 | | | |
| Neutralizing antibody positive | 3 | | | |

Notes:

[16] - Participants who received blinatumomab with available post-baseline antibody data.

### Statistical analyses

No statistical analyses for this end point

## Secondary: Time to a 10-point Decrease From Baseline in Global Health Status and Quality of Life or Death

| End point title | Time to a 10-point Decrease From Baseline in Global Health Status and Quality of Life or Death |
|---|---|

End point description:

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) is a 30-item questionnaire that assesses the health related quality of life of cancer patients. The EORTC QLQ-C30 consists of a global health status/quality of life (QoL) scale, 5 functional scales, 3 symptom scales, and 6 single items.
The global health/QoL scale consists of 2 questions that ask participants to rate their overall health and overall quality of life durig the past week on a scale from 1 (very poor) to 7 (excellent). The scale score was derived as the sum of each score and transformed to a scale from 0 to 100 where higher scores represent a high QoL.
Time to a ≥10-point decrease from baseline GHS/QoL or death, whichever came first, was calculated from baseline. Participants still alive and without a 10-point decrease in GHS/QoL EORTC QLQ-C30 were censored on their last EORTC QLQ-C30 assessment date.

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

End point timeframe:

From randomization until the data cut-off date of 04 January 2016; EORTC QLQ-C30 was assessed on day 1, 8, 15, and 29 during cycle 1; days 1, 15, and 29 in cycle 2 and each consolidation cycle, and 30-days following the last dose of drug treatment.

| End point values | Standard of Care Chemotherapy | Blinatumomab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 95[17] | 247[18] | | |
| Units: months | | | | |
| median (confidence interval 95%) | 1.0 (0.5 to 1.5) | 1.7 (1.1 to 3.6) | | |

Notes:

[17] - Subjects with non-missing baseline and at least 1 postbaseline result of any QLQ-C30 scales/item

[18] - Subjects with non-missing baseline and at least 1 postbaseline result of any QLQ-C30 scales/item

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From first dose of protocol-specified therapy until 30 days after the last dose; median duration of treatment was 5 days in the SOC group and 70 days in the blinatumomab group.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 20.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Standard of Care Chemotherapy |

Reporting group description:

Participants received one of four prespecified, investigator-chosen chemotherapy regimens for 2 induction cycles. Participants who achieved a bone marrow response, CR/CRh*/CRi within 2 induction cycles of treatment could receive up to 3 additional consolidation cycles of SOC chemotherapy.
Participants who received 2 induction and up to 3 consolidation cycles of therapy and continued to have a bone marrow response or CR/CRh*/CRi could continue to receive SOC therapy for an additional 12 months.

| | |
|---|---|
| Reporting group title | Blinatumomab |

Reporting group description:

Participants received blinatumomab by continuous intravenous infusion (CIVI) over 4 weeks followed by a 2 week treatment-free interval for 2 induction cycles. Participants who achieved a bone marrow response, complete remission, or complete remission with partial or incomplete hematologic recovery (CR/CRh*/CRi) within 2 induction cycles of treatment could receive up to 3 additional consolidation cycles of blinatumomab.
Participants who received 2 induction and up to 3 consolidation cycles of therapy and continued to have a bone marrow response or CR/CRh*/CRi could continue to receive blinatumomab for an additional 12 months (4 cycles), where 1 cycle consisted of 4 weeks of CIVI followed by an 8-week treatment-free period.
The initial dose of blinatumomab was 9 µg/day for the first 7 days of treatment, increased to 28 µg/day starting on day 8 through day 29 and for all subsequent cycles.

| **Serious adverse events** | Standard of Care Chemotherapy | Blinatumomab | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 49 / 109 (44.95%) | 168 / 267 (62.92%) | |
| number of deaths (all causes) | 78 | 180 | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Acute lymphocytic leukaemia | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Chloroma | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Leukaemic infiltration extramedullary | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Leukaemic infiltration pulmonary | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tumour associated fever | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Aortic occlusion | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypotension | | | |
| subjects affected / exposed | 2 / 109 (1.83%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Shock | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgical and medical procedures | | | |
| Catheter placement | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration | | | |

| | | | |
|---|---|---|---|
| site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 2 / 267 (0.75%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Complication associated with device | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Death | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Discomfort | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General physical health deterioration | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 2 / 267 (0.75%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Hyperthermia | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Multiple organ dysfunction syndrome | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 4 / 267 (1.50%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 3 | |
| Oedema peripheral | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 16 / 267 (5.99%) | |
| occurrences causally related to treatment / all | 1 / 1 | 6 / 20 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Systemic inflammatory response syndrome | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| Acute graft versus host disease in skin | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anaphylactic shock | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cytokine release syndrome | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 7 / 267 (2.62%) | |
| occurrences causally related to treatment / all | 0 / 0 | 7 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Graft versus host disease | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Graft versus host disease in liver | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal | | | |

| | | | |
|---|---|---|---|
| disorders | | | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 2 / 267 (0.75%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 2 | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 2 / 267 (0.75%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 2 / 267 (0.75%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemoptysis | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 2 / 267 (0.75%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoxia | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung infiltration | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonitis | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pneumothorax | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 109 (0.92%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory arrest | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pulmonary oedema | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 2 / 267 (0.75%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Respiratory failure | | | |
| subjects affected / exposed | 2 / 109 (1.83%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 2 | 1 / 1 | |
| Stridor | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Completed suicide | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Mental status changes | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 2 / 267 (0.75%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood lactate dehydrogenase | | | |

| | | | |
|---|---|---|---|
| increased | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CSF cell count abnormal | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Platelet count decreased | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transaminases increased | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Weight increased | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| White blood cell count decreased | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| White blood cell count increased | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Accidental overdose | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 3 / 267 (1.12%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Ankle fracture | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 0 / 267 (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 | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Medication error | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Overdose | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 8 / 267 (3.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subdural haematoma | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subdural haemorrhage | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Congenital, familial and genetic disorders | | | |
| Aplasia | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| 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 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial flutter | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| 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 / 109 (0.92%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac tamponade | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cardiopulmonary failure | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 2 / 267 (0.75%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Pericardial effusion | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |

| | | | |
|---|---|---|---|
| Aphasia | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 3 / 267 (1.12%) | |
| occurrences causally related to treatment / all | 0 / 0 | 4 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ataxia | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cognitive disorder | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Depressed level of consciousness | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Encephalopathy | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 4 / 267 (1.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 4 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Generalised tonic-clonic seizure | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhage intracranial | | | |
| subjects affected / exposed | 2 / 109 (1.83%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Haemorrhagic stroke | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Hemianopia | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hemiparesis | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hemiplegia | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoaesthesia | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intention tremor | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Leukoencephalopathy | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neurological symptom | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Paraesthesia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Seizure | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sensory loss | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Somnolence | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Status epilepticus | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tremor | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Agranulocytosis | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile bone marrow aplasia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 12 / 109 (11.01%) | 24 / 267 (8.99%) | |
| occurrences causally related to treatment / all | 11 / 12 | 12 / 29 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Histiocytosis haematophagic | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 3 / 267 (1.12%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperleukocytosis | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Leukocytosis | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 2 / 267 (0.75%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Leukopenia | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lymphadenopathy | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenia | | | |
| subjects affected / exposed | 2 / 109 (1.83%) | 2 / 267 (0.75%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancytopenia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 109 (0.92%) | 4 / 267 (1.50%) | |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 2 / 267 (0.75%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colitis | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric haemorrhage | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 2 / 267 (0.75%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal inflammation | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal necrosis | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematemesis | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower gastrointestinal haemorrhage | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mouth haemorrhage | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Stomatitis | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 2 / 267 (0.75%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Acute hepatic failure | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholestasis | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 109 (0.92%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatitis | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin ulcer | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 2 / 109 (1.83%) | 3 / 267 (1.12%) | |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 3 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 1 | |
| Hydronephrosis | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ureterolithiasis | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary bladder haemorrhage | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 0 / 267 (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 | | | |

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|---|---|---|---|
| disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 2 / 267 (0.75%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bone pain | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 4 / 267 (1.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteitis | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Abscess fungal | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bacteraemia | | | |
| subjects affected / exposed | 3 / 109 (2.75%) | 2 / 267 (0.75%) | |
| occurrences causally related to treatment / all | 2 / 3 | 1 / 2 | |
| deaths causally related to treatment / all | 1 / 2 | 0 / 0 | |
| Bacterial infection | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 2 / 267 (0.75%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Bacterial sepsis | | | |
| subjects affected / exposed | 2 / 109 (1.83%) | 6 / 267 (2.25%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Brain abscess | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |

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|---|---|---|---|
| Bronchitis | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchopulmonary aspergillosis | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 4 / 267 (1.50%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 2 | |
| Catheter site infection | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 2 / 267 (0.75%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Citrobacter infection | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Central nervous system abscess | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Citrobacter sepsis | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device related infection | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 109 (0.92%) | 6 / 267 (2.25%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device related sepsis | | | |
| subjects affected / exposed | 2 / 109 (1.83%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Encephalitis enteroviral | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enterococcal bacteraemia | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enterococcal infection | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Escherichia infection | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 2 / 267 (0.75%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fungaemia | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fungal infection | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fungal sepsis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 109 (0.00%) | 2 / 267 (0.75%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Fusarium infection | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 2 / 267 (0.75%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatosplenic candidiasis | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infection | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infection in an immunocompromised host | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Influenza | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Lower respiratory tract infection fungal | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung infection | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Mastoiditis | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Meningitis bacterial | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mucormycosis | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Muscle abscess | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| 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 / 109 (0.92%) | 3 / 267 (1.12%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 2 | |
| Osteomyelitis | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Otitis media acute | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 2 / 109 (1.83%) | 10 / 267 (3.75%) | |
| occurrences causally related to treatment / all | 1 / 2 | 3 / 10 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 2 | |
| Pneumonia bacterial | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia fungal | | | |
| subjects affected / exposed | 2 / 109 (1.83%) | 2 / 267 (0.75%) | |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 2 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Pneumonia pseudomonal | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia respiratory syncytial viral | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Progressive multifocal leukoencephalopathy | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pseudomonal sepsis | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 3 / 267 (1.12%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pseudomonas infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 109 (0.92%) | 3 / 267 (1.12%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 3 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Pulmonary mycosis | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory syncytial virus bronchiolitis | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rhinovirus infection | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 7 / 109 (6.42%) | 13 / 267 (4.87%) | |
| occurrences causally related to treatment / all | 5 / 9 | 3 / 13 | |
| deaths causally related to treatment / all | 2 / 4 | 2 / 8 | |
| Sepsis syndrome | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Septic shock | | | |
| subjects affected / exposed | 3 / 109 (2.75%) | 8 / 267 (3.00%) | |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 6 | |
| Sinusitis | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Soft tissue infection | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Staphylococcal infection | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 3 / 267 (1.12%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Staphylococcal sepsis | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Streptococcal sepsis | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Systemic candida | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Tooth infection | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Varicella zoster virus infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 109 (0.00%) | 2 / 267 (0.75%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 2 / 267 (0.75%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperuricaemia | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 2 / 267 (0.75%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 2 / 267 (0.75%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypophosphataemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 109 (0.00%) | 2 / 267 (0.75%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lactic acidosis | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolic acidosis | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Tumour lysis syndrome | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 3 / 267 (1.12%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| **Non-serious adverse events** | Standard of Care Chemotherapy | Blinatumomab | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 106 / 109 (97.25%) | 251 / 267 (94.01%) | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 9 / 109 (8.26%) | 18 / 267 (6.74%) | |
| occurrences (all) | 9 | 20 | |
| Hypotension | | | |
| subjects affected / exposed | 11 / 109 (10.09%) | 33 / 267 (12.36%) | |
| occurrences (all) | 16 | 38 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 11 / 109 (10.09%) | 20 / 267 (7.49%) | |
| occurrences (all) | 15 | 32 | |
| Chest pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 6 / 109 (5.50%) | 6 / 267 (2.25%) | |
| occurrences (all) | 6 | 7 | |
| Chills | | | |
| subjects affected / exposed | 12 / 109 (11.01%) | 20 / 267 (7.49%) | |
| occurrences (all) | 16 | 24 | |
| Fatigue | | | |
| subjects affected / exposed | 14 / 109 (12.84%) | 36 / 267 (13.48%) | |
