



## Clinical trial results:

### An Open-label, Multi-center, Expanded Access Protocol of Blinatumomab for the Treatment of Pediatric and Adolescent Subjects with Relapsed and/or Refractory B precursor Acute Lymphoblastic Leukemia (ALL)

#### Summary

|                          |                 |
|--------------------------|-----------------|
| EudraCT number           | 2014-001700-21  |
| Trial protocol           | GB DE IT AT FR  |
| Global end of trial date | 10 January 2020 |

#### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 16 July 2020 |
| First version publication date | 16 July 2020 |

#### Trial information

##### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | 20130320 |
|-----------------------|----------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02187354 |
| 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? | Yes |

Notes:

## Results analysis stage

|                                                      |                 |
|------------------------------------------------------|-----------------|
| Analysis stage                                       | Final           |
| Date of interim/final analysis                       | 10 January 2020 |
| Is this the analysis of the primary completion data? | No              |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 10 January 2020 |
| Was the trial ended prematurely?                     | No              |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this study was to estimate the incidence rate of treatment emergent and treatment related adverse events during treatment with blinatumomab in pediatric and adolescent subjects with B cell precursor ALL in second or later bone marrow relapse, in any marrow relapse after allogeneic HSCT, or refractory to other treatments.

Protection of trial subjects:

This study was conducted in accordance with International Council on Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines. The regulations or guidelines were applicable to all regions where the study was conducted and in accordance with the ethical principles set forth in the Declaration of Helsinki. All study centers complied with the local regulations.

The investigator or his/her designee informed the subject (or their legal representative) of all aspects regarding the subject's participation in the study before any screening procedures were performed.

Background therapy: -

Evidence for comparator: -

|                                                           |                 |
|-----------------------------------------------------------|-----------------|
| Actual start date of recruitment                          | 29 January 2015 |
| 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 | Austria: 3        |
| Country: Number of subjects enrolled | France: 8         |
| Country: Number of subjects enrolled | Germany: 32       |
| Country: Number of subjects enrolled | Italy: 47         |
| Country: Number of subjects enrolled | Switzerland: 4    |
| Country: Number of subjects enrolled | United Kingdom: 7 |
| Country: Number of subjects enrolled | United States: 9  |
| Worldwide total number of subjects   | 110               |
| EEA total number of subjects         | 97                |

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) | 13 |
| Children (2-11 years)                    | 63 |
| Adolescents (12-17 years)                | 34 |
| Adults (18-64 years)                     | 0  |
| From 65 to 84 years                      | 0  |
| 85 years and over                        | 0  |

## Subject disposition

### Recruitment

Recruitment details:

This study was conducted at 16 centers: 13 in Europe and 3 in the United States. The first subject was enrolled on 29 January 2015 and the last subject was enrolled on 25 July 2018.

### Pre-assignment

Screening details:

During the 2-week screening and prephase period, administration of dexamethasone or hydroxyurea was permitted to reduce tumor burden and the incidence of tumor lysis syndrome.

### Period 1

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

### Arms

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

Arm description:

Up to 5 6-week cycles of blinatumomab treatment (4 weeks of treatment followed by a 2-week treatment-free interval).

In the first cycle, subjects with an M3 bone marrow received an initial dose of 5µg/m<sup>2</sup>/day for the first 7 days, escalated to 15µg/m<sup>2</sup>/day on Days 8-29. All subsequent cycles were dosed at 15µg/m<sup>2</sup>/day for 4 weeks of continuous treatment.

Subjects with M2 bone marrow or M1 bone marrow with a minimal residual disease (MRD) relapse at screening, started at an initial dose of 15µg/m<sup>2</sup>/day for the first 7 days of treatment with no dose step at Day 8. All subsequent cycles were dosed at 15µg/m<sup>2</sup>/day for 4 weeks of continuous treatment.

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

Dosage and administration details:

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

| Number of subjects in period 1 | Blinatumomab |
|--------------------------------|--------------|
| Started                        | 110          |
| Completed                      | 47           |
| Not completed                  | 63           |
| Consent withdrawn by subject   | 6            |
| Death                          | 57           |

## Baseline characteristics

### Reporting groups

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

Reporting group description:

Up to 5 6-week cycles of blinatumomab treatment (4 weeks of treatment followed by a 2-week treatment-free interval).

In the first cycle, subjects with an M3 bone marrow received an initial dose of  $5\mu\text{g}/\text{m}^2/\text{day}$  for the first 7 days, escalated to  $15\mu\text{g}/\text{m}^2/\text{day}$  on Days 8-29. All subsequent cycles were dosed at  $15\mu\text{g}/\text{m}^2/\text{day}$  for 4 weeks of continuous treatment.

Subjects with M2 bone marrow or M1 bone marrow with a minimal residual disease (MRD) relapse at screening, started at an initial dose of  $15\mu\text{g}/\text{m}^2/\text{day}$  for the first 7 days of treatment with no dose step at Day 8. All subsequent cycles were dosed at  $15\mu\text{g}/\text{m}^2/\text{day}$  for 4 weeks of continuous treatment.

| Reporting group values                    | Blinatumomab | Total |  |
|-------------------------------------------|--------------|-------|--|
| Number of subjects                        | 110          | 110   |  |
| Age Categorical<br>Units: Subjects        |              |       |  |
| 0 to < 2 years                            | 13           | 13    |  |
| 2 to 6 years                              | 31           | 31    |  |
| 7 to 17 years                             | 66           | 66    |  |
| Age Continuous<br>Units: years            |              |       |  |
| arithmetic mean                           | 8.5          | -     |  |
| standard deviation                        | $\pm 5.0$    | -     |  |
| Gender Categorical<br>Units: Subjects     |              |       |  |
| Female                                    | 48           | 48    |  |
| Male                                      | 62           | 62    |  |
| Race<br>Units: Subjects                   |              |       |  |
| American Indian or Alaska Native          | 1            | 1     |  |
| Asian                                     | 3            | 3     |  |
| Multiple (Asian/White)                    | 1            | 1     |  |
| Native Hawaiian or Other Pacific Islander | 1            | 1     |  |
| White                                     | 93           | 93    |  |
| Other, Not Specified                      | 3            | 3     |  |
| Missing                                   | 8            | 8     |  |
| Ethnicity<br>Units: Subjects              |              |       |  |
| Hispanic/Latino                           | 18           | 18    |  |
| Not Hispanic/Latino                       | 92           | 92    |  |

## End points

### End points reporting groups

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

Reporting group description:

Up to 5 6-week cycles of blinatumomab treatment (4 weeks of treatment followed by a 2-week treatment-free interval).

In the first cycle, subjects with an M3 bone marrow received an initial dose of  $5\mu\text{g}/\text{m}^2/\text{day}$  for the first 7 days, escalated to  $15\mu\text{g}/\text{m}^2/\text{day}$  on Days 8-29. All subsequent cycles were dosed at  $15\mu\text{g}/\text{m}^2/\text{day}$  for 4 weeks of continuous treatment.

Subjects with M2 bone marrow or M1 bone marrow with a minimal residual disease (MRD) relapse at screening, started at an initial dose of  $15\mu\text{g}/\text{m}^2/\text{day}$  for the first 7 days of treatment with no dose step at Day 8. All subsequent cycles were dosed at  $15\mu\text{g}/\text{m}^2/\text{day}$  for 4 weeks of continuous treatment.

### Primary: Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) and Treatment-Related Adverse Events (TRAEs)

|                 |                                                                                                                               |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) and Treatment-Related Adverse Events (TRAEs) <sup>[1]</sup> |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------|

End point description:

An adverse event (AE) is defined as any untoward medical occurrence. A serious AE is defined as an AE meeting at least 1 of the following serious criteria: fatal; life threatening; requires in-patient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; congenital anomaly/birth defect; other medically important serious event. TEAEs were those occurring after the first dose of study drug through 30 days after the last dose of study drug. Severity was graded as 1=mild, 2=moderate, 3=severe, 4=life-threatening, 5=death. Events of interest included neurologic events, infections, cytokine release syndrome, elevated liver enzyme, infusion reactions, tumor lysis syndrome, capillary leak syndrome, medication errors, decreased immunoglobulins, embolic and thrombotic events, leukoencephalopathy, neutropenia and febrile neutropenia, and acute pancreatitis.

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

End point timeframe:

From the first dose of study drug through 30 days post-dose. Median overall duration of each treatment cycle was 31.4 days (range: 3 to 140 days); median number of cycles started and completed was 1.0 (range: 1.0 to 5.0).

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: Descriptive statistics are presented per protocol.

| End point values                                   | Blinatumomab    |  |  |  |
|----------------------------------------------------|-----------------|--|--|--|
| Subject group type                                 | Reporting group |  |  |  |
| Number of subjects analysed                        | 110             |  |  |  |
| Units: subjects                                    |                 |  |  |  |
| TEAE                                               | 109             |  |  |  |
| TEAE Grade $\geq 3$                                | 71              |  |  |  |
| TEAE Grade $\geq 4$                                | 31              |  |  |  |
| TEAE, Serious                                      | 50              |  |  |  |
| TEAE, Fatal                                        | 9               |  |  |  |
| TEAE Leading to Discontinuation (DC) of Study Drug | 7               |  |  |  |
| TEAE Leading to DC of Study Drug, Serious          | 6               |  |  |  |
| TEAE Leading to DC of Study Drug, Fatal            | 2               |  |  |  |

|                                                  |     |  |  |  |
|--------------------------------------------------|-----|--|--|--|
| TEAE Leading to Interruption (INT) of Study Drug | 25  |  |  |  |
| TEAE Leading to INT of Study Drug, Serious       | 17  |  |  |  |
| TEAE Leading to INT of Study Drug, Fatal         | 3   |  |  |  |
| TEAE, Events of Interest                         | 101 |  |  |  |
| TRAЕ                                             | 81  |  |  |  |
| TRAЕ Grade $\geq 3$                              | 29  |  |  |  |
| TRAЕ Grade $\geq 4$                              | 3   |  |  |  |
| TRAЕ, Serious                                    | 21  |  |  |  |
| TRAЕ, Fatal                                      | 0   |  |  |  |
| TRAЕ Leading to DC of Study Drug                 | 4   |  |  |  |
| TRAЕ Leading to DC of Study Drug, Serious        | 4   |  |  |  |
| TRAЕ Leading to DC of Study Drug, Fatal          | 0   |  |  |  |
| TRAЕ Leading to INT of Study Drug                | 18  |  |  |  |
| TRAЕ Leading to INT of Study Drug, Serious       | 11  |  |  |  |
| TRAЕ Leading to INT of Study Drug, Fatal         | 0   |  |  |  |
| TRAЕ, Events of Interest                         | 68  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects With Complete Response (CR) Within the First 2 Cycles of Blinatumomab

|                 |                                                                                              |
|-----------------|----------------------------------------------------------------------------------------------|
| End point title | Percentage of Subjects With Complete Response (CR) Within the First 2 Cycles of Blinatumomab |
|-----------------|----------------------------------------------------------------------------------------------|

End point description:

CR was defined as having < 5% blasts in the bone marrow (M1 bone marrow) and no evidence of disease (M1 bone marrow with full recovery of peripheral blood counts or M1 bone marrow with incomplete recovery of peripheral blood counts or M1 bone marrow with neither full nor incomplete recovery of peripheral blood counts).

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

End point timeframe:

Within the first 2 cycles (data cutoff 27 September 2018). The median (range) duration of the first treatment cycle was 27.9 (3 to 31) days, and 27.9 (0 to 37) days for the second treatment cycle.

|                                  |                     |  |  |  |
|----------------------------------|---------------------|--|--|--|
| <b>End point values</b>          | Blinatumomab        |  |  |  |
| Subject group type               | Reporting group     |  |  |  |
| Number of subjects analysed      | 110                 |  |  |  |
| Units: percentage of subjects    |                     |  |  |  |
| number (confidence interval 95%) | 62.7 (53.0 to 71.8) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants With a Minimal Residual Disease (MRD) Response Within the First 2 Cycles of Blinatumomab

|                 |                                                                                                                     |
|-----------------|---------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Participants With a Minimal Residual Disease (MRD) Response Within the First 2 Cycles of Blinatumomab |
|-----------------|---------------------------------------------------------------------------------------------------------------------|

End point description:

MRD response is defined as a quantifiable MRD load of  $< 10^{-4}$  by the end of the first 2 cycles of blinatumomab. MRD response only included subjects who reached CR. CR was defined as having  $< 5\%$  blasts in the bone marrow (M1 bone marrow) and no evidence of disease (M1 bone marrow with full recovery of peripheral blood counts or M1 bone marrow with incomplete recovery of peripheral blood counts or M1 bone marrow with neither full nor incomplete recovery of peripheral blood counts).

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

End point timeframe:

Within the first 2 cycles (data cutoff 27 September 2018). The median (range) duration of the first treatment cycle was 27.9 (3 to 31) days, and 27.9 (0 to 37) days for the second treatment cycle.

| End point values                 | Blinatumomab        |  |  |  |
|----------------------------------|---------------------|--|--|--|
| Subject group type               | Reporting group     |  |  |  |
| Number of subjects analysed      | 69 <sup>[2]</sup>   |  |  |  |
| Units: percentage of subjects    |                     |  |  |  |
| number (confidence interval 95%) |                     |  |  |  |
| MRD Response                     | 82.6 (71.6 to 90.7) |  |  |  |
| MRD Non-Response                 | 14.5 (7.2 to 25.0)  |  |  |  |
| No MRD Response Data             | 2.9 (0.4 to 10.1)   |  |  |  |

Notes:

[2] - subjects with a CR

## Statistical analyses

No statistical analyses for this end point

### Secondary: Kaplan-Meier Estimate of Relapse-Free Survival (RFS), Subjects With a CR

|                 |                                                                          |
|-----------------|--------------------------------------------------------------------------|
| End point title | Kaplan-Meier Estimate of Relapse-Free Survival (RFS), Subjects With a CR |
|-----------------|--------------------------------------------------------------------------|

End point description:

RFS was calculated as the time to an event of relapse, defined as high-risk extramedullary disease, or death (all cause). Progressive disease, defined as an increase from baseline of at least 25% or an absolute increase of at least 5000 cells/iL (whichever is greater) in the number of circulating leukemia cells, development of extramedullary disease, or other laboratory or clinical evidence of progressive

disease, was also counted as an event.

RFS only included subjects who reached CR. CR was defined as having < 5% blasts in the bone marrow (M1 bone marrow) and no evidence of disease (M1 bone marrow with full recovery of peripheral blood counts or M1 bone marrow with incomplete recovery of peripheral blood counts or M1 bone marrow with neither full nor incomplete recovery of peripheral blood counts).

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

End point timeframe:

From the first dose of study drug through final data cutoff (10 January 2020). Median follow up time was 11.5 months (range: 0.0 to 16.3 months).

|                                  |                   |  |  |  |
|----------------------------------|-------------------|--|--|--|
| <b>End point values</b>          | Blinatumomab      |  |  |  |
| Subject group type               | Reporting group   |  |  |  |
| Number of subjects analysed      | 68 <sup>[3]</sup> |  |  |  |
| Units: months                    |                   |  |  |  |
| median (confidence interval 95%) | 8.5 (4.7 to 14.0) |  |  |  |

Notes:

[3] - subjects with a CR

## Statistical analyses

No statistical analyses for this end point

## Secondary: Kaplan-Meier Estimate of Overall Survival

|                 |                                           |
|-----------------|-------------------------------------------|
| End point title | Kaplan-Meier Estimate of Overall Survival |
|-----------------|-------------------------------------------|

End point description:

Overall survival was calculated relative to the start of protocol-directed therapy until death (due to any cause), and was summarized by the Kaplan Meier methodology. Subjects still alive at the time of the analysis were censored at the date last known to be alive.

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

End point timeframe:

From the first dose of study drug through final data cutoff (10 January 2020). Median follow up time was 18.2 months (range: 1.1 to 25.6 months).

|                                  |                     |  |  |  |
|----------------------------------|---------------------|--|--|--|
| <b>End point values</b>          | Blinatumomab        |  |  |  |
| Subject group type               | Reporting group     |  |  |  |
| Number of subjects analysed      | 110                 |  |  |  |
| Units: months                    |                     |  |  |  |
| median (confidence interval 95%) | 14.6 (11.0 to 24.5) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

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**Secondary: Percentage of Subjects With Allogeneic Hematopoietic Stem Cell Transplant (HSCT) After Blinatumomab, Subjects With a CR**

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|                 |                                                                                                                         |
|-----------------|-------------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Subjects With Allogeneic Hematopoietic Stem Cell Transplant (HSCT) After Blinatumomab, Subjects With a CR |
|-----------------|-------------------------------------------------------------------------------------------------------------------------|

End point description:

Percentage of subjects receiving allogeneic HSCT after blinatumomab, in subjects with a CR within the first 2 cycles of treatment. CR was defined as having < 5% blasts in the bone marrow (M1 bone marrow) and no evidence of disease (M1 bone marrow with full recovery of peripheral blood counts or M1 bone marrow with incomplete recovery of peripheral blood counts or M1 bone marrow with neither full nor incomplete recovery of peripheral blood counts).

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

End point timeframe:

From the first dose of study drug through final data cutoff (10 January 2020). Median follow up time was 18.2 months (range: 1.1 to 25.6 months).

---

| End point values                 | Blinatumomab        |  |  |  |
|----------------------------------|---------------------|--|--|--|
| Subject group type               | Reporting group     |  |  |  |
| Number of subjects analysed      | 68 <sup>[4]</sup>   |  |  |  |
| Units: percentage of subjects    |                     |  |  |  |
| number (confidence interval 95%) |                     |  |  |  |
| HSCT after CR                    | 73.5 (61.4 to 83.5) |  |  |  |
| No HSCT after CR                 | 26.5 (16.5 to 38.6) |  |  |  |

Notes:

[4] - Subjects with a CR

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**Statistical analyses**

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No statistical analyses for this end point

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**Secondary: Percentage of Subjects With Allogeneic HSCT After Blinatumomab, Subjects Without CR**

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|                 |                                                                                     |
|-----------------|-------------------------------------------------------------------------------------|
| End point title | Percentage of Subjects With Allogeneic HSCT After Blinatumomab, Subjects Without CR |
|-----------------|-------------------------------------------------------------------------------------|

End point description:

Percentage of subjects receiving allogeneic HSCT after blinatumomab, in subjects without a CR within the first 2 cycles of treatment. CR was defined as having < 5% blasts in the bone marrow (M1 bone marrow) and no evidence of disease (M1 bone marrow with full recovery of peripheral blood counts or M1 bone marrow with incomplete recovery of peripheral blood counts or M1 bone marrow with neither full nor incomplete recovery of peripheral blood counts).

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

End point timeframe:

From the first dose of study drug through final data cutoff (10 January 2020). Median follow up time was 18.2 months (range: 1.1 to 25.6 months).

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| End point values                 | Blinatumomab        |  |  |  |
|----------------------------------|---------------------|--|--|--|
| Subject group type               | Reporting group     |  |  |  |
| Number of subjects analysed      | 25 <sup>[5]</sup>   |  |  |  |
| Units: percentage of subjects    |                     |  |  |  |
| number (confidence interval 95%) |                     |  |  |  |
| HSCT                             | 24.0 (9.4 to 45.1)  |  |  |  |
| No HSCT                          | 76.0 (54.9 to 90.6) |  |  |  |

Notes:

[5] - subjects without a CR

### Statistical analyses

No statistical analyses for this end point

### Secondary: Kaplan-Meier Estimate of 100-day Mortality After Allogeneic HSCT, Subjects With a CR

|                 |                                                                                      |
|-----------------|--------------------------------------------------------------------------------------|
| End point title | Kaplan-Meier Estimate of 100-day Mortality After Allogeneic HSCT, Subjects With a CR |
|-----------------|--------------------------------------------------------------------------------------|

End point description:

Percentage of subjects experiencing death (any cause) 100 days after allogeneic HSCT, estimated by Kaplan Meier method, for subjects with a CR within the first 2 cycles who received an HSCT. CR was defined as having < 5% blasts in the bone marrow (M1 bone marrow) and no evidence of disease (M1 bone marrow with full recovery of peripheral blood counts or M1 bone marrow with incomplete recovery of peripheral blood counts or M1 bone marrow with neither full nor incomplete recovery of peripheral blood counts).

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

End point timeframe:

From the first dose of study drug through final data cutoff (10 January 2020). Median follow up time was 18.2 months (range: 1.1 to 25.6 months).

| End point values                 | Blinatumomab      |  |  |  |
|----------------------------------|-------------------|--|--|--|
| Subject group type               | Reporting group   |  |  |  |
| Number of subjects analysed      | 50 <sup>[6]</sup> |  |  |  |
| Units: percentage of subjects    |                   |  |  |  |
| number (confidence interval 95%) | 4.0 (1.0 to 15.1) |  |  |  |

Notes:

[6] - subjects with a CR who received an allogeneic HSCT

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From the first dose of study drug through 30 days post-dose. Median overall duration of each treatment cycle was 31.4 days (range: 3 to 140 days); median number of cycles started and completed was 1.0 (range: 1.0 to 5.0).

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

### Dictionary used

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

### Reporting groups

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

Reporting group description:

Up to 5 6-week cycles of blinatumomab treatment (4 weeks of treatment followed by a 2-week treatment-free interval). In the first cycle, subjects with an M3 bone marrow received an initial dose of 5µg/m<sup>2</sup>/day for the first 7 days, escalated to 15µg/m<sup>2</sup>/day on Days 8-29. All subsequent cycles were dosed at 15µg/m<sup>2</sup>/day for 4 weeks of continuous treatment. Subjects with M2 bone marrow or M1 bone marrow with an MRD relapse at screening, started at an initial dose of 15µg/m<sup>2</sup>/day for the first 7 days of treatment with no dose step at Day 8. All subsequent cycles were dosed at 15µg/m<sup>2</sup>/day for 4 weeks of continuous treatment.

| Serious adverse events                                              | Blinatumomab      |  |  |
|---------------------------------------------------------------------|-------------------|--|--|
| Total subjects affected by serious adverse events                   |                   |  |  |
| subjects affected / exposed                                         | 50 / 110 (45.45%) |  |  |
| number of deaths (all causes)                                       | 58                |  |  |
| number of deaths resulting from adverse events                      |                   |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                   |  |  |
| Acute lymphocytic leukaemia                                         |                   |  |  |
| subjects affected / exposed                                         | 5 / 110 (4.55%)   |  |  |
| occurrences causally related to treatment / all                     | 0 / 5             |  |  |
| deaths causally related to treatment / all                          | 0 / 5             |  |  |
| Acute lymphocytic leukaemia recurrent                               |                   |  |  |
| subjects affected / exposed                                         | 2 / 110 (1.82%)   |  |  |
| occurrences causally related to treatment / all                     | 0 / 2             |  |  |
| deaths causally related to treatment / all                          | 0 / 1             |  |  |
| Acute myeloid leukaemia                                             |                   |  |  |
| subjects affected / exposed                                         | 1 / 110 (0.91%)   |  |  |
| occurrences causally related to treatment / all                     | 1 / 1             |  |  |
| deaths causally related to treatment / all                          | 0 / 0             |  |  |

|                                                      |                   |  |  |
|------------------------------------------------------|-------------------|--|--|
| Leukaemia recurrent                                  |                   |  |  |
| subjects affected / exposed                          | 2 / 110 (1.82%)   |  |  |
| occurrences causally related to treatment / all      | 1 / 2             |  |  |
| deaths causally related to treatment / all           | 0 / 0             |  |  |
| Lymphocytic leukaemia                                |                   |  |  |
| subjects affected / exposed                          | 1 / 110 (0.91%)   |  |  |
| occurrences causally related to treatment / all      | 0 / 1             |  |  |
| deaths causally related to treatment / all           | 0 / 1             |  |  |
| General disorders and administration site conditions |                   |  |  |
| Chest pain                                           |                   |  |  |
| subjects affected / exposed                          | 1 / 110 (0.91%)   |  |  |
| occurrences causally related to treatment / all      | 0 / 1             |  |  |
| deaths causally related to treatment / all           | 0 / 0             |  |  |
| Pyrexia                                              |                   |  |  |
| subjects affected / exposed                          | 11 / 110 (10.00%) |  |  |
| occurrences causally related to treatment / all      | 8 / 14            |  |  |
| deaths causally related to treatment / all           | 0 / 0             |  |  |
| Immune system disorders                              |                   |  |  |
| Cytokine release syndrome                            |                   |  |  |
| subjects affected / exposed                          | 5 / 110 (4.55%)   |  |  |
| occurrences causally related to treatment / all      | 4 / 5             |  |  |
| deaths causally related to treatment / all           | 0 / 0             |  |  |
| Product issues                                       |                   |  |  |
| Device defective                                     |                   |  |  |
| subjects affected / exposed                          | 1 / 110 (0.91%)   |  |  |
| occurrences causally related to treatment / all      | 0 / 1             |  |  |
| deaths causally related to treatment / all           | 0 / 0             |  |  |
| Investigations                                       |                   |  |  |
| C-reactive protein increased                         |                   |  |  |
| subjects affected / exposed                          | 2 / 110 (1.82%)   |  |  |
| occurrences causally related to treatment / all      | 1 / 2             |  |  |
| deaths causally related to treatment / all           | 0 / 0             |  |  |
| Hepatic enzyme increased                             |                   |  |  |

|                                                  |                 |  |  |
|--------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                      | 1 / 110 (0.91%) |  |  |
| occurrences causally related to treatment / all  | 0 / 1           |  |  |
| deaths causally related to treatment / all       | 0 / 0           |  |  |
| Platelet count decreased                         |                 |  |  |
| subjects affected / exposed                      | 1 / 110 (0.91%) |  |  |
| occurrences causally related to treatment / all  | 0 / 1           |  |  |
| deaths causally related to treatment / all       | 0 / 0           |  |  |
| White blood cell count decreased                 |                 |  |  |
| subjects affected / exposed                      | 1 / 110 (0.91%) |  |  |
| occurrences causally related to treatment / all  | 0 / 1           |  |  |
| deaths causally related to treatment / all       | 0 / 0           |  |  |
| White blood cell count increased                 |                 |  |  |
| subjects affected / exposed                      | 1 / 110 (0.91%) |  |  |
| occurrences causally related to treatment / all  | 0 / 1           |  |  |
| deaths causally related to treatment / all       | 0 / 1           |  |  |
| Injury, poisoning and procedural complications   |                 |  |  |
| Accidental overdose                              |                 |  |  |
| subjects affected / exposed                      | 1 / 110 (0.91%) |  |  |
| occurrences causally related to treatment / all  | 1 / 1           |  |  |
| deaths causally related to treatment / all       | 0 / 0           |  |  |
| Inappropriate schedule of product administration |                 |  |  |
| subjects affected / exposed                      | 1 / 110 (0.91%) |  |  |
| occurrences causally related to treatment / all  | 0 / 1           |  |  |
| deaths causally related to treatment / all       | 0 / 0           |  |  |
| Cardiac disorders                                |                 |  |  |
| Cardiac failure                                  |                 |  |  |
| subjects affected / exposed                      | 1 / 110 (0.91%) |  |  |
| occurrences causally related to treatment / all  | 0 / 1           |  |  |
| deaths causally related to treatment / all       | 0 / 0           |  |  |
| Nervous system disorders                         |                 |  |  |
| Amnesia                                          |                 |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 1 / 110 (0.91%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Aphasia                                         |                 |  |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Depressed level of consciousness                |                 |  |  |
| subjects affected / exposed                     | 2 / 110 (1.82%) |  |  |
| occurrences causally related to treatment / all | 3 / 3           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Meningism                                       |                 |  |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Seizure                                         |                 |  |  |
| subjects affected / exposed                     | 2 / 110 (1.82%) |  |  |
| occurrences causally related to treatment / all | 2 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| VIth nerve paralysis                            |                 |  |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Blood and lymphatic system disorders            |                 |  |  |
| Disseminated intravascular coagulation          |                 |  |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Febrile neutropenia                             |                 |  |  |
| subjects affected / exposed                     | 5 / 110 (4.55%) |  |  |
| occurrences causally related to treatment / all | 1 / 6           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Neutropenia                                     |                 |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 2 / 110 (1.82%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Gastrointestinal disorders                      |                 |  |  |
| Constipation                                    |                 |  |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hepatobiliary disorders                         |                 |  |  |
| Bile duct stone                                 |                 |  |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hepatic failure                                 |                 |  |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Renal and urinary disorders                     |                 |  |  |
| Acute kidney injury                             |                 |  |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Urinary retention                               |                 |  |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Musculoskeletal and connective tissue disorders |                 |  |  |
| Pain in extremity                               |                 |  |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Infections and infestations                     |                 |  |  |
| Bacteraemia                                     |                 |  |  |

|                                                 |                 |  |  |  |
|-------------------------------------------------|-----------------|--|--|--|
| subjects affected / exposed                     | 1 / 110 (0.91%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Bacterial infection                             |                 |  |  |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Bacterial sepsis                                |                 |  |  |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Bronchitis                                      |                 |  |  |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Device related infection                        |                 |  |  |  |
| subjects affected / exposed                     | 3 / 110 (2.73%) |  |  |  |
| occurrences causally related to treatment / all | 2 / 3           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Device related sepsis                           |                 |  |  |  |
| subjects affected / exposed                     | 4 / 110 (3.64%) |  |  |  |
| occurrences causally related to treatment / all | 2 / 4           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Gastroenteritis viral                           |                 |  |  |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Infection                                       |                 |  |  |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Influenza                                       |                 |  |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 1 / 110 (0.91%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Lymph gland infection                           |                 |  |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pseudomonas infection                           |                 |  |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Sepsis                                          |                 |  |  |
| subjects affected / exposed                     | 4 / 110 (3.64%) |  |  |
| occurrences causally related to treatment / all | 0 / 4           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Soft tissue infection                           |                 |  |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Metabolism and nutrition disorders              |                 |  |  |
| Hypoalbuminaemia                                |                 |  |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) |  |  |
| 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                           | 105 / 110 (95.45%) |  |  |
| Vascular disorders                                    |                    |  |  |
| Hypertension                                          |                    |  |  |
| subjects affected / exposed                           | 9 / 110 (8.18%)    |  |  |
| occurrences (all)                                     | 12                 |  |  |
| Hypotension                                           |                    |  |  |

|                                                         |                         |  |  |
|---------------------------------------------------------|-------------------------|--|--|
| subjects affected / exposed<br>occurrences (all)        | 14 / 110 (12.73%)<br>17 |  |  |
| General disorders and administration<br>site conditions |                         |  |  |
| Chills                                                  |                         |  |  |
| subjects affected / exposed                             | 7 / 110 (6.36%)         |  |  |
| occurrences (all)                                       | 10                      |  |  |
| Fatigue                                                 |                         |  |  |
| subjects affected / exposed                             | 7 / 110 (6.36%)         |  |  |
| occurrences (all)                                       | 7                       |  |  |
| Pain                                                    |                         |  |  |
| subjects affected / exposed                             | 18 / 110 (16.36%)       |  |  |
| occurrences (all)                                       | 19                      |  |  |
| Pyrexia                                                 |                         |  |  |
| subjects affected / exposed                             | 90 / 110 (81.82%)       |  |  |
| occurrences (all)                                       | 183                     |  |  |
| Immune system disorders                                 |                         |  |  |
| Cytokine release syndrome                               |                         |  |  |
| subjects affected / exposed                             | 17 / 110 (15.45%)       |  |  |
| occurrences (all)                                       | 17                      |  |  |
| Respiratory, thoracic and mediastinal<br>disorders      |                         |  |  |
| Cough                                                   |                         |  |  |
| subjects affected / exposed                             | 19 / 110 (17.27%)       |  |  |
| occurrences (all)                                       | 20                      |  |  |
| Epistaxis                                               |                         |  |  |
| subjects affected / exposed                             | 6 / 110 (5.45%)         |  |  |
| occurrences (all)                                       | 7                       |  |  |
| Investigations                                          |                         |  |  |
| Alanine aminotransferase increased                      |                         |  |  |
| subjects affected / exposed                             | 11 / 110 (10.00%)       |  |  |
| occurrences (all)                                       | 20                      |  |  |
| Aspartate aminotransferase<br>increased                 |                         |  |  |
| subjects affected / exposed                             | 7 / 110 (6.36%)         |  |  |
| occurrences (all)                                       | 7                       |  |  |
| Fluid balance positive                                  |                         |  |  |

|                                                                                                     |                         |  |  |
|-----------------------------------------------------------------------------------------------------|-------------------------|--|--|
| subjects affected / exposed<br>occurrences (all)                                                    | 11 / 110 (10.00%)<br>17 |  |  |
| Gamma-glutamyltransferase increased<br>subjects affected / exposed<br>occurrences (all)             | 6 / 110 (5.45%)<br>7    |  |  |
| Platelet count decreased<br>subjects affected / exposed<br>occurrences (all)                        | 11 / 110 (10.00%)<br>36 |  |  |
| Cardiac disorders<br>Tachycardia<br>subjects affected / exposed<br>occurrences (all)                | 6 / 110 (5.45%)<br>6    |  |  |
| Nervous system disorders<br>Headache<br>subjects affected / exposed<br>occurrences (all)            | 27 / 110 (24.55%)<br>47 |  |  |
| Tremor<br>subjects affected / exposed<br>occurrences (all)                                          | 8 / 110 (7.27%)<br>13   |  |  |
| Blood and lymphatic system disorders<br>Anaemia<br>subjects affected / exposed<br>occurrences (all) | 20 / 110 (18.18%)<br>45 |  |  |
| Febrile neutropenia<br>subjects affected / exposed<br>occurrences (all)                             | 6 / 110 (5.45%)<br>9    |  |  |
| Neutropenia<br>subjects affected / exposed<br>occurrences (all)                                     | 9 / 110 (8.18%)<br>13   |  |  |
| Thrombocytopenia<br>subjects affected / exposed<br>occurrences (all)                                | 10 / 110 (9.09%)<br>15  |  |  |
| Gastrointestinal disorders<br>Abdominal pain<br>subjects affected / exposed<br>occurrences (all)    | 12 / 110 (10.91%)<br>13 |  |  |

|                                                                          |                         |  |  |
|--------------------------------------------------------------------------|-------------------------|--|--|
| Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all) | 6 / 110 (5.45%)<br>8    |  |  |
| Constipation<br>subjects affected / exposed<br>occurrences (all)         | 10 / 110 (9.09%)<br>11  |  |  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)            | 10 / 110 (9.09%)<br>13  |  |  |
| Nausea<br>subjects affected / exposed<br>occurrences (all)               | 20 / 110 (18.18%)<br>31 |  |  |
| Stomatitis<br>subjects affected / exposed<br>occurrences (all)           | 8 / 110 (7.27%)<br>8    |  |  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)             | 30 / 110 (27.27%)<br>41 |  |  |
| Skin and subcutaneous tissue disorders                                   |                         |  |  |
| Dry skin<br>subjects affected / exposed<br>occurrences (all)             | 6 / 110 (5.45%)<br>6    |  |  |
| Pruritus<br>subjects affected / exposed<br>occurrences (all)             | 7 / 110 (6.36%)<br>7    |  |  |
| Rash<br>subjects affected / exposed<br>occurrences (all)                 | 12 / 110 (10.91%)<br>13 |  |  |
| Musculoskeletal and connective tissue disorders                          |                         |  |  |
| Back pain<br>subjects affected / exposed<br>occurrences (all)            | 10 / 110 (9.09%)<br>12  |  |  |
| Bone pain<br>subjects affected / exposed<br>occurrences (all)            | 6 / 110 (5.45%)<br>7    |  |  |
| Pain in extremity                                                        |                         |  |  |

|                                                                                                                                                                                                                                                                                                                                      |                                                                                                             |  |  |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------|--|--|
| subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                                                                                     | 13 / 110 (11.82%)<br>16                                                                                     |  |  |
| Infections and infestations<br>Rhinitis<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                                          | 8 / 110 (7.27%)<br>9                                                                                        |  |  |
| Metabolism and nutrition disorders<br>Fluid overload<br>subjects affected / exposed<br>occurrences (all)<br><br>Fluid retention<br>subjects affected / exposed<br>occurrences (all)<br><br>Hypocalcaemia<br>subjects affected / exposed<br>occurrences (all)<br><br>Hypokalaemia<br>subjects affected / exposed<br>occurrences (all) | 6 / 110 (5.45%)<br>6<br><br>7 / 110 (6.36%)<br>9<br><br>6 / 110 (5.45%)<br>7<br><br>12 / 110 (10.91%)<br>14 |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 22 July 2014    | <ul style="list-style-type: none"><li>• Addition of hematology (CBC with differential), blood chemistry, and coagulation laboratory assessments during screening/prephase, as well as on cycle 1 days 1 and 2 for the monitoring of TLS, and prior to the start of treatment in subsequent cycles</li><li>• Revision of eligibility criteria to be inclusive of a broader population of pediatric subjects with relapsed/refractory ALL</li><li>• Refinement of guidelines for adverse event and serious adverse event reporting to minimize safety reporting burden on investigators:<ul style="list-style-type: none"><li>o Only CTCAE grade 3-5 adverse events, irrespective of etiology, were required to be reported</li><li>o Only related serious adverse events were required to be reported after the protocol-required reporting period</li><li>o Events from a prespecified list of expected disease-related serious adverse events were not required to be reported to Amgen within 24 hours following the investigator's knowledge of the event</li></ul></li></ul>                                                                                                                                                                              |
| 27 October 2014 | <ul style="list-style-type: none"><li>• Addition of hematology (CBC with differential), blood chemistry, and coagulation laboratory assessments during screening/prephase, as well as on cycle 1 days 1 and 2 for the monitoring of TLS, and prior to the start of treatment in subsequent cycles</li><li>• Revision of eligibility criteria to be inclusive of a broader population of pediatric subjects with relapsed/refractory ALL</li><li>• Refinement of guidelines for adverse event and serious adverse event reporting to minimize safety reporting burden on investigators:<ul style="list-style-type: none"><li>o Only CTCAE grade 3-5 adverse events, irrespective of etiology, are required to be reported</li><li>o Only related serious adverse events were required to be reported after the protocol-required reporting period</li><li>o Events from a prespecified list of expected disease-related serious adverse events were not required to be reported to Amgen within 24 hours following the investigator's knowledge of the event</li></ul></li><li>• Inclusion of references to country-specific protocol procedures and requirements</li><li>• Clarification made to definition of end of enrollment in a given country</li></ul> |

|                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 21 December 2015 | <ul style="list-style-type: none"> <li>To align regional requests into 1 global protocol, including changes that were requested by the EU agencies and that were assembled in a protocol supplement for the EU region.</li> <li>Additional changes included: <ul style="list-style-type: none"> <li>An increase of the sample size from ~ 40 to ~ 80 subjects</li> <li>Implementation of the following dosing changes and changes in treatment schedule to be aligned with other pediatric and adult blinatumomab studies at Amgen: <ul style="list-style-type: none"> <li>Subjects with M2 bone marrow at screening will start treatment at 15 µg/m<sup>2</sup>/day and not have a dose step</li> <li>The maximum dose administered was 28 µg/day</li> <li>Hydroxyurea may be used instead of dexamethasone for prephase treatment</li> </ul> </li> <li>Rules for infusion interruptions after CNS events and rules for treatment discontinuation were adapted, as well as some clarifications on premedication requirements for restart of infusion after interruptions added.</li> <li>Changes to the contraception requirements post blinatumomab in line with a request from the EMA.</li> <li>Overdoses &gt; 10% were defined as medically important events that were to be reported as serious adverse events</li> <li>Lactation and Pregnancy Notification Worksheets were replaced with the current version</li> <li>Correction and clarification of some inconsistencies in the protocol</li> <li>The definition of complete response was updated in Appendix E of the SAP</li> <li>Appendix H of the SAP Pregnancy and Contraceptive Guidelines were added.</li> </ul> </li> </ul> |
| 20 April 2016    | <ul style="list-style-type: none"> <li>Added sections to the protocol to align with recent updates to the protocol template (v13).</li> <li>Section 6.2.1 dosage language changed to set limits on daily dosing of blinatumomab. Rationale: Previously, dosage was based on BSA without an upper limit; change reflects an upper limit regardless of BSA, cytomorphology, or immunophenotype.</li> <li>Updated contraceptive language to align with the recent ICF amendment (v5) and changes to the Core Risk and Discomforts document (contraception requirement changed from 24 hours after last dose to 48 hours).</li> <li>Updated safety and safety reporting language to align with Amgen's adverse and serious adverse events policy, as well as align with recent updates to the protocol template (v13).</li> <li>Updated the safety event form and Lactation and Pregnancy Notification Worksheets to current versions.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| 23 August 2016   | <ul style="list-style-type: none"> <li>Replaced all event reporting time frames from "1 business day" to "24 hours" per an EU request</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| 13 March 2017    | <ul style="list-style-type: none"> <li>Updated Section 2.3 (Pediatric Risk Assessment) to include the most current number of adults and pediatric/adolescent subjects that have received study drug in research studies</li> <li>Updated inclusion criterion to broaden the level of blasts in bone marrow at study enrollment.</li> <li>Updated Section 5 (Subject Enrollment) and Section 7 (Study Procedures) to include the Product History Form for subjects who were enrolled in a previous Amgen blinatumomab study</li> <li>To align Section 9 (Safety Data Collection, Recording, and Reporting), Section 12.6 (Publication Policy), and End of Study language with current protocol template language</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| 07 July 2017     | <ul style="list-style-type: none"> <li>Increased sample size from 80 to 100 subjects</li> <li>Moved the endpoint of MRD remission rate within 2 cycles of treatment with blinatumomab from the final analysis to the primary analysis</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| 07 June 2018     | <ul style="list-style-type: none"> <li>Extended the long-term follow-up in the study past 18 months for pediatric subjects who did not receive a transplantation after blinatumomab treatment (maintenance therapy).</li> <li>Clarified the frequency and types of data that will be collected for subjects in the extended long-term follow-up group until they are 18 years old.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |

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Notes:

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported