



Clinical trial results:

A Phase 2 Single Arm, Multicenter Trial to Evaluate the Efficacy of the BiTE® Antibody Blinatumomab in Adult Subjects With Relapsed/Refractory Philadelphia Positive B-precursor Acute Lymphoblastic Leukemia (Alcantara Study)

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2013-000706-36 |
| Trial protocol | IT GB DE |
| Global end of trial date | 06 January 2017 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 30 December 2017 |
| First version publication date | 30 December 2017 |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | 20120216 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02000427 |
| 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 | 06 January 2017 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|-----------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 06 January 2017 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate the rate of complete remission (CR)/complete remission with partial hematological recovery (CRh*) in adult subjects with relapsed/refractory Philadelphia chromosome (Ph)-positive B-precursor acute lymphoblastic leukemia (ALL).

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) and United States Food and Drug Administration regulations/guidelines. The study protocol and all amendments were reviewed by an independent ethics committee (IEC) or institutional review board (IRB).

Before a subject's participation in the clinical study, the investigator was responsible for obtaining written informed consent from the subject or legally acceptable representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any investigational products were administered.

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 | 18 Months |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | United States: 11 |
| Country: Number of subjects enrolled | Italy: 14 |
| Country: Number of subjects enrolled | France: 11 |
| Country: Number of subjects enrolled | Germany: 6 |
| Country: Number of subjects enrolled | United Kingdom: 3 |
| Worldwide total number of subjects | 45 |
| EEA total number of subjects | 34 |

Notes:

Subjects enrolled per age group

| | |
|--|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 | 0 |

| | |
|--|----|
| wk | |
| 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) | 33 |
| From 65 to 84 years | 12 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 19 centers in 4 European countries and the United States: 3 centers in France, 3 in Germany, 5 in Italy, 1 in the United Kingdom, and 7 in the United States.

The first participant enrolled on 03 January 2014 and the last participant enrolled on 12 January 2015.

Pre-assignment

Screening details:

This was a single-arm, Simon 2-stage design, multicenter study that consisted of a 3-week screening and prephase period for the administration of dexamethasone to reduce both tumor burden and the incidence of tumor lysis syndrome, an induction phase of 2 cycles of blinatumomab, a consolidation phase, and a long-term follow-up phase.

Period 1

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

Arms

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

Arm description:

Participants received blinatumomab by continuous intravenous (CIV) infusion over 4 weeks followed by a treatment-free interval of 2 weeks for 2 cycles. Participants who achieved a complete remission or complete remission with partial or incomplete hematologic recovery within 2 induction cycles of treatment could receive up to 3 additional consolidation cycles of blinatumomab.

The initial dose was 9 µg/day for the first 7 days of treatment, increased to 28 µg/day starting on day 8 and for all subsequent cycles of treatment.

| | |
|--|----------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Blinatumomab |
| Investigational medicinal product code | MT103 |
| Other name | AMG 103 Blincyto® |
| 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). A single cycle of blinatumomab treatment is 6 weeks in duration, which includes 4 weeks of blinatumomab followed by a 2-week treatment-free interval.

| Number of subjects in period 1 | Blinatumomab |
|--------------------------------|--------------|
| Started | 45 |
| Completed | 8 |
| Not completed | 37 |
| Death | 37 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---------------|
| Reporting group title | Overall Study |
|-----------------------|---------------|

Reporting group description:

Participants received blinatumomab by continuous intravenous (CIV) infusion over 4 weeks followed by a treatment-free interval of 2 weeks for 2 cycles. Participants who achieved a complete remission or complete remission with partial or incomplete hematologic recovery within 2 induction cycles of treatment could receive up to 3 additional consolidation cycles of blinatumomab.

The initial dose was 9 µg/day for the first 7 days of treatment, increased to 28 µg/day starting on day 8 and for all subsequent cycles of treatment.

| Reporting group values | Overall Study | Total | |
|---|---------------|-------|--|
| Number of subjects | 45 | 45 | |
| Age Categorical | | | |
| Units: Subjects | | | |
| 18 to < 35 years | 5 | 5 | |
| 35 to < 55 years | 17 | 17 | |
| 55 to < 65 years | 11 | 11 | |
| ≥ 65 years | 12 | 12 | |
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 52.8 | | |
| standard deviation | ± 15.0 | - | |
| Gender Categorical | | | |
| Units: Subjects | | | |
| Female | 21 | 21 | |
| Male | 24 | 24 | |
| Ethnicity | | | |
| Units: Subjects | | | |
| Hispanic/Latino | 2 | 2 | |
| not Hispanic/Latino | 43 | 43 | |
| Race | | | |
| Units: Subjects | | | |
| White | 39 | 39 | |
| Asian | 1 | 1 | |
| Black (or African American) | 3 | 3 | |
| Other | 2 | 2 | |
| Prior Tyrosine Kinase Inhibitor (TKI) Treatment | | | |
| Units: Subjects | | | |
| 1 TKI | 7 | 7 | |
| 2 TKIs | 21 | 21 | |
| 3 TKIs | 13 | 13 | |
| 4 TKIs | 4 | 4 | |
| Number of Prior Relapses | | | |
| Units: Subjects | | | |
| No relapses | 3 | 3 | |
| 1 relapse | 25 | 25 | |
| 2 relapses | 13 | 13 | |

| | | | |
|---|--------|----|--|
| ≥ 3 relapses | 4 | 4 | |
| Number of Prior Salvage Regimens | | | |
| Units: Subjects | | | |
| No prior regimens | 14 | 14 | |
| 1 prior regimen | 12 | 12 | |
| 2 prior regimens | 11 | 11 | |
| ≥ 3 prior regimens | 8 | 8 | |
| Prior Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) | | | |
| Units: Subjects | | | |
| Yes | 20 | 20 | |
| No | 25 | 25 | |
| Time From Initial Diagnosis | | | |
| Units: months | | | |
| arithmetic mean | 27.3 | | |
| standard deviation | ± 26.1 | - | |

End points

End points reporting groups

| | |
|---|--------------|
| Reporting group title | Blinatumomab |
| Reporting group description: | |
| Participants received blinatumomab by continuous intravenous (CIV) infusion over 4 weeks followed by a treatment-free interval of 2 weeks for 2 cycles. Participants who achieved a complete remission or complete remission with partial or incomplete hematologic recovery within 2 induction cycles of treatment could receive up to 3 additional consolidation cycles of blinatumomab. The initial dose was 9 µg/day for the first 7 days of treatment, increased to 28 µg/day starting on day 8 and for all subsequent cycles of treatment. | |

Primary: Percentage of Participants With Complete Remission/Complete Remission With Partial Hematological Recovery (CR/CRh*) During the First Two Treatment Cycles

| | |
|-----------------|--|
| End point title | Percentage of Participants With Complete Remission/Complete Remission With Partial Hematological Recovery (CR/CRh*) During the First Two Treatment Cycles ^[1] |
|-----------------|--|

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 meeting all 3 of the following criteria:

- less than or equal to 5% blasts in the bone marrow;
- no evidence of disease
- full recovery of peripheral blood counts: platelets > 100,000/µl, and absolute neutrophil count (ANC) > 1000/µl.

Complete remission with partial hematological recovery (CRh*) was defined as meeting all 3 of the following criteria:

- less than or equal to 5% blasts in the bone marrow
- no evidence of disease
- partial recovery of peripheral blood counts: platelets > 50,000/µl, and ANC > 500/µl.

The analysis was based on the full analysis set which included all participants who received an infusion of blinatumomab. Participants without a post-baseline disease assessment were considered non-responders.

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

End point timeframe:

Approximately 12 weeks

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical analyses were not performed in this single-arm study.

| End point values | Blinatumomab | | | |
|-----------------------------------|---------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 45 | | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 35.6 (21.9 to 51.2) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Minimal Residual Disease (MRD) Remission During the First 2 Cycles of Treatment

| | |
|--|---|
| End point title | Percentage of Participants With Minimal Residual Disease (MRD) Remission During the First 2 Cycles of Treatment |
| End point description: Bone marrow samples were evaluated for MRD remission by a central laboratory using bcr-abl fusion gene reverse transcription polymerase chain reaction (RT-PCR). An MRD response was defined as MRD < 10 ⁻⁴ measured by PCR. The analysis was based on the full analysis set. Participants with no post-baseline MRD assessment were considered non-responders. | |
| End point type | Secondary |
| End point timeframe: Approximately 12 weeks | |

| | | | | |
|-----------------------------------|---------------------|--|--|--|
| End point values | Blinatumomab | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 45 | | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 40.0 (25.7 to 55.7) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of CR or CRh* Response

| | |
|---|---------------------------------|
| End point title | Duration of CR or CRh* Response |
| End point description: Duration of response was measured for participants in remission (CR/CRh*), and was measured from the time the participant first achieved remission until first documented relapse or death from disease progression. Participants without a documented relapse (hematological or extramedullary) and who did not die were censored at the time of the last bone marrow assessment or the last survival follow-up visit to confirm remission. Participants who died without having reported hematological relapse or without showing any clinical sign of disease progression were censored on their date of death. The analysis was based on the full analysis set with a CR or CRh* response during the first 2 treatment cycles. "99999" indicates data that could not be estimated. | |
| End point type | Secondary |
| End point timeframe: Up to the final analysis cut-off date; median observation time was 16.1 months | |

| | | | | |
|----------------------------------|--------------------|--|--|--|
| End point values | Blinatumomab | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 16 | | | |
| Units: months | | | | |
| median (confidence interval 95%) | 6.8 (4.5 to 99999) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Complete Remission (CR) During the First Two Treatment Cycles

| | |
|-----------------|---|
| End point title | Percentage of Participants With Complete Remission (CR) During the First Two Treatment Cycles |
|-----------------|---|

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 meeting all 3 of the following criteria:

- less than or equal to 5% blasts in the bone marrow;
- no evidence of disease;
- full recovery of peripheral blood counts: platelets > 100,000/ μ l, and absolute neutrophil count (ANC) > 1000/ μ l.

The analysis was based on the full analysis set. Participants without a post-baseline disease assessment were considered non-responders.

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

End point timeframe:

Approximately 12 weeks

| | | | | |
|-----------------------------------|---------------------|--|--|--|
| End point values | Blinatumomab | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 45 | | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 31.1 (18.2 to 46.6) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Complete Remission With Partial Hematological Recovery (CRh*) During the First Two Treatment Cycles

| | |
|-----------------|---|
| End point title | Percentage of Participants With Complete Remission With Partial Hematological Recovery (CRh*) During the First Two Treatment Cycles |
|-----------------|---|

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 with partial hematological recovery (CRh*) was defined as meeting all 3 of the following criteria:

- less than or equal to 5% blasts in the bone marrow;
- no evidence of disease;

- partial recovery of peripheral blood counts: platelets > 50,000/ μ l, and ANC > 500/ μ l.
- The analysis was based on the full analysis set. Participants without a post-baseline disease assessment were considered non-responders.

| | |
|------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Approximately 12 weeks | |

| | | | | |
|-----------------------------------|-------------------|--|--|--|
| End point values | Blinatumomab | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 45 | | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 4.4 (0.5 to 15.1) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Complete Remission/Complete Remission With Partial Hematological Recovery/Complete Remission With Incomplete Hematological Recovery (CR/CRh*/CRI) During the First Two Treatment Cycles

| | |
|-----------------|---|
| End point title | Percentage of Participants With Complete Remission/Complete Remission With Partial Hematological Recovery/Complete Remission With Incomplete Hematological Recovery (CR/CRh*/CRI) During the First Two Treatment Cycles |
|-----------------|---|

End point description:

Complete remission was defined as meeting the following criteria:

- less than or equal to 5% blasts in the bone marrow;
- no evidence of disease;
- full recovery of peripheral blood counts: platelets > 100,000/ μ l, and ANC > 1000/ μ l.

Complete remission with partial hematological recovery was defined as meeting the following criteria:

- less than or equal to 5% blasts in the bone marrow;
- no evidence of disease;
- partial recovery of peripheral blood counts: platelets > 50,000/ μ l, and ANC > 500/ μ l.

Complete remission with incomplete hematologic recovery was defined as meeting all of the following criteria:

- less than or equal to 5% blasts in the bone marrow;
- no evidence of disease;
- incomplete recovery of peripheral blood counts: platelets > 100,000/ μ l or ANC > 1000/ μ l.

The analysis was based on the full analysis set. Participants without a post-baseline disease assessment were considered non-responders.

| | |
|------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Approximately 12 weeks | |

| | | | | |
|-----------------------------------|---------------------|--|--|--|
| End point values | Blinatumomab | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 45 | | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 40.0 (25.7 to 55.7) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

| | |
|-----------------|------------------|
| End point title | Overall Survival |
|-----------------|------------------|

End point description:

Overall survival was assessed from the date the participant received the first infusion of blinatumomab until death from any cause or the date of the last follow-up.

Participants still alive at the data cut-off date were censored on the last documented visit date or the date of the last contact when the patient was last known to have been alive.

The analysis was based on the full analysis set.

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

End point timeframe:

From first dose of blinatumomab until the final analysis data cut-off date; median observation time was 25.1 months.

| | | | | |
|----------------------------------|-------------------|--|--|--|
| End point values | Blinatumomab | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 45 | | | |
| Units: months | | | | |
| median (confidence interval 95%) | 9.0 (5.7 to 13.5) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Received an Allogeneic Hematopoietic Stem Cell Transplant (HSCT) During Blinatumomab Induced Remission

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

End point description:

Participants who achieved remission (CR/CRh*) during the first 2 cycles of treatment and received an allogeneic HSCT.

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

End point timeframe:

Up to the final analysis data cut-off date; maximum duration on study was 26.1 months.

| | | | | |
|-----------------------------------|---------------------|--|--|--|
| End point values | Blinatumomab | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 16 | | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 43.8 (19.8 to 70.1) | | | |

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 received an allogeneic HSCT while in remission (CR/CRh*) after 2 cycles of blinatumomab treatment and did not receive any additional antileukemic treatment. 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.

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

End point timeframe:

From the date of allogeneic HSCT until the final analysis data cut-off date; maximum observation time was 16.9 months.

| | | | | |
|-----------------------------------|--------------------|--|--|--|
| End point values | Blinatumomab | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 4 | | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 25.0 (3.9 to 87.2) | | | |

Statistical analyses

No statistical analyses for this end point

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 the first dose of blinatumomab until 30 days after the last dose; the median duration of treatment was 53.8 days.

| End point values | Blinatumomab | | | |
|---|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 45 | | | |
| Units: participants | | | | |
| Any adverse event | 45 | | | |
| AE grade ≥ 3 | 38 | | | |
| AE grade ≥ 4 | 18 | | | |
| Serious adverse events | 28 | | | |
| Leading to discontinuation of blinatumomab | 3 | | | |
| Leading to interruption of blinatumomab | 17 | | | |
| Fatal adverse events | 5 | | | |
| Treatment-related adverse events | 41 | | | |
| Treatment-related AE grade ≥ 3 | 20 | | | |
| Treatment-related AE grade ≥ 4 | 7 | | | |
| Treatment-related serious adverse events | 12 | | | |
| TRAE leading to discontinuation of blinatumomab | 2 | | | |
| TRAE leading to interruption of blinatumomab | 12 | | | |
| Treatment-related fatal adverse events | 1 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Developed Anti-blinatumomab Antibodies

| | |
|-----------------|---|
| End point title | Number of Participants Who Developed Anti-blinatumomab Antibodies |
|-----------------|---|

End point description:

Anti-blinatumomab binding antibodies were evaluated with a validated blinatumomab anti-drug antibody assay with the electrochemiluminescence detection technology.

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Day 29 of each treatment period and 30 days after the last dose | |

| | | | | |
|-----------------------------|-------------------|--|--|--|
| End point values | Blinatumomab | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 31 ^[2] | | | |
| Units: participants | | | | |
| number (not applicable) | 0 | | | |

Notes:

[2] - Participants with available post-baseline antibody results

Statistical analyses

No statistical analyses for this end point

Secondary: Steady State Concentration of Blinatumomab

| | |
|------------------------|--|
| End point title | Steady State Concentration of Blinatumomab |
| End point description: | |

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Cycle 1, day 8, 6 to 8 hours after the dose step to 28 µg/day, and Cycle 2, day 1, 6 to 8 hours after blinatumomab infusion | |

| | | | | |
|---|-------------------|--|--|--|
| End point values | Blinatumomab | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 28 ^[3] | | | |
| Units: pg/mL | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Cycle 1 | 452 (± 122.0) | | | |
| Cycle 2 (N = 20) | 598 (± 102.7) | | | |

Notes:

[3] - Participants with available serum concentration data

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first dose of blinatumomab until 30 days after the last dose; the median duration of treatment was 53.8 days.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 19.1 |
|--------------------|------|

Reporting groups

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

Reporting group description:

Participants received blinatumomab by continuous intravenous (CIV) infusion over 4 weeks followed by a treatment-free interval of 2 weeks for 2 cycles. Participants who achieved a complete remission or complete remission with partial or incomplete hematologic recovery within 2 induction cycles of treatment could receive up to 3 additional consolidation cycles of blinatumomab.

The initial dose was 9 µg/day for the first 7 days of treatment, increased to 28 µg/day starting on day 8 and for all subsequent cycles of treatment.

| Serious adverse events | Blinatumomab | | |
|--|------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 28 / 45 (62.22%) | | |
| number of deaths (all causes) | 37 | | |
| number of deaths resulting from adverse events | | | |
| General disorders and administration site conditions | | | |
| General physical health deterioration | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Multiple organ dysfunction syndrome | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 2 / 45 (4.44%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pyrexia | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 2 / 45 (4.44%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Immune system disorders | | | |
| Acute graft versus host disease | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cytokine release syndrome | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Alveolitis | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary haemorrhage | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory failure | | | |
| subjects affected / exposed | 2 / 45 (4.44%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Product issues | | | |
| Device infusion issue | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Device malfunction | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|----------------|--|--|
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Chest X-ray abnormal | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Femur fracture | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Overdose | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Congenital, familial and genetic disorders | | | |
| Aplasia | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Aphasia | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cerebral haemorrhage | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 45 (2.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Depressed level of consciousness | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Encephalopathy | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hemiplegia | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Spinal cord compression | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tremor | | | |
| subjects affected / exposed | 3 / 45 (6.67%) | | |
| occurrences causally related to treatment / all | 3 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 4 / 45 (8.89%) | | |
| occurrences causally related to treatment / all | 3 / 7 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Leukocytosis | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 2 / 45 (4.44%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lymph node pain | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lymphoblastosis | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pancytopenia | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Colitis | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nausea | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| Hepatic failure | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue | | | |

| | | | | |
|---|----------------|--|--|--|
| disorders | | | | |
| Arthritis | | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Bone pain | | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Myalgia | | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infections and infestations | | | | |
| Catheter site infection | | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Device related infection | | | | |
| subjects affected / exposed | 3 / 45 (6.67%) | | | |
| occurrences causally related to treatment / all | 1 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Lung infection | | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Neutropenic sepsis | | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pneumonia | | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |

| | | | |
|---|----------------|--|--|
| Sepsis | | | |
| subjects affected / exposed | 3 / 45 (6.67%) | | |
| occurrences causally related to treatment / all | 1 / 3 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Septic shock | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 1 / 1 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tumour lysis syndrome | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | Blinatumomab | | |
|---|-------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 45 / 45 (100.00%) | | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 4 / 45 (8.89%) | | |
| occurrences (all) | 4 | | |
| Hypotension | | | |
| subjects affected / exposed | 6 / 45 (13.33%) | | |
| occurrences (all) | 7 | | |
| General disorders and administration site conditions | | | |

| | | | |
|---|------------------|--|--|
| Asthenia | | | |
| subjects affected / exposed | 6 / 45 (13.33%) | | |
| occurrences (all) | 8 | | |
| Chest pain | | | |
| subjects affected / exposed | 5 / 45 (11.11%) | | |
| occurrences (all) | 5 | | |
| Chills | | | |
| subjects affected / exposed | 4 / 45 (8.89%) | | |
| occurrences (all) | 4 | | |
| Fatigue | | | |
| subjects affected / exposed | 6 / 45 (13.33%) | | |
| occurrences (all) | 6 | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 8 / 45 (17.78%) | | |
| occurrences (all) | 9 | | |
| Pain | | | |
| subjects affected / exposed | 8 / 45 (17.78%) | | |
| occurrences (all) | 9 | | |
| Pyrexia | | | |
| subjects affected / exposed | 26 / 45 (57.78%) | | |
| occurrences (all) | 57 | | |
| Immune system disorders | | | |
| Cytokine release syndrome | | | |
| subjects affected / exposed | 3 / 45 (6.67%) | | |
| occurrences (all) | 3 | | |
| Hypogammaglobulinaemia | | | |
| subjects affected / exposed | 3 / 45 (6.67%) | | |
| occurrences (all) | 3 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 5 / 45 (11.11%) | | |
| occurrences (all) | 8 | | |
| Dyspnoea | | | |
| subjects affected / exposed | 6 / 45 (13.33%) | | |
| occurrences (all) | 8 | | |
| Epistaxis | | | |

| | | | |
|--|----------------------|--|--|
| subjects affected / exposed occurrences (all) | 5 / 45 (11.11%) 5 | | |
| Psychiatric disorders | | | |
| Confusional state | | | |
| subjects affected / exposed | 5 / 45 (11.11%) | | |
| occurrences (all) | 7 | | |
| Insomnia | | | |
| subjects affected / exposed | 3 / 45 (6.67%) | | |
| occurrences (all) | 3 | | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 5 / 45 (11.11%) | | |
| occurrences (all) | 12 | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 6 / 45 (13.33%) | | |
| occurrences (all) | 10 | | |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 3 / 45 (6.67%) | | |
| occurrences (all) | 3 | | |
| Blood calcium decreased | | | |
| subjects affected / exposed | 3 / 45 (6.67%) | | |
| occurrences (all) | 3 | | |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 3 / 45 (6.67%) | | |
| occurrences (all) | 7 | | |
| Tachycardia | | | |
| subjects affected / exposed | 4 / 45 (8.89%) | | |
| occurrences (all) | 4 | | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 4 / 45 (8.89%) | | |
| occurrences (all) | 4 | | |
| Headache | | | |
| subjects affected / exposed | 15 / 45 (33.33%) | | |
| occurrences (all) | 24 | | |

| | | | |
|---|------------------------|--|--|
| Paraesthesia subjects affected / exposed occurrences (all) | 6 / 45 (13.33%) 8 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia subjects affected / exposed occurrences (all) | 12 / 45 (26.67%) 24 | | |
| Febrile neutropenia subjects affected / exposed occurrences (all) | 15 / 45 (33.33%) 23 | | |
| Neutropenia subjects affected / exposed occurrences (all) | 3 / 45 (6.67%) 5 | | |
| Thrombocytopenia subjects affected / exposed occurrences (all) | 10 / 45 (22.22%) 21 | | |
| Gastrointestinal disorders | | | |
| Constipation subjects affected / exposed occurrences (all) | 7 / 45 (15.56%) 7 | | |
| Abdominal pain subjects affected / exposed occurrences (all) | 3 / 45 (6.67%) 3 | | |
| Diarrhoea subjects affected / exposed occurrences (all) | 9 / 45 (20.00%) 9 | | |
| Haemorrhoids subjects affected / exposed occurrences (all) | 3 / 45 (6.67%) 3 | | |
| Nausea subjects affected / exposed occurrences (all) | 6 / 45 (13.33%) 10 | | |
| Vomiting subjects affected / exposed occurrences (all) | 5 / 45 (11.11%) 7 | | |
| Skin and subcutaneous tissue disorders | | | |

| | | | |
|--|-----------------------|--|--|
| Erythema subjects affected / exposed occurrences (all) | 5 / 45 (11.11%) 5 | | |
| Hyperhidrosis subjects affected / exposed occurrences (all) | 3 / 45 (6.67%) 3 | | |
| Petechiae subjects affected / exposed occurrences (all) | 4 / 45 (8.89%) 4 | | |
| Pruritus subjects affected / exposed occurrences (all) | 3 / 45 (6.67%) 3 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia subjects affected / exposed occurrences (all) | 4 / 45 (8.89%) 5 | | |
| Back pain subjects affected / exposed occurrences (all) | 4 / 45 (8.89%) 8 | | |
| Bone pain subjects affected / exposed occurrences (all) | 8 / 45 (17.78%) 12 | | |
| Musculoskeletal pain subjects affected / exposed occurrences (all) | 5 / 45 (11.11%) 5 | | |
| Pain in extremity subjects affected / exposed occurrences (all) | 3 / 45 (6.67%) 3 | | |
| Infections and infestations | | | |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 3 / 45 (6.67%) 3 | | |
| Staphylococcal infection subjects affected / exposed occurrences (all) | 3 / 45 (6.67%) 3 | | |
| Urinary tract infection | | | |

| | | | |
|--|---------------------|--|--|
| subjects affected / exposed occurrences (all) | 4 / 45 (8.89%) 4 | | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 3 / 45 (6.67%) | | |
| occurrences (all) | 3 | | |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 3 / 45 (6.67%) | | |
| occurrences (all) | 8 | | |
| Hypocalcaemia | | | |
| subjects affected / exposed | 3 / 45 (6.67%) | | |
| occurrences (all) | 3 | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 8 / 45 (17.78%) | | |
| occurrences (all) | 11 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--|
| 27 June 2013 | Added an external independent data monitoring committee (DMC) to oversee the interim analysis and assess safety approximately every 6 months provided an adequate enrollment rate. |
| 15 September 2014 | <ul style="list-style-type: none">- Clarified timing and scope of study procedures- Specified that tyrosine kinase inhibitor therapy within 2 weeks before start of blinatumomab was not exclusionary, but was to be completed before start of treatment- Provided updated information on packaging and presentation of blinatumomab investigational product- Replaced the term "CNS events" with the term "neurologic events" throughout to describe clinically relevant neurologic events associated with introduction to blinatumomab- Provided instructions on blinatumomab overdose reporting (> 10%) as a serious adverse event under the criterion of "other medically important serious event"- Clarified requirements for medical coverage and safety monitoring in the outpatient setting- Provided specific guidance for blinatumomab dose modifications from grade 3 infection events- Clarified criteria for discontinuation of blinatumomab and withdrawal of subjects- Clarified definitions for evaluation of treatment response- Clarified objectives, endpoints, and scope of statistical analyses |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported