



Clinical trial results:

A Phase 2/3 Multicenter Study to Evaluate the Safety and Efficacy of Blinatumomab in Subjects With Relapsed/Refractory Aggressive B-cell Non Hodgkin Lymphoma

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2016-002044-16 |
| Trial protocol | GB BE ES IT |
| Global end of trial date | 12 March 2020 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 10 March 2021 |
| First version publication date | 10 March 2021 |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | 20150292 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02910063 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Amgen Inc. |
| Sponsor organisation address | One Amgen Center Drive, Thousand Oaks, CA, United States, |
| Public contact | IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, medinfo@amgen.com |
| Scientific contact | IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, medinfo@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 | 12 March 2020 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 12 March 2020 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

The main objective of this trial was to estimate the complete metabolic response (CMR) rate after blinatumomab monotherapy administered in the second salvage treatment of transplant-eligible participants with relapsed/refractory (R/R) aggressive B cell non Hodgkin lymphoma who have not achieved CMR after standard platinum based first salvage chemotherapy.

Protection of trial subjects:

This study was conducted in accordance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) and other regulations/guidelines as applicable.

Background therapy: -

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 23 January 2017 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Belgium: 3 |
| Country: Number of subjects enrolled | Italy: 7 |
| Country: Number of subjects enrolled | Spain: 3 |
| Country: Number of subjects enrolled | United Kingdom: 8 |
| Country: Number of subjects enrolled | United States: 6 |
| Country: Number of subjects enrolled | Australia: 14 |
| Worldwide total number of subjects | 41 |
| EEA total number of subjects | 13 |

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) | 33 |
| From 65 to 84 years | 8 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at 19 research centers in Australia, Belgium, Italy, Spain, the United Kingdom, and the United States from 23 January 2017 to 15 January 2018.

Pre-assignment

Screening details:

Phase 3 part of the study was not initiated after Phase 2 data was reviewed. No participants were screened or enrolled for Phase 3.

Period 1

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

Arms

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

Arm description:

Phase 2: Participants entered a single 70-day dose step cycle, and received a total of 56 days of blinatumomab continuous infusion which was administered as 7 days at 9 microgram (µg)/day, 7 days at 28 µg/day, and 42 days at 112 µg/day, followed by a treatment-free period of 14 days. Eligible participants could then enter an optional Cycle 2, 2 to 4 weeks after the end of the previous cycle. The optional Cycle 2 consisted of a 28-day cycle of blinatumomab continuous infusion administered as 7 days at 9 µg/day, 7 days at 28 µg/day, and 14 days at 112 µg/day.

Phase 3: The decision made to not proceed with Phase 3 and no participants were enrolled.

| | |
|--|-----------------|
| Arm type | Experimental |
| Investigational medicinal product name | Blinatumomab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Participants received doses ranging from 9 µg/day to 112 µg/day. Blinatumomab was administered as an intravenous (IV) infusion.

| Number of subjects in period 1 | Blinatumomab |
|--------------------------------|------------------|
| Started | 41 |
| Started Phase 2 | 41 |
| Started Cycle 1 | 41 |
| Started Optional Cycle 2 | 4 ^[1] |
| Started Phase 3 | 0 ^[2] |
| Completed | 13 |
| Not completed | 28 |
| Adverse event, serious fatal | 24 |
| Consent withdrawn by subject | 3 |

| | |
|-------------------|---|
| Lost to follow-up | 1 |
|-------------------|---|

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Cycle 2 was an optional cycle that participants did not need to complete to complete the overall study. Phase 3 part of the study was not initiated after Phase 2 data was reviewed. No participants were screened or enrolled for Phase 3.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Cycle 2 was an optional cycle that participants did not need to complete to complete the overall study. Phase 3 part of the study was not initiated after Phase 2 data was reviewed. No participants were screened or enrolled for Phase 3.

Baseline characteristics

Reporting groups

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

Reporting group description: -

| Reporting group values | Overall Study | Total | |
|---|---------------|-------|--|
| Number of subjects | 41 | 41 | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 33 | 33 | |
| From 65-84 years | 8 | 8 | |
| 85 years and over | 0 | 0 | |
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 54.7 | | |
| standard deviation | ± 12.4 | - | |
| Sex: Female, Male | | | |
| Units: | | | |
| Female | 13 | 13 | |
| Male | 28 | 28 | |
| Ethnicity (NIH/OMB) | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 6 | 6 | |
| Not Hispanic or Latino | 35 | 35 | |
| Unknown or Not Reported | 0 | 0 | |
| Race (NIH/OMB) | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | |
| Asian | 1 | 1 | |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | |
| Black or African American | 1 | 1 | |
| White | 38 | 38 | |
| More than one race | 0 | 0 | |
| Unknown or Not Reported | 1 | 1 | |

End points

End points reporting groups

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

Reporting group description:

Phase 2: Participants entered a single 70-day dose step cycle, and received a total of 56 days of blinatumomab continuous infusion which was administered as 7 days at 9 microgram (μg)/day, 7 days at 28 μg /day, and 42 days at 112 μg /day, followed by a treatment-free period of 14 days. Eligible participants could then enter an optional Cycle 2, 2 to 4 weeks after the end of the previous cycle. The optional Cycle 2 consisted of a 28-day cycle of blinatumomab continuous infusion administered as 7 days at 9 μg /day, 7 days at 28 μg /day, and 14 days at 112 μg /day.

Phase 3: The decision made to not proceed with Phase 3 and no participants were enrolled.

| | |
|----------------------------|--|
| Subject analysis set title | Phase 2: Blinatumomab 9 μg /day |
| Subject analysis set type | Full analysis |

Subject analysis set description:

All participants who received blinatumomab 9 μg /day continuous infusion which was administered for 7 days of in Week 1 of Cycle 1 (Cycle 1 was 70 days in length).

| | |
|----------------------------|---|
| Subject analysis set title | Phase 2: Blinatumomab 28 μg /day |
| Subject analysis set type | Full analysis |

Subject analysis set description:

All participants who received blinatumomab 28 μg /day continuous infusion which was administered for 7 days in Week 2 of Cycle 1 (Cycle 1 was 70 days in length).

| | |
|----------------------------|--|
| Subject analysis set title | Phase 2: Blinatumomab 112 μg /day |
| Subject analysis set type | Full analysis |

Subject analysis set description:

All participants who received blinatumomab 112 μg /day continuous infusion which was administered for 7 days in Week 3 of Cycle 1 (Cycle 1 was 70 days in length).

Primary: Phase 2: Percentage of Participants who Achieved Complete Metabolic Response (CMR)

| | |
|-----------------|---|
| End point title | Phase 2: Percentage of Participants who Achieved Complete Metabolic Response (CMR) ^[1] |
|-----------------|---|

End point description:

Complete metabolic response (CMR) was determined by central radiographic assessment of positron emission tomography and computed tomography (PET/CT) scans using the Lugano Classification.

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

End point timeframe:

Up to 12 weeks after first dose of blinatumomab

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: No formal statistics were planned

| | | | | |
|-----------------------------------|---------------------|--|--|--|
| End point values | Blinatumomab | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 41 ^[2] | | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 22.0 (10.6 to 37.6) | | | |

Notes:

[2] - Full analysis set (FAS): All participants who received blinatumomab

Statistical analyses

No statistical analyses for this end point

Primary: Phase 3: Number of Participants who Achieved Complete Metabolic Response (CMR)

| | |
|-----------------|---|
| End point title | Phase 3: Number of Participants who Achieved Complete Metabolic Response (CMR) ^[3] |
|-----------------|---|

End point description:

Complete metabolic response (CMR) was determined by central radiographic assessment of positron emission tomography and computed tomography (PET/CT) scans using the Lugano Classification.

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

End point timeframe:

Up to 12 weeks after first dose of study treatment

Notes:

[3] - 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: No formal statistics were planned.

| End point values | Blinatumomab | | | |
|-----------------------------|------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 0 ^[4] | | | |
| Units: Participants | | | | |
| number (not applicable) | | | | |

Notes:

[4] - No participants were enrolled in Phase 3.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Overall Survival (OS)

| | |
|-----------------|--------------------------------|
| End point title | Phase 2: Overall Survival (OS) |
|-----------------|--------------------------------|

End point description:

OS was defined as the time from the date of randomization until death due to any cause.

OS was calculated using Kaplan-Meier estimates.

99999 = no data to present. The upper limit was not reached.

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

End point timeframe:

From randomization until the end of study, up to 30 months

| End point values | Blinatumomab | | | |
|----------------------------------|---------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 41 ^[5] | | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 11.2 (5.9 to 99999) | | | |

Notes:

[5] - FAS: All participants who received blinatumomab

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Objective Response Rate (ORR)

| | |
|-----------------|--|
| End point title | Phase 2: Objective Response Rate (ORR) |
|-----------------|--|

End point description:

ORR is inclusive of all participants who achieved CMR or those who achieved partial metabolic response (PMR), as determined by central radiographic assessment of PET/CT scans using the Lugano Classification.

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

End point timeframe:

Up to 12 weeks after first dose of blinatumomab

| End point values | Blinatumomab | | | |
|-----------------------------------|---------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 41 ^[6] | | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 36.6 (22.1 to 53.1) | | | |

Notes:

[6] - FAS: All participants who received blinatumomab

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Progression Free Survival (PFS)

| | |
|-----------------|--|
| End point title | Phase 2: Progression Free Survival (PFS) |
|-----------------|--|

End point description:

PFS was defined as the time from start of treatment with blinatumomab until the date of diagnosis of progression of lymphoma, or date of death, whichever is earliest. PFS was estimated using Kaplan-Meier method.

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

End point timeframe:

From first dose of blinatumomab until the end of study, up to 30 months

| | | | | |
|----------------------------------|-------------------|--|--|--|
| End point values | Blinatumomab | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 41 ^[7] | | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 2.9 (2.3 to 5.3) | | | |

Notes:

[7] - FAS: All participants who received blinatumomab

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Duration of Response (DOR)

| | |
|--|-------------------------------------|
| End point title | Phase 2: Duration of Response (DOR) |
| End point description: | |
| DOR was calculated only for participants who achieve a response (CMR or PMR). The duration was calculated from the date a response, CMR or PMR, was first achieved until the earliest date of a disease assessment indicating disease progression or death, whichever occurred first. DOR was estimated using Kaplan-Meier method. | |
| End point type | Secondary |
| End point timeframe: | |
| From first dose of blinatumomab up to 12 weeks | |

| | | | | |
|----------------------------------|-------------------|--|--|--|
| End point values | Blinatumomab | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 41 ^[8] | | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 6.1 (2.5 to 10.7) | | | |

Notes:

[8] - FAS: All participants who received blinatumomab

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Percentage of Participants who Experienced Successful Mobilization

| | |
|---|---|
| End point title | Phase 2: Percentage of Participants who Experienced Successful Mobilization |
| End point description: | |
| Successful mobilization rate was defined as the percentage of participants who initiated mobilization while in remission and without any other anti-tumor therapy where the mobilization procedure had an outcome of 'Successful'. Successful mobilization was dictated by institutional standards and defined when the target cell dose was no less than 2×10^6 CD34+ cells/kg. | |
| Responder Analysis Set: All participants who had a CMR or PMR per central review during the first 12 weeks after initiation of blinatumomab. | |
| End point type | Secondary |

End point timeframe:

From first dose of blinatumomab until the end of study, up to 30 months

| End point values | Blinatumomab | | | |
|-----------------------------------|---------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 15 ^[9] | | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 40.0 (16.3 to 67.7) | | | |

Notes:

[9] - Responder Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Percentage of Participants who had Allogeneic or Autologous Post-baseline Hematopoietic Stem Cell Transplant (HSCT)

| | |
|-----------------|--|
| End point title | Phase 2: Percentage of Participants who had Allogeneic or Autologous Post-baseline Hematopoietic Stem Cell Transplant (HSCT) |
|-----------------|--|

End point description:

The percentage of responders per investigator's review (participants who achieved either CMR or PMR during the treatment) who have undergone allogeneic (allo) HSCT or autologous (auto) HSCT while in remission and without any other anti-cancer treatment.

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

End point timeframe:

From baseline HSCT until the end of study, up to 30 months

| End point values | Blinatumomab | | | |
|-----------------------------------|---------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 41 ^[10] | | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| AlloHSCT | 6.7 (0.2 to 31.9) | | | |
| AutoHSCT | 53.3 (26.6 to 78.7) | | | |

Notes:

[10] - FAS: All participants who received blinatumomab.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Cumulative Incidence Function Estimate of 100-day Mortality After HSCT Presented as Percentage of Participants that Died Not Due to Relapse,

with Relapse and Death Due to Relapse as Competing Events

| | |
|-----------------|---|
| End point title | Phase 2: Cumulative Incidence Function Estimate of 100-day Mortality After HSCT Presented as Percentage of Participants that Died Not Due to Relapse, with Relapse and Death Due to Relapse as Competing Events |
|-----------------|---|

End point description:

Non-relapse mortality rate at 100 days after HSCT was calculated as the percentage of participants who died not due to relapse. Only participants who achieved a response per investigator's review and underwent autoHSCT are included.

AutoHSCT Analysis Set: All participants who achieved a response and underwent autoHSCT while in remission and without any other anti-cancer treatment.

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

End point timeframe:

100 days after HSCT

| | | | | |
|-----------------------------------|-------------------|--|--|--|
| End point values | Blinatumomab | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 9 ^[11] | | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 0.0 (0.0 to 0.0) | | | |

Notes:

[11] - AutoHSCT Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Blinatumomab Steady State Concentrations (Css)

| | |
|-----------------|---|
| End point title | Phase 2: Blinatumomab Steady State Concentrations (Css) |
|-----------------|---|

End point description:

Pharmacokinetic (PK) parameters were estimated by non compartmental analysis. The Css of blinatumomab was summarized as the observed concentrations collected after at least 24 hours after the start of continuous IV infusion or start of dose step, where appropriate.

PK analysis Set: All participants who received blinatumomab at each individual dose and had at least one PK sample collected.

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

End point timeframe:

Pre-dose on Day 1, and post-dose on Days 2, 9 and 16 of Cycle 1 (Cycle 1 was 70 days)

| | | | | |
|--------------------------------------|--------------------------------------|---------------------------------------|--|--|
| End point values | Phase 2: Blinatumomab 9 µg/day | Phase 2: Blinatumomab 28 µg/day | Phase 2: Blinatumomab 112 µg/day | |
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 41 ^[12] | 38 ^[13] | 32 ^[14] | |
| Units: Picograms/milliliter (pg/mL) | | | | |
| arithmetic mean (standard deviation) | 249 (± 200) | 804 (± 513) | 3470 (± 3700) | |

Notes:

[12] - PK Analysis Set

[13] - PK Analysis Set

[14] - PK Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Blinatumomab Clearance (CL)

| | |
|-----------------|--------------------------------------|
| End point title | Phase 2: Blinatumomab Clearance (CL) |
|-----------------|--------------------------------------|

End point description:

Serum blinatumomab CL was calculated as $CL = R_0 / C_{ss,DN}$; where R_0 is the infusion rate ($\mu\text{g/hr}$) and $C_{ss,DN}$ is the dose normalized average C_{ss} . For the CL calculation, the $C_{ss,DN}$ was normalized to the $112 \mu\text{g/day}$ dose in which the value of dose in units of $\mu\text{g/hr}$ was used for the infusion rate.

PK analysis Set: All subjects who received blinatumomab at each individual dose and had at least one PK sample collected.

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

End point timeframe:

Pre-dose on Day 1, and post-dose on Days 2, 9 and 16 of Cycle 1 (Cycle 1 was 70 days)

| End point values | Blinatumomab | | | |
|--------------------------------------|---------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 41 ^[15] | | | |
| Units: Liter/hour (L/hr) | | | | |
| arithmetic mean (standard deviation) | 1.78 (\pm 0.747) | | | |

Notes:

[15] - PK Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Half-life of Blinatumomab

| | |
|-----------------|------------------------------------|
| End point title | Phase 2: Half-life of Blinatumomab |
|-----------------|------------------------------------|

End point description:

Blinatumomab half-life was not reported as the serum blinatumomab concentration data collected for PK assessments did not support its estimation. This is in adherence with the considerations for reporting of PK assessments as detailed in Protocol Section 10.6.

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

End point timeframe:

Pre-dose on Day 1, and Days 2, 9 and 16 of Cycle 1 (Cycle 1 was 70 days)

| End point values | Blinatumomab | | | |
|--------------------------------------|-------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 0 ^[16] | | | |
| Units: Hours | | | | |
| arithmetic mean (standard deviation) | () | | | |

Notes:

[16] - Insufficient data collected.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Number of Participants who Experienced a Treatment-emergent Adverse Event (TEAE)

| | |
|-----------------|---|
| End point title | Phase 2: Number of Participants who Experienced a Treatment-emergent Adverse Event (TEAE) |
|-----------------|---|

End point description:

Treatment-emergent adverse events were events with an onset after the administration of the first dose of blinatumomab.

TEAEs were graded using the Common Terminology Criteria for Adverse Events (CTCAE).

Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limited age appropriate instrumental activities of daily life (ADL).

Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolonged hospitalization indicated; disabling; limited self care ADL.

Grade 4 Life-threatening consequences; urgent interventions indicated.

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

End point timeframe:

From first dose of blinatumomab until 30 days after last dose. The maximum treatment duration for blinatumomab was 114 days

| End point values | Blinatumomab | | | |
|--|--------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 41 ^[17] | | | |
| Units: Participants | | | | |
| TEAEs | 41 | | | |
| Grade ≥ 2 TEAEs | 37 | | | |
| Grade ≥ 3 TEAEs | 29 | | | |
| Grade ≥ 4 TEAEs | 12 | | | |
| Serious TEAEs | 20 | | | |
| TEAEs leading to discontinuation of blinatumomab | 7 | | | |
| TEAEs leading to interruption of blinatumomab | 13 | | | |
| Fatal TEAEs | 7 | | | |

Notes:

[17] - FAS: All participants who received blinatumomab

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 3: Objective Response Rate (ORR)

| | |
|-----------------|--|
| End point title | Phase 3: Objective Response Rate (ORR) |
|-----------------|--|

End point description:

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

End point timeframe:

Up to 12 weeks after first dose of study treatment

| End point values | Blinatumomab | | | |
|-----------------------------------|-------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 0 ^[18] | | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |

Notes:

[18] - No participants were enrolled for Phase 3.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 3: Progression Free Survival (PFS)

| | |
|-----------------|--|
| End point title | Phase 3: Progression Free Survival (PFS) |
|-----------------|--|

End point description:

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

End point timeframe:

From first dose of study treatment until the end of study, up to 30 months

| End point values | Blinatumomab | | | |
|-------------------------------|-------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 0 ^[19] | | | |
| Units: Months | | | | |
| median (full range (min-max)) | (to) | | | |

Notes:

[19] - No participants were enrolled in Phase 3.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 3: Duration of Response (DOR)

| | |
|-----------------|-------------------------------------|
| End point title | Phase 3: Duration of Response (DOR) |
|-----------------|-------------------------------------|

End point description:

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

End point timeframe:

From first dose of study treatment up to 12 weeks

| End point values | Blinatumomab | | | |
|----------------------------------|-------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 0 ^[20] | | | |
| Units: Months | | | | |
| median (confidence interval 95%) | (to) | | | |

Notes:

[20] - No participants were enrolled in Phase 3.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 3: Percentage of Participants who Experienced Successful Mobilization

| | |
|-----------------|---|
| End point title | Phase 3: Percentage of Participants who Experienced Successful Mobilization |
|-----------------|---|

End point description:

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

End point timeframe:

From baseline until the end of study, up to 30 months

| End point values | Blinatumomab | | | |
|-----------------------------------|-------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 0 ^[21] | | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | | | | |

Notes:

[21] - No participants were enrolled in Phase 3.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 3: Percentage of Participants who had Allogeneic or Autologous Post-baseline Hematopoietic Stem Cell Transplant (HSCT)

| | |
|-----------------|---|
| End point title | Phase 3: Percentage of Participants who had Allogeneic or |
|-----------------|---|

End point description:

End point type Secondary

End point timeframe:

From baseline HSCT until the end of study, up to 30 months

| End point values | Blinatumomab | | | |
|-----------------------------------|-------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 0 ^[22] | | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | | | | |

Notes:

[22] - No participants were enrolled in Phase 3.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 3: Percentage of Participants who Died within 100 Days after Hematopoietic Stem Cell Transplantation (HSCT) that was Not Due to Relapse

| | |
|-----------------|---|
| End point title | Phase 3: Percentage of Participants who Died within 100 Days after Hematopoietic Stem Cell Transplantation (HSCT) that was Not Due to Relapse |
|-----------------|---|

End point description:

End point type Secondary

End point timeframe:

100 days after HSCT

| End point values | Blinatumomab | | | |
|-----------------------------------|-------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 0 ^[23] | | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | | | | |

Notes:

[23] - No participants were enrolled in Phase 3.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 3: Change from Baseline in Patient Reported Clinical Outcome Assessments Quality of Life (QOLCOA) Scores

| | |
|-----------------|--|
| End point title | Phase 3: Change from Baseline in Patient Reported Clinical |
|-----------------|--|

End point description:

End point type Secondary

End point timeframe:

Up to 30 days after last dose after study treatment

| | | | | |
|-----------------------------------|-------------------|--|--|--|
| End point values | Blinatumomab | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 0 ^[24] | | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | | | | |

Notes:

[24] - No participants were enrolled in Phase 3.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 3: Number of Participants who Experienced a Treatment-emergent Adverse Event (TEAE)

End point title Phase 3: Number of Participants who Experienced a Treatment-emergent Adverse Event (TEAE)

End point description:

End point type Secondary

End point timeframe:

From first dose of study treatment until 30 days after last dose

| | | | | |
|-----------------------------|-------------------|--|--|--|
| End point values | Blinatumomab | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 0 ^[25] | | | |
| Units: Participants | | | | |
| number (not applicable) | | | | |

Notes:

[25] - No participants were enrolled in Phase 3.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 3: Serum Blinatumomab Steady State Concentration (Css)

End point title Phase 3: Serum Blinatumomab Steady State Concentration (Css)

End point description:

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

End point timeframe:

24 hours after first dose of blinatumomab

| End point values | Blinatumomab | | | |
|--------------------------------------|-------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 0 ^[26] | | | |
| Units: pg/mL | | | | |
| arithmetic mean (standard deviation) | () | | | |

Notes:

[26] - No participants were enrolled in Phase 3.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 3: Blinatumomab Clearance (CL)

| | |
|-----------------|--------------------------------------|
| End point title | Phase 3: Blinatumomab Clearance (CL) |
|-----------------|--------------------------------------|

End point description:

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

End point timeframe:

Pre-dose on Day 1, and Days 2, 9 and 16 of Cycle 1 (Cycle 1 was 70 days)

| End point values | Blinatumomab | | | |
|--------------------------------------|-------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 0 ^[27] | | | |
| Units: L/hr | | | | |
| arithmetic mean (standard deviation) | () | | | |

Notes:

[27] - No participants were enrolled in Phase 3.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 3: Half-life of Blinatumomab

| | |
|-----------------|------------------------------------|
| End point title | Phase 3: Half-life of Blinatumomab |
|-----------------|------------------------------------|

End point description:

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

End point timeframe:

Pre-dose on Day 1, and Days 2, 9 and 16 of Cycle 1 (Cycle 1 was 70 days)

| | | | | |
|--------------------------------------|-------------------|--|--|--|
| End point values | Blinatumomab | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 0 ^[28] | | | |
| Units: Hours | | | | |
| arithmetic mean (standard deviation) | () | | | |

Notes:

[28] - No participants were enrolled in Phase 3.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of blinatumomab until 30 days after last dose. The maximum treatment duration for blinatumomab was 114 days

Adverse event reporting additional description:

All-cause mortality, serious adverse events and other adverse events are reported for all participants who received at least one dose of study drug.

No data is available for Phase 3, In March 2019, the decision was made to not proceed with Phase 3 and no participants were enrolled. The data below is only inclusive of participants in Phase 2.

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

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 22.1 |

Reporting groups

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

Reporting group description:

Phase 2: Participants entered a single 70-day dose step cycle, and received a total of 56 days of blinatumomab continuous infusion which was administered as 7 days at 9 microgram (µg)/day, 7 days at 28 µg/day, and 42 days at 112 µg/day, followed by a treatment-free period of 14 days. Eligible participants could then enter an optional Cycle 2, 2 to 4 weeks after the end of the previous cycle. The optional Cycle 2 consisted of a 28-day cycle of blinatumomab continuous infusion administered as 7 days at 9 µg/day, 7 days at 28 µg/day, and 14 days at 112 µg/day.

Phase 3: The decision made to not proceed with Phase 3 and no participants were enrolled.

| Serious adverse events | Blinatumomab | | |
|---|------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 20 / 41 (48.78%) | | |
| number of deaths (all causes) | 25 | | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| B-cell lymphoma | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Diffuse large B-cell lymphoma | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Diffuse large B-cell lymphoma refractory | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 2 / 41 (4.88%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 2 | | |
| Lymphoma | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Non-Hodgkin's lymphoma | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Orthostatic hypotension | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | | |
| occurrences causally related to treatment / all | 3 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Hemiparesis | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neurotoxicity | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|--|----------------|--|--|
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pancreatitis acute | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Confusional state | | | |
| subjects affected / exposed | 3 / 41 (7.32%) | | |
| occurrences causally related to treatment / all | 3 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pain in extremity | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |

| | | | |
|---|----------------|--|--|
| Bacteraemia | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sepsis | | | |
| subjects affected / exposed | 2 / 41 (4.88%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 1 / 1 | | |
| Staphylococcal bacteraemia | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | | |
| 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 | 29 / 41 (70.73%) | | |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 3 / 41 (7.32%) | | |
| occurrences (all) | 5 | | |
| Nervous system disorders | | | |
| Aphasia | | | |
| subjects affected / exposed | 3 / 41 (7.32%) | | |
| occurrences (all) | 4 | | |
| Headache | | | |

| | | | |
|--|------------------|--|--|
| subjects affected / exposed | 10 / 41 (24.39%) | | |
| occurrences (all) | 16 | | |
| Paraesthesia | | | |
| subjects affected / exposed | 3 / 41 (7.32%) | | |
| occurrences (all) | 3 | | |
| Tremor | | | |
| subjects affected / exposed | 9 / 41 (21.95%) | | |
| occurrences (all) | 19 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 6 / 41 (14.63%) | | |
| occurrences (all) | 13 | | |
| Neutropenia | | | |
| subjects affected / exposed | 5 / 41 (12.20%) | | |
| occurrences (all) | 8 | | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 3 / 41 (7.32%) | | |
| occurrences (all) | 4 | | |
| Fatigue | | | |
| subjects affected / exposed | 4 / 41 (9.76%) | | |
| occurrences (all) | 6 | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 8 / 41 (19.51%) | | |
| occurrences (all) | 14 | | |
| Pyrexia | | | |
| subjects affected / exposed | 9 / 41 (21.95%) | | |
| occurrences (all) | 15 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 4 / 41 (9.76%) | | |
| occurrences (all) | 5 | | |
| Constipation | | | |
| subjects affected / exposed | 6 / 41 (14.63%) | | |
| occurrences (all) | 7 | | |
| Diarrhoea | | | |

| | | | |
|---|-----------------------|--|--|
| subjects affected / exposed occurrences (all) | 4 / 41 (9.76%) 4 | | |
| Nausea subjects affected / exposed occurrences (all) | 6 / 41 (14.63%) 8 | | |
| Stomatitis subjects affected / exposed occurrences (all) | 3 / 41 (7.32%) 3 | | |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 3 / 41 (7.32%) 9 | | |
| Psychiatric disorders Confusional state subjects affected / exposed occurrences (all) | 4 / 41 (9.76%) 6 | | |
| Insomnia subjects affected / exposed occurrences (all) | 5 / 41 (12.20%) 5 | | |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 4 / 41 (9.76%) 4 | | |
| Back pain subjects affected / exposed occurrences (all) | 9 / 41 (21.95%) 11 | | |
| Pain in extremity subjects affected / exposed occurrences (all) | 4 / 41 (9.76%) 7 | | |
| Metabolism and nutrition disorders Hypoalbuminaemia subjects affected / exposed occurrences (all) | 4 / 41 (9.76%) 4 | | |
| Hypomagnesaemia subjects affected / exposed occurrences (all) | 5 / 41 (12.20%) 6 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---------------|--|
| 16 March 2017 | <p>The following changes were made:</p> <ul style="list-style-type: none">• Clarified duration of cycle and dose steps for blinatumomab for consistency within the protocol• Added specification of the duration between end of cycle 1 and beginning of optional cycle 2 of blinatumomab• Clarified that creatinine was to be calculated using the Cockcroft Gault equation• Added the dose and duration of each step in the dosing schema of blinatumomab optional cycle 2 to clarify procedures• Added mantle cell lymphoma as a histology that excluded eligibility for enrollment• Added procedure by which scans were to be submitted to determine eligibility for participants who have had only 1 cycle of previous chemotherapy• Revised requirements for blinatumomab infusion interruptions and dose modifications per request of the Food and Drug Administration (FDA)• Updated blinatumomab stopping and/or withholding rules to include cytokine storm• Added time point at week 68 for collection of cell pellet sample for optional pharmacogenetic testing• Specified that lipase samples should be collected at the investigator's discretion if pancreatitis was suspected• Clarified that vital signs to be monitored every 4 to 8 hours postdose• Clarified that participants are prohibited from receiving additional chemotherapy after the last response assessment before enrollment• Clarified that PET imaging of the neck to be done as clinically indicated• Clarified procedures for bone marrow biopsy• Added the EuroQol- 5 Dimension (EQ-5D) and Functional Assessment of Cancer Therapy - Lymphoma (FACT Lym) instruments as appendices |
| 16 March 2017 | <p>Amendment dated 16 March 2017 continued:</p> <ul style="list-style-type: none">• Specified that disease progression is considered a disease related event and procedures for recording as an adverse event• Revised list of disease-related adverse events• Added reporting of events for participants who are partial response/minor response at baseline per Lugano who do not go to transplantation within 30 days of first response assessment• Revised procedures for reporting laboratory abnormalities as adverse events |
| 07 May 2019 | <p>This following changes were made:</p> <ul style="list-style-type: none">• Provided post facto option of not proceeding to Phase 3• Provided 2 years of long term follow up for Phase 2 cohort• Clarified end of study and end of follow up for Phase 2• Redefined primary and final analyses endpoints |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Phase 3 part of the study was not initiated after Phase 2 data was reviewed. No participants were screened or enrolled for Phase 3.

Notes: