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## STATISTICAL ANALYSIS PLAN

A Phase 1b/2 Study of Blinatumomab in Japanese Subjects With  
Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia (ALL)  
(Horai Study)

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| Version Number       | Date<br>(DDMMYYYY) | Summary of Changes,<br>including rationale for changes   |
|----------------------|--------------------|--|
| Original (v 1.0)     |                    |  |
| [Amendment 1 (v2.0)] | 06Oct2016          | <ul style="list-style-type: none"> <li>• The clarification of primary efficacy endpoint for adult subjects (both Phase 1b and Phase 2) to be CR/CRh*. The terms of “complete remission”, “CR”, “CR/CRh*/CRI”, “CR/CRh*” were used interchangeably in the protocol.</li> <li>• The clarification of primary efficacy endpoint for pediatric subjects to be M1 remission.</li> <li>• The clarification of RFS and Duration of Response endpoints for subjects who met primary efficacy endpoint (CR/CRh* for adult subjects and M1 remission for pediatric subjects).</li> <li>• Clarification for time to event analyses for OS, RFS, and TTHR that those analyses will only be done when sample size allows.</li> <li>• Clarification of subgroup analyses based on planned covariates in <a href="#">Section 4.2</a> that subgroup analyses will only be done when sample size allows.</li> <li>• Update of language for concomitant medication summary in <a href="#">Section 10.7.6</a>.</li> <li>• Addition of language for potential interim analysis based on Phase 1b data only to support early JNDA filing in <a href="#">Section 8</a>.</li> </ul> |
| [Amendment 2 (v3.0)] | 12Apr2019          | <ul style="list-style-type: none"> <li>• Added endpoints, analysis set, analysis to be performed for Expansion cohort.</li> <li>• Removed CR/CRh* as secondary efficacy endpoint from table 3 as it has already been identified as primary efficacy endpoint for adults in Phase 1b.</li> <li>• Updated the language in table 4 to be consistent with CSR for Primary analysis.</li> <li>• Removed MRD analysis set because MRD response and Complete MRD response will be analyzed based on FAS and this is consistent with Protocol.</li> <li>• Some editorial changes are also made to be consistent with protocol.</li> </ul>  |

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## Table of Abbreviations

| Abbreviation or Term | Definition/Explanation                                    |
|----------------------|---|
| AE                   | adverse event   |
| ALL                  | acute lymphoblastic leukemia                              |
| alloHSCT             | allogeneic hematopoietic stem cell transplant             |
| ANC                  | absolute neutrophil count                                 |
| BiTE®                | bispecific T-cell engager                                 |
| CI                   | confidence interval                                       |
| CIVI                 | continuous intravenous infusion                           |
| CMV                  | Cytomegalovirus   |
| CNS                  | central nervous system                                    |
| CR                   | complete remission  |
| CRF                  | case report form  |
| CRh*                 | complete remission with partial hematological recovery    |
| CRi                  | complete remission with incomplete hematological recovery |
| CRS                  | cytokine release syndrome                                 |
| CSR                  | clinical study report                                     |
| CSF                  | cerebrospinal fluid                                       |
| CTCAE                | common terminology criteria for adverse events            |
| DLT                  | dose limiting toxicity                                    |
| DRC                  | data review committee                                     |
| DSMB                 | Data Safety Monitoring Board                              |
| ECOG                 | Eastern Cooperative Oncology Group                        |
| EOI                  | AEs of interest   |
| FAS                  | full analysis set   |
| HAMA                 | human anti-mouse antibodies                               |
| HSCT                 | hematopoietic stem cell transplant                        |
| ITT                  | intent-to-treat   |
| IV                   | Intravenous   |
| K-M                  | Kaplan-Meier  |
| MAD                  | maximum administered dose                                 |
| MedDRA               | Medical Dictionary for Regulatory Activities              |
| MRD                  | minimal residual disease                                  |
| MTD                  | maximum tolerated dose                                    |
| OS                   | overall survival  |
| PCR                  | polymerase chain reaction                                 |

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| Abbreviation or Term | Definition/Explanation        |
|----------------------|-------------------------------|
| PD                   | pharmacodynamics              |
| PK                   | pharmacokinetics              |
| PPS                  | per protocol set              |
| PR                   | partial response              |
| R/R                  | relapsed/refractory           |
| RFS                  | relapse free survival         |
| SAP                  | statistical analysis plan     |
| TTHR                 | time to hematological relapse |
| ULN                  | upper limit of normal         |
| WHO                  | World Health Organization     |

## 1. Introduction

The purpose of this statistical analysis plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocol for blinatumomab Study 20130265, **Amendment 5 (20 March 2019)**, entitled “A Phase 1b/2 Study of Blinatumomab in Japanese Subjects With Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia (ALL) (Horai Study)”.

The scope of this plan includes the interim analysis, the primary analysis, and the final analysis (**including expansion cohort**) that are planned and will be executed by Amgen’s Global Biostatistical Sciences department unless otherwise specified. Pharmacokinetics (PK) analysis will be provided by Department of Clinical Pharmacology, Modeling and Simulation (CPMS). Changes to the statistical analysis plan should be allowed to the extent that such deviations from the original plan would provide more reliable and valid analyses of the current data. Any “post hoc” or “data driven” analyses will be identified as such in the final clinical study report (CSR).

## 2. Objectives

### 2.1 Primary Objectives

Phase 1b

- To determine the maximum tolerated dose (MTD) of blinatumomab in adult and pediatric subjects with R/R B-precursor ALL.

Phase 2

- To further evaluate in adults the recommended dose identified in the Phase 1b portion of the study and to evaluate the rate of CR/CRh\* in adult subjects with R/R B-precursor ALL who receive blinatumomab.

### Expansion Cohort

- **To observe the incidence of treatment-emergent and treatment-related adverse events during treatment with blinatumomab in adult and pediatric subjects with R/R B-precursor ALL**

### 2.2 Secondary Objectives

Phase 1b

- To evaluate the safety, efficacy, pharmacokinetics (PK), and pharmacodynamics (PD) of blinatumomab in adult and pediatric subjects with R/R B-precursor ALL.



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## Phase 2

- To evaluate other measures of efficacy, safety and PK in adult subjects with R/R B-precursor ALL at the blinatumomab regimen selected based on the Phase 1b data.

### Expansion Cohort

- **To evaluate the efficacy of blinatumomab in adult and pediatric subjects with R/R B-precursor ALL.**

## 3. Study Overview

### 3.1 Study Design

This is an open-label **combined** two-part multi-center clinical study to evaluate the efficacy, safety, and tolerability of blinatumomab in adult and pediatric Japanese subjects with R/R B-precursor ALL. The Phase 1b part will investigate the safety, efficacy, PK, and PD of blinatumomab to determine the MTD in adult and pediatric Japanese subjects respectively with R/R B-precursor ALL. In adult subjects, the Phase 2 part will assess the safety and efficacy of the recommended dose level of blinatumomab identified in the Phase 1b portion of the study in the adult study population. No phase 2 part is planned for the pediatric population in this study.

The study design for Phase 1b, Phase 2 **and Expansion** parts include:

- A 2-week Screening and Pre-Phase Period  
The pre-phase period within the screening period is permitted for the administration of dexamethasone to reduce tumor burden and the incidence of tumor lysis syndrome.
- Induction Phase  
Up to two induction cycles of blinatumomab. A single cycle of blinatumomab is defined as 6 weeks in duration, which includes 4 weeks of continuous intravenous infusion (CIVI) of blinatumomab followed by a 2-week treatment-free interval.
- Consolidation Phase  
Subjects who achieve a bone marrow response (blasts  $\leq 5\%$ ) within 2 induction cycles of treatment may continue to receive additional consolidation cycles of blinatumomab (up to a maximum of 5 total induction and consolidation cycles, or disease progression, intolerable adverse event or withdrawal of consent) under the same schedule as outlined in the induction treatment phase above.

- A safety follow-up visit is required 30 ( $\pm$  3) days after last dose of blinatumomab. Following the safety follow-up visit, subjects will be followed at 3, 6, 9, 12, 18, and 24 months ( $\pm$  2 weeks) after treatment start for disease **and survival status**. Subjects will return to the clinic for assessments until relapse, with the following exceptions:
  - Subjects who fail to achieve a bone marrow response (blasts  $\leq$  5%) within 2 induction cycles of blinatumomab treatment will undergo the safety follow-up visit and will be followed by telephone contacts in the long-term follow-up phase of the study.
  - Subjects who go on to receive allogeneic hematopoietic stem cell transplant (alloHSCT) or begin other treatment for ALL at any time following the first treatment cycle will undergo the safety follow-up visit and will be followed by telephone contacts in the long-term follow-up phase of the study.
- **For Expansion cohort, subjects will not be followed after safety follow-up visit. The subject will complete the study at the time of the safety follow-up visit.**

The overall study design is described by a study schema at the end of the protocol synopsis section.

### 3.2 Sample Size

The maximum sample size of 57 subjects (maximum of 36 for the Phase 1b part, 21 for the Phase 2 part) will be enrolled into this study. **Approximately 65 subjects (not restricted), including adult and pediatric subjects, may be enrolled in the expansion cohort.**

#### Phase 1b Part

No formal sample size estimation and statistical testing will be applied to the Phase 1b part of the study. The sample size for the dose finding phase of this study will be determined by the incidence and severity of adverse events in a rolling six Phase 1b design. For each population (adults and pediatric subjects), a minimum of 2 and up to 6 evaluable subjects will be enrolled at each dose level for determination of the dose to be selected for the Phase 2 efficacy part of the study, for a total of between 12 and 36 subjects.

#### Phase 2 Part

For the Phase 2 part of the study, the sample size estimation is based on the primary efficacy endpoint of hematological response. Simon's mini-max 2-stage design (Simon, 1989) is used with a sample size (13 subjects in the first stage, 21 evaluable

subjects total) based on a 1-sided type 1 error of 0.025 and a power of 90% to detect the effective response rate assumption of  $\geq 40\%$  over an ineffective treatment rate of  $\leq 10\%$ . The study will be stopped at the first stage if 1 or fewer out of 13 subjects are observed with CR/CRh\* in the first stage. If at least 6 or more out of 21 subjects show CR/CRh\* within 2 cycles of treatment with blinatumomab at the end of the second stage, one will be able to reject study's ineffective treatment assumption (refer to [Table 1](#)).

### **Expansion cohort**

For the expansion cohort of the study, the sample size is based on the enrollment rate in the Phase 1b and Phase 2 portion of the study in consideration of the expected time frame in which blinatumomab will be available in the commercial market in Japan.

**Table 1. CR/CRh\* Rates With Confidence Intervals for Phase 2 Part**

| Number of Subjects Reporting CR/CRh* at the end of cycle 2 | Observed CR/CRh* Rate (%) (N=21) | Exact 95% CI |
|--|----------------------------------|--------------|
| 5  | 23.8                             | (8.2, 47.2)  |
| 6  | 28.6                             | (11.3, 52.2) |
| 8  | 38.1                             | (18.1, 61.6) |
| 12   | 57.1                             | (34.0, 78.2) |
| 14   | 66.7                             | (43.0, 85.4) |

CR/CRh\* = complete remission/complete remission with partial hematological recovery.

## **4. Study Endpoints and Covariates**

### **4.1 Study Endpoints**

#### **4.1.1 Phase 1b Endpoints**

##### **Phase 1b Primary Endpoint:**

- Incidence of DLTs

##### **Phase 1b Secondary Endpoints:**

- CR/CRh\* within **first** 2 cycles of treatment with blinatumomab for adult subjects
- M1 remission within first 2 cycles of treatment with blinatumomab for pediatric subjects
- Duration of response (or Time to hematological relapse, TTHR)
- Relapse free survival (RFS)
- Overall survival (OS)
- Incidence and severity of adverse events

- Blinatumomab PK parameters (eg, steady state concentration [C<sub>ss</sub>] and clearance of blinatumomab)
- Serum cytokine concentrations
- Incidence of anti-blinatumomab antibody formation

**Phase 1b Exploratory Endpoints:**

- Minimal Residual Disease (MRD) response
- Complete MRD response

**4.1.2 Phase 2 Endpoints**

**Phase 2 Primary Endpoint:**

- CR/CRh\* within 2 cycles of treatment with blinatumomab

**Phase 2 Secondary Endpoints:**

- Duration of response (or TTHR)
- RFS
- Allogeneic HSCT (alloHSCT) treatment with blinatumomab
- Best overall response within 2 cycles of treatment with blinatumomab
- OS
- Incidence and severity of adverse events
- 100-day mortality after alloHSCT
- Blinatumomab PK parameters (eg, steady state concentration [C<sub>ss</sub>] and clearance of blinatumomab)
- Serum cytokine concentrations
- Incidence of anti-blinatumomab antibody formation

**Phase 2 Exploratory Endpoints:**

- MRD response
- Complete MRD response
- Peripheral blood lymphocyte subsets
- Neurological exam abnormalities and changes from baseline

**4.1.3 Expansion Endpoints**

**Expansion Primary Endpoint:**

- Incidence of treatment-emergent and treatment-related adverse events

**Expansion Secondary Endpoint:**

- **CR/CRh\* within first 2 cycles of treatment with blinatumomab for adult subjects**
- **M1 remission within first 2 cycles of treatment with blinatumomab for pediatric subjects**

**Expansion Exploratory Endpoint:**

- **MRD remission within first 2 cycles of blinatumomab**

**4.2 Planned Covariates**

Adult subjects and pediatric subjects will be summarized separately. Endpoints for adult subjects may also be described using the following subgroups as appropriate:

- Age ( $\leq 34$  yrs, 35-64 yrs,  $\geq 65$  yrs)
- Number of previous salvage therapies
- No prior HSCT, at least one prior HSCT
- Primary refractory or 1 relapse, 2 relapses, > 2 relapses prior to study entry
- Platelet counts at baseline (< 50,000; 50,000 to < 100,000;  $\geq 100,000/ \mu\text{L}$ )

Endpoints for Phase 1b part may not be described by the subgroup due to limited sample size. **Due to limited sample size endpoints for pediatric subjects will not be described by the subgroups.** Subgroup analyses will only be performed if there are at least two categories with at least 5 subjects in each of the categories.

**5. Hypotheses and/or Estimations**

**5.1 Phase 1b**

No formal hypothesis will be tested in Phase 1b part of the study.

**5.2 Phase 2**

The clinical hypothesis for the phase 2 part of the study is that blinatumomab will have clinical activity in the treatment of adult R/R ALL as measured by the rate of CR/CRh\* within 2 cycles. The study will test a null hypothesis that the level of clinical activity is an ineffective level of 10% or less. The assumed level of effective clinical activity is at least 40%.

**5.3 Expansion cohort**

**No formal hypothesis will be tested in Expansion cohort of the study.**

## 6. Definitions

### **Baseline**

Baseline is defined as the value taken on day 1 of the first cycle before start of infusion of blinatumomab. If such value is not available it may be replaced by the latest available value taken before start of the first blinatumomab infusion during the study.

### **Blast free hypoplastic or aplastic bone marrow**

For adult subjects:

Less than or equal to 5% blasts in the bone marrow, No evidence of disease, and insufficient recovery of peripheral blood counts: platelets  $\leq 50,000/\mu\text{L}$  and/or ANC  $\leq 500/\mu\text{L}$ .

For pediatric subjects, this treatment outcome will be considered as part of M1 remission.

### **Complete MRD response**

Complete MRD response is defined as having no detectable leukemia cells by PCR (**or flow cytometry**). Sensitivity and quantitative measurement range of assay need to be at least  $10^{-4}$ .

### **Complete remission (CR)**

CR is defined as  $\leq 5\%$  blasts in the bone marrow, no evidence of disease, and full recovery of peripheral blood counts: platelets  $> 100,000/\mu\text{L}$  and ANC  $> 1,000/\mu\text{L}$ .

### **Complete remission with partial hematological recovery (CRh\*)**

CRh\* is defined as  $\leq 5\%$  blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts: platelets  $> 50,000/\mu\text{L}$  and ANC  $> 500/\mu\text{L}$  (but not a CR).

### **DLT observation period**

The time for the DLT assessment will be the first 14 days of treatment based on the observation that most adverse events are usually observed within a few days of treatment initiation and dose step. If the dose modification for pediatric subjects per [Table 2](#) is followed, time for the DLT assessment will be the first 21 days. An observed DLT will be attributed to the blinatumomab dose level administered at the time at which the DLT occurred.

**Table 2. Treatment Modification for Reversible CRS, Tumor Lysis Syndrome, and DIC**

| Current Dose              | Week 1                      | Week 2 (Day 8)            | Week 3-4 (Day 15)         |
|---------------------------|-----------------------------|---------------------------|---------------------------|
| 5 µg/m <sup>2</sup> /day  | 3.75 µg/m <sup>2</sup> /day | 5 µg/m <sup>2</sup> /day  | 15 µg/m <sup>2</sup> /day |
| 15 µg/m <sup>2</sup> /day | 5 µg/m <sup>2</sup> /day    | 15 µg/m <sup>2</sup> /day | 15 µg/m <sup>2</sup> /day |
| 10 µg/m <sup>2</sup> /day | 5 µg/m <sup>2</sup> /day    | 10 µg/m <sup>2</sup> /day | 10 µg/m <sup>2</sup> /day |

In addition, an incomplete treatment cycle with a treatment duration of less than 2 weeks will not be counted as an evaluable cycle for the primary endpoint and will have to be repeated (eg, if cycle 1 was interrupted on day 8 for more than 7 days, the next cycle will be denoted as cycle 1.1 and the same assessments will be performed as in cycle 1.)

**Dose limiting toxicity (DLT)**

A DLT will be defined as follows:

- Any CTCAE grade  $\geq 3$  adverse event related to blinatumomab, with exceptions noted below.
- Persistent CTCAE grade  $\geq 2$  non-hematologic adverse events related to blinatumomab that are deemed intolerable by the subject or the treating physician that do not respond to appropriate medical management within 5 days and lead to treatment discontinuation.
- Non-hematologic or non-infection adverse events related to blinatumomab leading to treatment discontinuation lasting  $>14$  days are to be considered DLTs by the DRC

The following will not be considered DLTs:

- Specific CTCAE grade  $\geq 3$  adverse events considered to be consistent with the current known safety profile of blinatumomab.
- CTCAE grade  $\geq 3$  fever or infection.
- Laboratory parameters of CTCAE grade  $\geq 3$  not considered clinically relevant and/or responding to routine medical management.

**End of study for individual subject**

Defined as the last day that protocol-specified procedures are conducted for an individual subject.

**Hematological Relapse (HR)**

For adult subjects:

Proportion of blasts in bone marrow  $> 5\%$  or blasts in peripheral blood after documented CR/CRh\* during the study.

For pediatric subjects:

Proportion of blasts in bone marrow > 25% following documented M1 remission.

An extramedullary relapse will be considered as a relapse event. The relapse may be subdivided in CD19 positive and CD19 negative relapses if available.

### **Hypocellular or acellular bone marrow**

For pediatric only:

Not achieve M1 bone marrow status, no evidence of disease, and Insufficient recovery of peripheral blood counts: Platelets  $50 \times 10^9/L$  and/or ANC  $\leq 0.5 \times 10^9/L$

### **M1 remission**

For pediatric subjects only: M1 remission is defined as  $\leq 5\%$  blasts (M1 bone marrow) in the bone marrow and no evidence of disease.

### **Maximal administered dose (MAD)**

The MAD to be tested for this study is  $28\mu g/day$  for adults and  $15 \mu g/m^2/day$  for pediatric subjects.

### **MRD progression**

Increase in the MRD level by one log as compared to the baseline level which is equal to a 10-fold increase in the number of MRD cells.

### **MRD relapse**

For adult subjects: Re-appearance of leukemic cells detectable by PCR (**or flow cytometry**).

For pediatric subjects: Increase of MRD level from last assessment by at least 1 log following an MRD response.

### **MRD response**

MRD  $< 10^{-4}$  measured by PCR (**or flow cytometry**).

### **Non-response**

For adult subjects only: None of CR, CRh\*, CRi, Blast free hypoplastic or aplastic bone marrow, Partial Remission or Progressive Disease.

### **Overall survival (OS)**

OS will be calculated relative to the start date of blinatumomab infusion in the first treatment cycle. All deaths will count as events on the date of death.



Patients alive will be censored on the last documented visit date or the date of the last phone contact when the patient was last known to have been alive. For patients who have withdrawn their informed consent, only information until the date of withdrawal will be used for analysis.

As a sensitivity analysis, OS may also be measured whereby survival will be censored at the time of HSCT.

### **Partial Remission (PR)**

For adult subjects:

Bone marrow blasts **> 5% - < 25%** with at least a 50% reduction from baseline

For pediatric subjects: complete disappearance of circulating blasts, achievement of M2 **bone** marrow status (**>5%** to **< 25%** blast cells), and appearance of normal progenitor cells.

### **Progressive Disease (PD)**

PD is defined as the followings:

**For adult subjects**, an increase from baseline of at least 25% of bone marrow blasts or an absolute increase of at least 5,000 cells/uL (whichever is greater), in the number of circulating leukemia cells.

**For Pediatric subjects**, an increase from baseline of at least 25% or an absolute increase of at least 5,000 cells/uL (whichever is greater), in the number of circulating leukemia cells, development of extramedullary disease, or other laboratory or clinical evidence of progressive disease.

### **Relapse-free survival (RFS)**

RFS is defined for subjects who achieved a response (CR/CRh\* for adult subjects or M1 remission for pediatric subjects) during the induction phase. It will be calculated relative to the date of bone marrow aspiration when response (CR/CRh\* for adult subjects or M1 remission for pediatric subjects) was detected for the first time during the induction phase. The date of bone marrow aspiration at which hematological relapse was first detected or the date of diagnosis on which the hematological or extra medullary relapse was documented or the date of death due to any cause will be used as the event date for relapse-free survival, whichever is earlier.

A patient who did not experience hematological relapse and did not die will be censored on the date of the last available bone marrow aspiration prior to data cutoff date of analysis.

As a sensitivity analysis, RFS may also be measured whereby censoring will occur at the time of HSCT.

### **Stable disease (SD)**

For pediatric patients only: fail to qualify for M1 remission, PR or PD.

### **Study completion**

#### **Phase 1b/2**

Patients who **have** completed the scheduled visits of induction **and consolidation** phase, **safety follow-up** and **long-term** follow-up period are deemed as study completion.

#### **Expansion cohort**

**Patients who have completed the scheduled visit of induction and consolidation phase and safety follow-up period are deemed as study completion. Long-term follow-up is not required for subjects participating in expansion phase.**

### **Study day 1**

Defined as the first day that protocol-specified investigational product(s)/protocol required therapies is/are administered to the subject.

### **Duration of response (or Time to hematological relapse, TTHR)**

The Duration of response will be calculated relative to the date of bone marrow aspiration when response (CR/CRh\* for adult subjects or M1 remission for pediatric subjects) was detected for the first time during the induction phase. Patients with response who did experience hematological relapse or PD, the end date of duration will be based on:

- the date of bone marrow aspiration at which hematological relapse or PD was first detected,
- the date of diagnosis on which the hematological or extra medullary relapse was documented,
- the date of death if patient died due to PD
- the date of end of induction phase if primary reason for treatment termination was hematological or extramedullary relapse

whichever is earlier and considered as reporting an event.

For a responder who did not report an event and was alive during the study, the end date of duration (censoring) will be based on the date of the last available bone marrow aspiration prior to data cutoff date of analysis.

Patients with response who did not report an event and did die due to other reason, the end date will be the date of death. Such deaths will be treated as competing risks in the analysis ([Hosmer, Lemeshow, and May, 2008](#)) using cumulative incidence function method when appropriate.

As a sensitivity analysis, duration of response may also be measured whereby censoring will occur at the time of HSCT.

### **Treatment emergent adverse events (TEAEs)**

TEAEs are defined as those, which start between the start of the first infusion of blinatumomab and 30 days after the end of the last infusion during the **treatment period**. In case the start time or the exact start date of the AE is not available and it is thus unclear, whether an AE started after start of first blinatumomab infusion or before 30 days after the end of last infusion then the AE will be included in the analysis as TEAE.

## **7. Analysis Subsets**

### **7.1 Full Analysis Set**

All subjects who received any infusion of blinatumomab are included in the full analysis set (FAS) for phase 1b and phase 2 portion of the study respectively. This definition is in line with the intent-to-treat (ITT) principle in single-arm open-label studies. The efficacy analysis will be based on subjects from the FAS.

### **7.2 Safety Analysis Set**

For each part of the study, the safety analysis set will be the same as the FAS for that part.

### **7.3 DLT Analysis Set**

For the assessment of DLTs, only DLT evaluable subjects will be included.

### **7.4 Per Protocol Set(s) (PPS)**

For each part of the study, the per protocol set will include all subjects from the FAS for that part who do not have any major relevant protocol violations which could have an impact on the efficacy evaluations.

### 7.5 Pooled Adult Analysis Set (PAS)

The pooled analysis set will be an exploratory pooled analysis set that will include adult subjects from the FAS from Phase 1b and from the FAS from Phase 2. This additional pooled analysis will be performed for safety data and the primary and secondary efficacy endpoints for adult subjects.

### 7.6 Pharmacokinetic/Pharmacodynamic Analyses Set(s)

All subjects who received any infusion of blinatumomab and had at least one PK sample collected will be included in the PK analysis set. These subjects will be evaluated for PK unless significant protocol deviations affect the data analysis or if key dosing, dosing interruption or sampling information is missing. All subjects who had cytokine and/or lymphocyte subset samples collected at any time during the study will be included in the PD analysis set.

### 7.7 Expansion Analysis Set (EAS)

**All subjects who are enrolled in the expansion cohort and received any infusion of blinatumomab will be included in the Expansion analysis set.**

## 8. Interim Analysis and Early Stopping Guidelines

An interim analysis will be performed at the latest during the Phase 2 part of the study after the first 13 adult subjects who are enrolled in the first stage have either discontinued treatment or completed their first 2 treatment cycles. The purpose of this interim analysis will **be to** determine whether the second stage of the Phase 2 part of the protocol should continue per the study design. The study will be stopped at the first stage if 1 or fewer out of 13 subjects are observed with any CR/CRh\* in the first stage of the Phase 2 part of the study. Should 2 or more subjects achieve a CR/CRh\* prior to first 13 subjects evaluated, the first stage criteria would be met. An interim analysis may be performed based on Phase 1b data only for early JNDA filing if needed.

Additional interim analyses may be performed to provide data for regulatory interactions. The purpose of these interim data analyses is to provide the safety and efficacy information updates.

For Phase 1b dose-cohort study de-escalation and stopping rules, please refer to protocol section 6.2.2. During phase 1b, DRC will review safety data from each cohort in the Phase 1b part to select a dose for the Phase 2 part. In addition, DSMB will also oversee safety approximately every 6 months.

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## **9. Data Screening and Acceptance**

### **9.1 General Principles**

The database will be subjected to edit checks outlined in the data validation specifications plan by Amgen Clinical Data Management (CDM) department. Any outstanding data issues will be communicated to CDM for resolution before the database is locked.

Quintiles Inc. will provide support for data management activities and assess the quantity, quality and statistical characteristics of the data relative to the requirements of the planned analyses.

### **9.2 Data Handling and Electronic Transfer of Data**

Amgen's CDM department will provide all data to be used in the planned analyses. This study will use the RAVE database.

The results of the central lab, such as cytomorphology (% of blasts in bone marrow), HAMA, and lymphocytes will be analyzed by central laboratory vendors. Antibody, Cytokine, and PK samples will be shipped from sites to the Biolanalytics department at Amgen for analysis. These additional laboratory data will be transferred to CDM and then loaded into the clinical database.

All data for this study will be submitted directly to CDM for inclusion into the clinical study database.

Once all data queries have been resolved, and source verified and initial locked, the database will be final locked. The final analysis will be conducted on the final lock data. The final SAS data sets will be archived.

### **9.3 Handling of Missing and Incomplete Data**

In general, missing data will be treated as missing, unless otherwise specified. For primary efficacy endpoint, patients with missing response will be considered as non-responders. Attempts will be made to characterize the missing data. Instead, it is recommended to perform a set of sensitivity analyses to demonstrate how missing values may influence estimates and the corresponding test decisions.

Data will be analyzed as retrieved from the database provided by CDM except for analyses requiring imputations. The imputed data will be written to the derived datasets but not to the raw data. The imputation algorithm will be described in the Data Definition Table (DDT). Please refer to [Appendix D](#) for the general imputation algorithm.

#### **9.4 Detection of Bias**

The sources of possible bias will be summarized and be considered while interpreting study results. Sources of bias to be considered may include protocol violations or informative censoring.

#### **9.5 Outliers**

No statistical test for outliers will be performed. Any suspected outliers will be investigated by the study team and will be included in the database unless determined to be an error or there is supporting evidence or explanation to justify the exclusion. Any outliers excluded from the analysis will be discussed in the CSR, including the reasons for exclusion and the impact of their exclusion on the study.

#### **9.6 Distributional Characteristics**

Due to the single-arm study, the summaries of analyses results are descriptive in nature.

#### **9.7 Validation of Statistical Analyses**

SAS<sup>®</sup> version 9.2 or higher will be utilized in programming for all statistical analyses, derived data and tables, listings and figures (TFL) creation. Where possible, the standard departmental macros will be used. Testing and validation plans for all programs will be developed in accordance with departmental guidelines or Metronomia procedures.

### **10. Statistical Methods of Analysis**

#### **10.1 General Principles**

Adult subjects and pediatric subjects will be summarized separately. Pediatric subjects will not enroll into phase 2 for hypothesis testing. The efficacy endpoint results of pediatric subjects will be listed and descriptive.

#### **Analysis for expansion cohort will be based on Expansion analysis set.**

A clinical study report will be generated for the primary analysis. The long-term follow-up period of the study will be updated in the report once all the subjects have completed long-term follow-up, until lost to follow-up, or until death (whichever occurs first). All documented parameters will be adequately evaluated. The data will be summarized overall, and by assigned dose cohort using suitable descriptive measures.

The DLT findings during the Phase 1b part will be tabulated. Descriptive statistics for demographic and baseline characteristics will be summarized.

For categorical variables, the number and percentage of subjects in each category will be summarized. Continuous variables will be summarized by n, mean, standard deviation, median, Q1 (25th percentile), Q3 (75th percentile), minimum, and maximum values.

Point estimates for efficacy endpoints incidences will be accompanied by 2-sided 95% exact binomial confidence intervals (CIs) (Clopper and Pearson, 1934). For time to event variables, the Kaplan-Meier (K-M) method (Kaplan and Meier, 1958) will be used to estimate the quartiles (median, 25th and 75th percentiles) of the variable, along with 95% two-sided CI (Brookmeyer and Crowley, 1982) or others specified. The range, first quartile, and the third quartile of the observation time will be provided in addition. K-M estimates will be presented graphically.

No adjustments for multiplicity are planned for the analyses of the efficacy endpoints. Additional exploratory analyses will be performed to adjust for the baseline covariates as deemed appropriate.

## **10.2 Subject Accountability**

The number of subjects who screened, enrolled, received at least one dose of blinatumomab, completed the first two cycles and follow-up period, completed study, prematurely withdrew, and the reason for premature withdrawal will be tabulated and summarized overall and by dose cohort.

## **10.3 Important Protocol Deviations**

Important protocol deviations will be listed. Decisions on the exclusion of a patient from the PPS are on a by-patient basis. All criteria and reasons for these decisions will be documented. Eligibility deviations are defined in the protocol.

## **10.4 Demographic and Baseline Characteristics**

Demographics and other baseline characteristics will be summarized overall by dose cohort by means of summary statistics (number of patients, number of patients with missing data, mean, standard deviations, minimum, median, maximum) for continuous variables and by frequencies for categorical variables.

Demographic data and other baseline characteristics will be summarized **using FAS for Phase 1b and Phase 2 part of the study whereas Expansion Analysis Set will be used for Expansion cohort.** For the following variables, frequency tables will be produced:

- Gender
- Race
- Age by group
- Disease evaluation (B-ALL subtype) and genetic abnormality
- Study entry criteria (Primary refractory, refractory to salvage therapy, first relapse with remission duration less than 12 months, untreated 2<sup>nd</sup> or greater relapse, and relapse after allo-HSCT)
- Any extramedullary disease
- Prior HSCT status
- Number of relapses
- Refractory
  - Number of patients primary refractory
  - Number of patients relapse refractory (refractory to salvage therapy)
- Number of prior salvage therapy
- ECOG (adults) or Lansky/Karnofsky (pediatric) performance status

The following continuous variables will be summarized:

- Age
- Time since last HSCT [months]
- Time since initial diagnosis [months]
- Time between initial diagnosis and first relapse [months]
- Time between latest relapse and first dose of blinatumomab [months]
- Time between last HSCT and latest relapse [months]

#### **10.5 DLT**

Incidence rate of DLT will be summarized for adult subjects and pediatric subjects separately for Phase 1b Part of the study. The DLT summary will be based on the DLT analysis set.

#### **10.6 Efficacy Analyses**

The efficacy analyses for phase 1b and phase 2 parts of the study were summarized in tables below.



**Table 3. Efficacy Endpoint Summary for Phase 1b**

| Phase 1b Endpoint   | Primary Summary and Analysis Method   | Sensitivity Analysis   |
|---|---|--|
| Primary Efficacy Endpoint   |   |  |
| Response: CR/CRh* for adult subjects or M1 remission for pediatric subjects | <ul style="list-style-type: none"> <li>Summary statistics of CR/CRh* rate for adult subjects or M1 remission rate for pediatric subjects within the first 2 cycles.</li> <li>Sub-categories will also be provided. The rate will be estimated along with its 95% exact CI. FAS subjects without response data will be treated as non-responders.</li> </ul> | <ul style="list-style-type: none"> <li>Repeat the analysis for subjects in the FAS who had non-missing post-baseline response data.</li> <li>May repeat the analysis for PPS when deemed appropriate.</li> </ul> |
| Secondary Efficacy Endpoints  |   |  |
| Duration of Response (or TTHR)  | <ul style="list-style-type: none"> <li>FAS subjects in first 2 cycles who achieved response (CR/CRh* for adult subjects or M1 remission for pediatric subjects) are included.</li> <li>Cumulative incidence function considering competing risk will be provided when sample size is appropriate.</li> </ul>  | <ul style="list-style-type: none"> <li>Censoring at the time of HSCT may be considered as deemed as appropriate.</li> </ul>  |
| Overall survival  | <ul style="list-style-type: none"> <li>FAS subjects in first cycle will be used</li> <li>K-M estimates will be utilized and 3, 6 and 12 months rates will be provided when sample size is enough.</li> </ul>  | <ul style="list-style-type: none"> <li>Censoring at the time of HSCT may be considered as deem as appropriate.</li> </ul>  |
| RFS   | <ul style="list-style-type: none"> <li>FAS subjects in first 2 cycles who achieved response (CR/CRh* for adult subjects or M1 remission for pediatric subjects) are included.</li> <li>K-M estimates will be utilized and 3, 6 and 12 months rates will be provided when sample size is appropriate.</li> </ul>   | <ul style="list-style-type: none"> <li>Censoring at the time of HSCT may be considered as deem as appropriate.</li> </ul>  |
| Exploratory Efficacy Endpoints  |   |  |
| MRD response  | <ul style="list-style-type: none"> <li>Summary statistics of MRD response in <b>FAS</b>. The rate will be estimated along with its 95% exact CI. <b>Response rate is based on the number of subjects with a CR/CRh* and evaluable MRD.</b></li> </ul>   |  |
| Complete MRD response   | <ul style="list-style-type: none"> <li>Summary statistics of Complete MRD response in <b>FAS</b>. The rate will be estimated along with its 95% exact CI. <b>Response rate is based on the number of subjects with a CR/CRh* and evaluable MRD.</b></li> </ul>  |  |

**Table 4. Efficacy Endpoint Summary for Phase II (Adults Only)**

| Phase II Endpoint                | Primary Summary and Analysis Method  | Sensitivity Analysis   |
|----------------------------------|--|--|
| Primary Endpoint                 |  |  |
| CR/CRh*                          | <ul style="list-style-type: none"> <li>Summary statistics of CR/CRh* rate within first 2 cycles. The rate will be estimated along with its 95% exact CI. FAS subjects without response assessment will be treated as non-responders.</li> </ul>                | <ul style="list-style-type: none"> <li>Repeat the analysis for subjects in the FAS who had non-missing post-baseline response data.</li> <li>May repeat the analysis for PPS when deemed appropriate.</li> </ul> |
| Secondary Endpoints              |  |  |
| Duration of Response (or TTHR)   | <ul style="list-style-type: none"> <li>FAS subjects <b>who achieved CR/CRh* in first 2 cycles</b> are included.</li> <li>Cumulative incidence function considering competing risk will be provided when sample size is appropriate.</li> </ul>                 | <ul style="list-style-type: none"> <li>Censoring at the time of HSCT may be considered as deem as appropriate.</li> </ul>  |
| Received AlloHSCT                | <ul style="list-style-type: none"> <li>Summary statistics of proportion of AlloHSCT in FAS.</li> </ul>   |  |
| Best overall response (ORR)      | <ul style="list-style-type: none"> <li>Summary statistics of ORR within first 2 cycles. FAS subjects without response will be included.</li> <li>The rate will be estimated along with its 95% exact CI.</li> </ul>  | <ul style="list-style-type: none"> <li>Additional sensitivity analysis will be conducted and will exclude those subjects without any post-baseline response assessment.</li> </ul>                               |
| Overall survival                 | <ul style="list-style-type: none"> <li>FAS subjects will be used</li> <li>K-M estimates will be <b>used</b> and 3, 6 and 12 months rates will be provided.</li> </ul>  | <ul style="list-style-type: none"> <li>Censoring at the time of HSCT may be considered as deem as appropriate.</li> </ul>  |
| RFS                              | <ul style="list-style-type: none"> <li>FAS subjects <b>who achieved CR /CRh* in the first 2 cycles</b> are included.</li> <li>K-M estimates will be <b>used</b> and 3, 6 and 12 months rates will be provided when sample size is appropriate.</li> </ul>      | <ul style="list-style-type: none"> <li>Censoring at the time of HSCT may be considered as deem as appropriate.</li> </ul>  |
| 100-day mortality after alloHSCT | <ul style="list-style-type: none"> <li><b>Subset of subjects who undergo an alloHSCT in the FAS will be included. 1 minus the K-M survival estimate at day 100 will be provided</b> when sample size is appropriate.</li> </ul>                                |  |
| Exploratory Endpoints            |  |  |
| MRD response                     | <ul style="list-style-type: none"> <li>Summary statistics of MRD response in <b>FAS</b>. The rate will be estimated along with its 95% exact CI. <b>Response rate is based on the number of subjects with a CR/CRh* and evaluable MRD.</b></li> </ul>          |  |
| Complete MRD response            | <ul style="list-style-type: none"> <li>Summary statistics of Complete MRD response in <b>FAS</b>. The rate will be estimated along with its 95% exact CI. <b>Response rate is based on the number of subjects with a CR/CRh* and evaluable MRD.</b></li> </ul> |  |

**Table 5. Efficacy Endpoints Summary for Expansion cohort**

| Expansion Cohort Endpoint   | Primary Summary and Analysis Method   | Sensitivity Analysis   |
|---|---|--|
| <b>Secondary Endpoints</b>  |   |  |
| CR/CRh* for adult subjects or M1 remission for pediatric subjects | <ul style="list-style-type: none"> <li>Summary statistics of CR/CRh* rate for adult subjects or M1 remission rate for pediatric subjects within the first 2 cycles.</li> <li>Sub-categories will also be provided. The rate will be estimated along with its 95% exact CI. EAS subjects without response data will be treated as non-responders.</li> </ul> | <ul style="list-style-type: none"> <li>Repeat the analysis for subjects in the EAS who had non-missing post-baseline response data.</li> </ul> <p>May repeat the analysis for PPS when deemed appropriate.</p> |
| <b>Exploratory Endpoints</b>                                      |   |  |
| MRD response  | <ul style="list-style-type: none"> <li>Summary statistics of MRD response in EAS analysis set. The rate will be estimated along with its 95% exact CI. Response rate is based on the number of subjects with a CR/CRh* and evaluable MRD.</li> </ul>  |  |

**10.6.1 Analyses of Primary Efficacy Endpoint**

The primary efficacy endpoint in the study is CR/CRh\* for adult subjects or M1 remission for pediatric subjects within the first 2 cycles of blinatumomab treatment. The analysis is based on the response evaluation recorded in the eCRF for subjects in the FAS. The best response within the first 2 cycles will determine the primary efficacy endpoint. The subjects without evaluable response assessment will be included and treated as missing response status. The rate will be estimated along with its 95% exact CI. Summary of other best responses status by each response category will also be provided.

Sensitivity analyses may be performed by repeating the above analyses for subjects who had non-missing post-baseline response assessments and for PPS.

**10.6.2 Analyses of Secondary Efficacy Endpoint(s)**

When sample size is deemed appropriate (ie, at least 10 subjects), RFS and OS will be summarized by K-M method. Duration of response (or TTHR) will be estimated by the

nonparametric methods for estimating cumulative incidence function by treating the death not due to PD as a competing risk (Hosmer, Lemeshow, and May, 2008). OS will be performed on FAS and the event time will be calculated relative to the start date of blinatumomab infusion in the first treatment cycle. RFS and Duration of Response (or TTHR) will include subjects in the FAS who achieved CR/CRh\* (for adult subjects) or M1 remission (for pediatric subjects). The event time will be calculated relative to the date of bone marrow aspiration when response was detected for the first time in this study. For RFS and OS, three, six and twelve month survival rates will be provided. Additional summary considering the censoring at the time of HSCT may be considered for the sensitivity analysis purpose.

Proportion of subjects who undergo alloHSCT in remission due to treatment with blinatumomab will be summarized based on FAS. Subjects who receive an HSCT later during the long-term follow-up time of the study will be reported separately.

**When sample size is deemed appropriate**, the analysis of 100-day mortality after alloHSCT will be based on FAS with alloHSCT while in any CR following treatment with blinatumomab. The 100-day mortality rate after alloHSCT will be estimated by taking 1 minus the K-M survival proportion at day 100 on the subset of subjects who undergo an alloHSCT in the FAS.

**Secondary efficacy endpoints for expansion cohort in the study is CR/CRh\* for adult subjects or M1 remission for pediatric subjects within the first 2 cycles of blinatumomab treatment. Analysis of these endpoints based on Expansion analysis set (EAS) will be the same as for primary efficacy endpoints in phase 2.**

### 10.6.3 Analyses of Exploratory Endpoints

MRD response and complete MRD response will be summarized based on **FAS for phase 1b/2**. For expansion cohort, analysis for MRD response will be based on **EAS. Response rate is based on CR/CRh\* responder who have evaluable MRD assessment**. The rate will be estimated along with its 95% exact CI.

Peripheral blood lymphocyte subsets and neurological exam abnormalities and findings will be summarized based on FAS.

### 10.7 Safety Analyses

Safety analyses will include blinatumomab administration, adverse events, concomitant medications, laboratory measurement, vital signs, and antibody testing. Statistical analyses of safety will be carried out on the safety analysis set. No statistical

comparison of the overall incidence of adverse events will be done between dose cohorts.

Results of physical and neurological examinations and the writing test will be listed only. All data of HAMA assessments, hospitalization, anti-blinatumomab immunogenicity testing and pregnancy tests will be listed only.

The regular assessments of CSF and the CNS event related CSF assessments will be listed only.

**Safety assessments (as defined above), for Phase 1b (adults and pediatrics), Phase 2 (adults) and Expansion cohort (adults and pediatrics) will be reported as illustrated in the sections below.**

#### **10.7.1 Adverse Events**

The Medical Dictionary for Regulatory Activities (MedDRA) version 16.1 or later will be used to code all adverse events (AE) to a system organ class and a preferred term. All adverse event tables will be summarized by treatment group. Please refer to [section 6](#) for TEAE definition. Severity will be coded using CTCAE version 4.0 or later.

The subject incidence of AEs will be summarized for all treatment-emergent AEs, grade 3 and above AEs, serious AEs, treatment-related AEs, AEs leading to withdrawal of investigational product, fatal AEs, and AEs of interest (EOI). Subject incidence of EOIs will be summarized by SOC and PT according to the EOI search strategy categories defined by the EOI steering committee.

Subject incidence of all treatment-emergent AEs, grade 3 and above AEs, serious AEs, treatment-related AEs, AEs leading to withdrawal of investigational product, and fatal AEs will be tabulated by system organ class and preferred term in descending order of frequency.

Summaries of treatment-emergent and serious AEs occurring in at least 5% of the subjects by preferred term in any treatment arm may be provided in descending order of frequency.

When appropriate, subgroup analyses (if there is a medical rationale) will be presented by system organ class and preferred term in descending order of frequency. All races (if appropriate) with less than 5% of the total enrolled subjects will be pooled together for summary purposes.

### 10.7.2 Laboratory Test Results

Shift tables between the worst post-baseline and baseline values for selected laboratory parameters will be provided (based on the Common Terminology Criteria for Adverse Events ).

Graphs for the development of the following lab parameters will be provided:

- Immunoglobulin
- Thrombocytes (platelets)
- Liver parameters: alanine transaminase, aspartate transaminase, alkaline phosphatase, total bilirubin

### 10.7.3 Vital Signs

Notable values of systolic blood pressure, diastolic blood pressure and heart rate will be summarized at selected time points.

### 10.7.4 Antibody Formation

A table or listing summarizing the number and percentage of subjects with anti-drug antibodies to blinatumomab will be provided.

### 10.7.5 Exposure to Investigational Product

Descriptive statistics will be produced to describe the exposure to investigational product by dose cohort group and overall.

#### 10.7.5.1 Definitions of Variables Related to Study Drug Exposure

The duration of infusion in days

- within each cycle
- across cycles

will be calculated using the exact start and stop times of start of infusion, start and end of possible interruptions and stop of infusion. Any missing time will be imputed using the first start time of infusion of the respective cycle.

The relative treatment duration is defined as the duration of infusion received at each respective dose level relative to the planned duration of infusion of each dose level.

The absolute cumulative dose [ $\mu\text{g}$ ] is defined as:

$$\sum (\text{duration of infusion [days]for each dose received} \times \text{dose received}[\mu\text{g}])$$

The percent of the intended dose will be summarized. For patients who receive two or fewer cycles, this may be calculated using the absolute cumulative dose received

divided by the planned cumulative dose patients should have received through two cycles. Each cycle that was interrupted and later on restarted will be counted as two time 28 days of planned infusion, ie, if the first or second cycle is re-started, then the planned cumulative dose for the first two cycles will be based on three times 28 days. If a cycle was not re-started but continued after a shorter interruption, then the planned cumulative dose will be based on 56 days for the first two cycles.

For patients who received consolidation cycles the complete cumulative dose will be divided by the intended cumulative dose of all cycles that were started to compute the percent of the intended dose.

The number of cycles started is defined as the sum of the number of cycles. The number of re-started cycles will be analyzed separately.

#### **10.7.5.2 Analysis of Study Drug Exposure**

Data on study drug administration will be listed as recorded in a CRF (including information on dose changes) together with the calculated variables as defined above.

The duration of infusion [days] and the cumulative dose [ $\mu\text{g}$ ] will be tabulated for each cycle and the whole infusion for the SAF.

The relative treatment duration and the percent of the intended dose will be tabulated for each cycle and across cycles for the SAF

The number and percentage of subjects receiving distinct numbers of complete or incomplete cycles of blinatumomab will be summarized.

The number of cycles (complete and incomplete together) received will also be summarized by mean, standard deviation, minimum, median and maximum for each analysis set.

Reason for treatment interruptions (including due to adverse event) as documented during each treatment cycle will be tabulated for each dose level and cycle for all analysis sets by display of display of number and percentage of patients with each reason for interruption.

#### **10.7.6 Exposure to Concomitant Medication**

The number and proportion of subjects receiving concomitant medications from study day 1 through safety follow-up will be summarized by preferred term as coded by the World Health Organization Drug (WHODRUG) dictionary in the SAF. In addition, the

number and proportion of subjects receiving anti-cancer therapies during long term follow-up will be summarized by WHODRUG preferred term for the SAF.

**Table 6. Definition of Different Types of Medication**

| Type of medication                         | Definition  |
|--|---|
| Prior medication                           | Start and stop before first blinatumomab infusion   |
| Concomitant medication                     | Start <=end of induction phase visit and stopped after first blinatumomab infusion or start during re-treatment |
| Medication started during follow-up period | Start day after end of induction phase visit, but not during re-treatment                                       |

## **10.8 Pharmacokinetic and Pharmacodynamic Analyses**

**For Expansion cohort no PK and PD analysis will be performed.**

### **10.8.1 Pharmacokinetic Analysis**

The PK analysis will be based on the PK analysis set. Blinatumomab serum concentration will be quantified in all patients at baseline (pre-dose) and during the first 2 treatment cycles of treatment. Non-compartmental analysis will be performed with PK data collected at different dose levels for adults and pediatrics, respectively. Phoenix WinNonlin version 6.4 software on Citrix (Pharsight®, St. Louis, MO) as part of the validated PKS system will be used for the non-compartmental analysis.

All concentration values less than the LLOQ were set to zero before pharmacokinetic analysis. Actual dose and actual sampling time will be used. Dosing interruptions or administration errors impacting blinatumomab pharmacokinetic assessments will be taken into account in the analysis. The related concentration values and estimated PK parameters will be excluded from summary statistics where appropriate.

PK parameters such as steady state concentration (C<sub>ss</sub>), clearance (CL), and elimination half-life (t<sub>1/2</sub>) will be estimated for subjects who have sufficient evaluable PK data. Summary statistics, including mean, standard deviation, median (range), geometric mean and CV% of geometric mean will be computed for each pharmacokinetic parameter and grouped by dose, treatment cycle and age groups. Individual concentration-time data will be tabulated and presented graphically. Mean concentration-time profiles for each dose will be provided.

### **10.8.2 Pharmacodynamic Analysis**

The PD analysis will be based on the PD analysis set. Descriptive statistics or graphic presentation will be used for data analysis.



Lymphocyte subsets: Cell counts of each cell type tested at baseline and over time will be presented graphically. Summary statistics of cell counts may be presented if data are sufficient. Individual data will be provided as a listing.

Cytokines: Summary statistical analysis of cytokine levels (eg, IL-2, IL-4, IL-6, IL-10, TNF- $\alpha$ , IFN- $\gamma$ ) prior to treatment and during blinatumomab infusion will be provided for each sampling collection time. Maximal cytokine concentration (Cmax) of each cytokine will be summarized by descriptive statistics. Individual data will be provided as a listing.

### 10.8.3 Exposure Response Analysis

Exploratory exposure-efficacy analyses may be performed to evaluate the relationship of efficacious exposure range and corresponding dose range if data are sufficient for conducting the analysis. Exposure-safety analyses may be performed as needed to evaluate the relationship of tolerable exposure and dose ranges. A separate exposure-response analysis plan will be generated and the results will be reported separately from the CSR.

## 11. Changes From Protocol-specified Analyses

- The clarification of primary efficacy endpoint for adult subjects (both Phase 1b and Phase 2) to be CR/CRh\*. The terms of “complete remission”, “CR”, “CR/CRh\*/CRi”, “CR/CRh\*” were used interchangeably in the protocol.
- The clarification of primary efficacy endpoint for pediatric subjects to be M1 remission.
- The clarification of RFS and Duration of Response endpoints for subjects who met primary efficacy endpoint (CR/CRh\* for adult subjects and M1 remission for pediatric subjects).
- **Sensitivity analysis for MRD response and complete MRD response is not performed because main analysis has already excluded subjects without any post-baseline response assessment.**

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## 12. Literature Citations / References

Brookmeyer, R. and Crowley, J. (1982) A Confidence Interval for the Median Survival Time, *Biometrics*, 38, 29 - 41.

Cheson BD, Bennett JM, Kopecky KJ, et al. (2003) Revised Recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. *J Clin Oncol*; 21, 4642-4649.

Clopper CJ and Pearson ES. (1934) The use of confidence or fiducial limits illustrated in the case of the binomial, *Biometrika*. 26(4):404-413.

Hosmer, D., Lemeshow, S., and May, S. (2008), *Applied Survival Analysis: Regression Modeling of Time-to-Event Data*, Second Edition, John Wiley & Sons

Kaplan EL and Meier P. (1958) Nonparametric estimation from incomplete observations, *J Am Stat Assoc*, 53:457-481.

Simon R. (1989) Optimal Two-Stage Designs for Phase II Clinical Trials. *Controlled Clinical Trials*.10:1-10.

13. Appendices

**Appendix A. Eastern Cooperative Oncology Group (ECOG) Performance Status Scale**

| ECOG Performance Status Scale |   |
|-------------------------------|---|
| Grade                         | Descriptions  |
| 0                             | Fully active, able to carry on all pre-disease performance without restriction.   |
| 1                             | Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work). |
| 2                             | Ambulatory and capable of all selfcare, but unable to carry out any work activities. Up and about more than 50% of waking hours.                          |
| 3                             | Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.   |
| 4                             | Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.  |
| 5                             | Dead  |

Source: Oken MM, Creech RH, Tormey DC et al.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5: 649-655

## Appendix B. Karnofsky Performance Status

| Karnofsky Performance Status Scale |   |
|------------------------------------|---|
| Grade                              | Descriptions  |
| 100                                | Normal no complaints; no evidence of disease  |
| 90                                 | Able to carry on normal activity; minor signs or symptoms of disease.               |
| 80                                 | Normal activity with effort; some signs or symptoms of disease.                     |
| 70                                 | Cares for self; unable to carry on normal activity or to do active work.            |
| 60                                 | Requires occasional assistance, but is able to care for most of his personal needs. |
| 50                                 | Requires considerable assistance and frequent medical care.                         |
| 40                                 | Disabled; requires special care and assistance.                                     |
| 30                                 | Severely disabled; hospital admission is indicated although death not imminent.     |
| 20                                 | Very sick; hospital admission necessary; active supportive treatment necessary.     |
| 10                                 | Moribund; fatal processes progressing rapidly.                                      |
| 0                                  | Dead  |

Sources: Schag CC, Heinrich RL, Ganz PA. Karnofsky performance status revisited: Reliability, validity, and guidelines. J Clin Oncology. 1984; 2:187-193.

### Appendix C. Lansky-Play Performance Status

| Lansky Play Performance Scale |  |
|-------------------------------|--|
| Grade                         | Descriptions   |
| 100%                          | Fully active, normal   |
| 90%                           | Minor restrictions in physically strenuous activity  |
| 80%                           | Active, but tires more quickly   |
| 70%                           | Both greater restriction of, and less time spent in play activity  |
| 60%                           | Up and around, but minimal active play; keeps busy with quieter activities   |
| 50%                           | Gets dressed but lies around much of the day; no active play; able to participate in all quiet play and activities |
| 40%                           | Mostly in bed; participates in quiet activities  |
| 30%                           | In bed; needs assistance even for quiet play   |
| 20%                           | Often sleeping; play entirely limited to very passive activities   |
| 10%                           | No play; does not get out of bed   |
| 5%                            | Unresponsive   |
| 0%                            | Dead   |

Source: Biomedical Data Stewardship, Version 5, 20 Mar 2015

**Appendix D. Handling of Dates, Incomplete Dates and Missing Date**

The following data will be imputed using the following algorithm:

Adverse Events

Concomitant Medications

**Table 7. Imputation Rules for Partial or Missing Start Dates**

| Start Date         |                                  | Stop Date                 |                           |                                     |                                     |                                   |                                   | missing |
|--------------------|----------------------------------|---------------------------|---------------------------|-------------------------------------|-------------------------------------|-----------------------------------|-----------------------------------|---------|
|                    |                                  | Complete:<br>yyyymmdd     |                           | Partial:<br>yyyymm                  |                                     | Partial:<br>yyyy                  |                                   |         |
|                    |                                  | < 1 <sup>st</sup><br>dose | ≥ 1 <sup>st</sup><br>dose | < 1 <sup>st</sup><br>dose<br>yyyymm | ≥ 1 <sup>st</sup><br>dose<br>yyyymm | < 1 <sup>st</sup><br>dose<br>yyyy | ≥ 1 <sup>st</sup><br>dose<br>yyyy |         |
| Partial:<br>yyyymm | = 1 <sup>st</sup> dose<br>yyyymm | 2                         | 1                         | 2                                   | 1                                   | n/a                               | 1                                 | 1       |
|                    | ≠ 1 <sup>st</sup> dose<br>yyyymm |                           | 2                         |                                     | 2                                   | 2                                 | 2                                 | 2       |
| Partial:<br>yyyy   | = 1 <sup>st</sup> dose<br>yyyy   | 3                         | 1                         | 3                                   | 1                                   | n/a                               | 1                                 | 1       |
|                    | ≠ 1 <sup>st</sup> dose<br>yyyy   |                           | 3                         |                                     | 3                                   | 3                                 | 3                                 | 3       |
| Missing            |                                  | 4                         | 1                         | 4                                   | 1                                   | 4                                 | 1                                 | 1       |

1 = Impute the date of first dose

2 = Impute the first of the month

3 = Impute January 1 of the year

4 = Impute January 1 of the stop year

Note: If the start date imputation leads to a start date that is after the stop date, then do not impute the start date.

**Imputation rules for partial or missing stop dates:**

Initial imputation

For partial stop date mmyyyy, impute the last of the month.

For partial stop date yyyy, impute December 31 of the year.

For completely missing stop date, do not impute.

If the stop date imputation leads to a stop date that is after the death date, then impute the stop date as the death date.

If the stop date imputation leads to a stop date that is before the start date, then there is a data error and do not impute the stop date. (ie, set the stop date as missing).

**Imputation rules for partial or missing death dates:**

If death year and month are available but day is missing:

If mmyyyy for last contact date = mmyyyy for death date, set death date to the day after the last contact date.

If mmyyyy for last contact date < mmyyyy for death date, set death date to the first day of the death month.

If mmyyyy for last contact date > mmyyyy for death date, data error and do not impute.

If both month and day are missing for death date or a death date is totally missing, do not impute.