| occurrences (all) | 15 | 52 | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 14 / 109 (12.84%) | 9 / 267 (3.37%) | |
| occurrences (all) | 15 | 10 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 16 / 109 (14.68%) | 39 / 267 (14.61%) | |
| occurrences (all) | 20 | 52 | |
| Pain | | | |
| subjects affected / exposed | 6 / 109 (5.50%) | 16 / 267 (5.99%) | |
| occurrences (all) | 6 | 20 | |
| Pyrexia | | | |
| subjects affected / exposed | 48 / 109 (44.04%) | 153 / 267 (57.30%) | |
| occurrences (all) | 73 | 326 | |
| Immune system disorders | | | |
| Cytokine release syndrome | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 35 / 267 (13.11%) | |
| occurrences (all) | 0 | 42 | |
| Hypogammaglobulinaemia | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 19 / 267 (7.12%) | |
| occurrences (all) | 1 | 31 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 6 / 109 (5.50%) | 42 / 267 (15.73%) | |
| occurrences (all) | 7 | 52 | |
| Dyspnoea | | | |
| subjects affected / exposed | 8 / 109 (7.34%) | 16 / 267 (5.99%) | |
| occurrences (all) | 9 | 17 | |
| Epistaxis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 9 / 109 (8.26%) | 16 / 267 (5.99%) | |
| occurrences (all) | 10 | 17 | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 7 / 109 (6.42%) | 15 / 267 (5.62%) | |
| occurrences (all) | 8 | 16 | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 6 / 109 (5.50%) | 14 / 267 (5.24%) | |
| occurrences (all) | 6 | 14 | |
| Insomnia | | | |
| subjects affected / exposed | 10 / 109 (9.17%) | 31 / 267 (11.61%) | |
| occurrences (all) | 12 | 44 | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 11 / 109 (10.09%) | 24 / 267 (8.99%) | |
| occurrences (all) | 35 | 47 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 10 / 109 (9.17%) | 15 / 267 (5.62%) | |
| occurrences (all) | 24 | 31 | |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 9 / 109 (8.26%) | 10 / 267 (3.75%) | |
| occurrences (all) | 23 | 19 | |
| Platelet count decreased | | | |
| subjects affected / exposed | 13 / 109 (11.93%) | 18 / 267 (6.74%) | |
| occurrences (all) | 72 | 60 | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 11 / 109 (10.09%) | 10 / 267 (3.75%) | |
| occurrences (all) | 28 | 23 | |
| White blood cell count decreased | | | |
| subjects affected / exposed | 6 / 109 (5.50%) | 14 / 267 (5.24%) | |
| occurrences (all) | 12 | 38 | |
| Cardiac disorders | | | |
| Sinus tachycardia | | | |
| subjects affected / exposed | 6 / 109 (5.50%) | 15 / 267 (5.62%) | |
| occurrences (all) | 8 | 19 | |
| Tachycardia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 10 / 109 (9.17%) | 18 / 267 (6.74%) | |
| occurrences (all) | 10 | 30 | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 8 / 109 (7.34%) | 18 / 267 (6.74%) | |
| occurrences (all) | 8 | 20 | |
| Headache | | | |
| subjects affected / exposed | 32 / 109 (29.36%) | 79 / 267 (29.59%) | |
| occurrences (all) | 39 | 106 | |
| Somnolence | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 14 / 267 (5.24%) | |
| occurrences (all) | 1 | 20 | |
| Tremor | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 26 / 267 (9.74%) | |
| occurrences (all) | 0 | 35 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 46 / 109 (42.20%) | 68 / 267 (25.47%) | |
| occurrences (all) | 144 | 222 | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 36 / 109 (33.03%) | 48 / 267 (17.98%) | |
| occurrences (all) | 42 | 55 | |
| Neutropenia | | | |
| subjects affected / exposed | 31 / 109 (28.44%) | 51 / 267 (19.10%) | |
| occurrences (all) | 50 | 108 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 32 / 109 (29.36%) | 48 / 267 (17.98%) | |
| occurrences (all) | 108 | 114 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 19 / 109 (17.43%) | 16 / 267 (5.99%) | |
| occurrences (all) | 25 | 19 | |
| Constipation | | | |
| subjects affected / exposed | 28 / 109 (25.69%) | 35 / 267 (13.11%) | |
| occurrences (all) | 34 | 46 | |
| Diarrhoea | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 38 / 109 (34.86%) | 59 / 267 (22.10%) | |
| occurrences (all) | 49 | 75 | |
| Dyspepsia | | | |
| subjects affected / exposed | 7 / 109 (6.42%) | 10 / 267 (3.75%) | |
| occurrences (all) | 7 | 11 | |
| Haemorrhoids | | | |
| subjects affected / exposed | 7 / 109 (6.42%) | 7 / 267 (2.62%) | |
| occurrences (all) | 7 | 7 | |
| Nausea | | | |
| subjects affected / exposed | 46 / 109 (42.20%) | 51 / 267 (19.10%) | |
| occurrences (all) | 69 | 73 | |
| Proctalgia | | | |
| subjects affected / exposed | 7 / 109 (6.42%) | 2 / 267 (0.75%) | |
| occurrences (all) | 8 | 2 | |
| Stomatitis | | | |
| subjects affected / exposed | 14 / 109 (12.84%) | 17 / 267 (6.37%) | |
| occurrences (all) | 16 | 18 | |
| Vomiting | | | |
| subjects affected / exposed | 26 / 109 (23.85%) | 33 / 267 (12.36%) | |
| occurrences (all) | 40 | 37 | |
| Skin and subcutaneous tissue disorders | | | |
| Petechiae | | | |
| subjects affected / exposed | 6 / 109 (5.50%) | 7 / 267 (2.62%) | |
| occurrences (all) | 6 | 7 | |
| Rash | | | |
| subjects affected / exposed | 13 / 109 (11.93%) | 20 / 267 (7.49%) | |
| occurrences (all) | 15 | 24 | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 6 / 109 (5.50%) | 8 / 267 (3.00%) | |
| occurrences (all) | 8 | 8 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 5 / 109 (4.59%) | 17 / 267 (6.37%) | |
| occurrences (all) | 5 | 20 | |
| Back pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 10 / 109 (9.17%) | 34 / 267 (12.73%) | |
| occurrences (all) | 14 | 40 | |
| Myalgia | | | |
| subjects affected / exposed | 6 / 109 (5.50%) | 19 / 267 (7.12%) | |
| occurrences (all) | 7 | 21 | |
| Bone pain | | | |
| subjects affected / exposed | 8 / 109 (7.34%) | 29 / 267 (10.86%) | |
| occurrences (all) | 9 | 42 | |
| Pain in extremity | | | |
| subjects affected / exposed | 8 / 109 (7.34%) | 25 / 267 (9.36%) | |
| occurrences (all) | 8 | 39 | |
| Infections and infestations | | | |
| Bacteraemia | | | |
| subjects affected / exposed | 6 / 109 (5.50%) | 3 / 267 (1.12%) | |
| occurrences (all) | 7 | 4 | |
| Device related infection | | | |
| subjects affected / exposed | 5 / 109 (4.59%) | 14 / 267 (5.24%) | |
| occurrences (all) | 5 | 17 | |
| Oral herpes | | | |
| subjects affected / exposed | 9 / 109 (8.26%) | 15 / 267 (5.62%) | |
| occurrences (all) | 10 | 16 | |
| Pneumonia | | | |
| subjects affected / exposed | 14 / 109 (12.84%) | 7 / 267 (2.62%) | |
| occurrences (all) | 16 | 7 | |
| Sinusitis | | | |
| subjects affected / exposed | 6 / 109 (5.50%) | 6 / 267 (2.25%) | |
| occurrences (all) | 6 | 7 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 20 / 267 (7.49%) | |
| occurrences (all) | 1 | 29 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 109 (1.83%) | 15 / 267 (5.62%) | |
| occurrences (all) | 2 | 20 | |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 15 / 267 (5.62%) | |
| occurrences (all) | 0 | 17 | |

| | | | |
|---|---|---|---|
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 15 / 109 (13.76%) | 20 / 267 (7.49%) | |
| occurrences (all) | 15 | 24 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 9 / 109 (8.26%) | 21 / 267 (7.87%) | |
| occurrences (all) | 15 | 29 | |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 11 / 109 (10.09%) | 14 / 267 (5.24%) | |
| occurrences (all) | 14 | 27 | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 18 / 109 (16.51%) | 28 / 267 (10.49%) | |
| occurrences (all) | 20 | 37 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 30 / 109 (27.52%) | 46 / 267 (17.23%) | |
| occurrences (all) | 43 | 78 | |
| Hypocalcaemia | | | |
| subjects affected / exposed | 10 / 109 (9.17%) | 12 / 267 (4.49%) | |
| occurrences (all) | 14 | 14 | |
| Hypophosphataemia | | | |
| subjects affected / exposed | 6 / 109 (5.50%) | 12 / 267 (4.49%) | |
| occurrences (all) | 6 | 20 | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 15 September 2014 | - Clarify timing, scope, and applicability of study procedures to treatment arms<br>- Clarify criteria for discontinuation and withdrawal of blinatumomab-treated subjects, clarify terms and definitions used in protocol, clarify secondary endpoints and analyses, clarify study participation, clarify requirements for medical coverage and safety monitoring in an outpatient setting Increase the number of study centers globally<br>- Provide updated information on packaging, presentation, dose modifications, and overdose (> 10%) of blinatumomab<br>- Provide dose modification guidance for SOC chemotherapy regimen<br>- Update Amgen publication policy guidelines and team contact information to facilitate the enrollment of subjects, entry criteria were modified to allow for the screening of serum for potential drugs of abuse in subjects receiving hemodialysis with no urine output and to remove the requirement of "no detectable viral RNA" for subjects known to have had hepatitis C |
| 10 March 2015 | - Clarify protocol-required procedures<br>- Updates made to align with current Amgen protocol templates |
| 09 September 2015 | - Update pregnancy, lactation, and contraception requirements to align with blinatumomab core risk and discomfort language<br>- Provide clarification on study design, and procedures for bone marrow aspirates, vital signs, and long-term follow-up |
| 20 April 2016 | - Update contraception timeframes to align with blinatumomab core risk and discomfort language<br>- Update sponsor contact information and definition of adverse events to align with current protocol template language |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported