2. SYNOPSIS

Name of Sponsor: Amgen Inc., Thousand Oaks, CA, USA; Amgen Astellas Biopharma K.K., Tokyo, Japan

Name of Finished Product: Blincyto

Name of Active Ingredient: Blinatumomab, a murine recombinant single-chain antibody derivative that combines in 1 molecule the binding specificity for both the pan-B cell antigen cluster of differentiation (CD) 19 and the epsilon chain of the T cell receptor/CD3 complex (AMG 103; MT103)

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

Investigators and Study Centers: This study is being conducted at 16 centers in Japan [redacted].

Publication(s): None as of the date of this report.

Study Period: The study is ongoing.

Development Phase: 1b/2

Previous Reports for This Study: 17 August 2017 (Interim analysis report)

Objectives:

The primary objective of the phase 1b part of the study was to determine the maximum tolerated dose (MTD) of blinatumomab in adult and pediatric Japanese subjects with relapsed/refractory B-precursor ALL. The secondary objectives of the phase 1b part of the study were to evaluate the safety, efficacy, pharmacokinetics (PK), and pharmacodynamics (PD) of blinatumomab in adult and pediatric Japanese subjects with relapsed/refractory B-precursor ALL.

The primary objective of the phase 2 part of the study is to further evaluate in adults the recommended dose identified in the phase 1b portion of the study and to evaluate the rate of complete remission (CR)/complete remission with partial hematologic recovery (CRh*) in adult Japanese subjects with relapsed/refractory B-precursor ALL who receive blinatumomab. The secondary objectives are to evaluate other measures of efficacy, safety, and PK in adult subjects with relapsed/refractory B-precursor ALL at the blinatumomab regimen selected based on the phase 1b data.

The purpose of this interim analysis CSR is to report results only from the phase 1b part of the study.

Methodology: This is an open-label, combined 2-part multicenter study to evaluate the efficacy, safety, and tolerability of blinatumomab in adult and pediatric Japanese subjects with relapsed/refractory B-precursor ALL. The phase 1b part investigated the safety, efficacy, PK, and PD of blinatumomab to determine the MTD in both adult and pediatric subjects. Once a dose was selected in the phase 1b part, the phase 2 part will assess the safety and efficacy of the recommended dose level of blinatumomab identified in the phase 1b part portion of the study in the adult study population.

Number of Subjects Planned: maximum 57: 36 for the phase 1b part, 21 for the phase 2 part.

Diagnosis and Main Criteria for Eligibility: Adult subjects ≥ 18 years of age at enrollment with Philadelphia-negative B-precursor ALL could be enrolled if they had any

of the following: relapsed or refractory after first line therapy with first remission duration ≤ 12 months; OR relapsed or refractory after first salvage therapy; OR relapsed or refractory within 12 months of allogenic hematopoietic stem cell transplant (alloHSCT). Pediatric subjects < 18 years old at enrollment with relapsed/refractory B-precursor ALL could be enrolled if they had any of the following: second or later bone marrow relapse; OR any marrow relapse after alloHSCT; OR refractory to other treatments. All subjects needed to have > 5% blasts in the bone marrow. Subjects with a history of malignancy other than ALL within 5 years before start of protocol specified treatment, diagnosis of Burkitt's leukemia, or isolated extramedullary disease were excluded from enrollment.

Investigational Products, Dose and Mode of Administration, Manufacturing Batch Number: Blinatumomab was supplied as single-use glass injection vials containing a sterile, preservative-free, white to off-white, lyophilized powder for intravenous (IV) administration after reconstitution with sterile water for injection and added to an IV bag containing [redacted]% sodium chloride and IV solution stabilizer. The supplied IV solution stabilizer functions to prevent adsorption of blinatumomab to surfaces of the infusion components. Sterile water for injection and supplies required for reconstitution and injection of blinatumomab were not provided to clinical sites. Blinatumomab was administered using infusion pumps approved for use by the Japanese regulatory authorities. All subjects received blinatumomab. Adult subjects received a dose of 9-28 µg/day; pediatric subjects received 5-15 µg/m^2/day.

Each cohort in the study received a combination of 2 dose levels. In the first induction cycle, the initial dose of blinatumomab was the lower assigned dose level for the first 7 days of treatment (to mitigate for potential cytokine release syndrome and neurologic events associated with introduction to blinatumomab), which then was increased (dose step) to the higher assigned dose level starting on day 8 (week 2) through day 29 (week 4). For all subsequent cycles (beginning with the second induction cycle and continuing through consolidation, for applicable subjects), the higher assigned dose level was the dose for all 4 weeks of continuous treatment.

[redacted]

Duration of Treatment: The length of participation included a 2-week screening period, an average of up to a 7.5-month treatment period (assumes 2 induction and 3 consolidation cycles, each induction cycle was 4 weeks of continuous IV infusion of blinatumomab followed by a 2-week treatment-free interval), a safety follow-up visit (30 days [± 3 days] after the last dose of study treatment), and a long-term follow-up period (24 months [± 2 weeks] after completion of the safety follow-up visit or until death, whichever occurred first).

Study Endpoints:

The phase 1b primary endpoint was incidence of dose-limiting toxicities (DLTs).
The phase 1b secondary endpoints were CR/CRh* within 2 cycles of treatment with blinatumomab for adult subjects or M1 remission within the first 2 cycles of treatment with blinatumomab for pediatric subjects, duration of response (or time to hematological relapse [TTHR]), overall survival (OS), relapse-free survival (RFS), incidence and severity of adverse events, blinatumomab PK parameters (eg, steady-state concentration [C_{ss}] and clearance of blinatumomab), serum cytokine concentrations, and incidence of anti-blinatumomab antibody formation. [redacted]

Statistical Methods:

No statistical hypothesis was defined for the phase 1b part of the study.

The efficacy analysis was to be based on the full analysis set (FAS), which would include all subjects who received any infusion of investigational product. The number and percentage of adult subjects achieving CR/CRh* or pediatric subjects achieving M1 remission within 2 cycles is summarized, and an exact binomial 95% CI is provided. Other responses listed in the secondary endpoints were also to be summarized by this approach. Overall survival and RFS were to be estimated by using the Kaplan-Meier method.

The incidence rate of DLTs was to be summarized for adult subjects and pediatric subjects separately for the phase 1b part of the study. Adverse events were to be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 20.0 and grouped by their system organ class and preferred term. Summary tables were to include the number and percentage of subjects with treatment-emergent adverse events, serious adverse events, fatal adverse events, and other adverse events of interest.

Summary of Results: This report presents interim analysis data for the phase 1b part of the study as of the data cutoff date of 19 December 2016.

Subject Disposition: A total of 8 adult subjects were screened, 5 were enrolled, received blinatumomab, and were included in the FAS. No subjects had completed the study; 4 subjects had discontinued and had died, and 1 subject was continuing in the study.

A total of 10 pediatric subjects were screened, 9 were enrolled in the study, received blinatumomab, and were included in the FAS. No subjects had completed the study; 3 subjects had discontinued and had died, and 6 subjects were continuing in the study.

Baseline Demographics:

Sex: adult subjects: 4 of 5 subjects (80.0%) were [redacted];
pediatric subjects: 5 of 9 subjects (55.6%) were [redacted]

Age, median (range): adult subjects: 58.0 [redacted]) years;
pediatric subjects: 11.0 ([redacted]) years

Efficacy Results:

In adult subjects, the CR/CRh* rate within the first 2 cycles of treatment was 80.0% (4/5 subjects; 95% CI: 28.4% to 99.5%); 3 subjects (60.0%) achieved CR and 1 subject achieved CRh* (20.0%). Of the 4 subjects (80.0%) who achieved CR/CRh* within the first 2 cycles of treatment, 1 subject was alive without relapse (censored at 5.6 months), 1 subject died because of other cause (censored at 9.9 months), and the other 2 subjects died because of disease progression at 4.2 and 13 months, respectively. For overall survival, 1 subject was alive at the time of the data cutoff and 4 subjects had died at 9.3, 10.2, 11.0, and 13.9 months. [redacted]

In pediatric subjects, the M1 remission rate within the first 2 cycles of treatment was 55.6% (5/9 subjects; 95% CI: 21.2% to 86.3%); 4 subjects (44.4%) achieved M1 with full recovery and 1 subject (11.1%) achieved M1 that did not qualify for full or incomplete recovery. Of the 5 subjects (55.6%) who had M1 remission within the first 2 cycles of treatment, 2 subjects were alive without relapse (censored at 0 and 4.9 months) and 3 subjects had relapsed at 1.1, 1.4, and 2.3 months. For overall survival, 6 subjects

were alive at the data cutoff date and 3 subjects had died at 0.9, 4.6, and 8.4 months. [redacted]

Pharmacokinetic Results: Blinatumomab was administered by continuous IV infusions of 9 and 28 µg/day to adult subjects and of 5 and 15 µg/m^2/day to pediatric subjects with relapsed/refractory B-precursor ALL. Blinatumomab mean (SD) serum C_{ss} in cycle 1 were 135 (41.7) pg/mL and 907 (403) pg/mL for the 9- and 28-µg/day dosage in adults, and 107 (42.7) pg/mL and 361 (137) pg/mL for the 5- and 15-µg/m^2/day dosage in pediatrics, respectively. The estimated mean (SD) clearance was 1.59 (0.998) L/hour in adults, and 1.83 (0.801) L/m^2/hour in pediatric subjects. Mean (SD) C_{ss} and clearance of blinatumomab estimated in Japanese subjects in this study were within the range of those previously reported in adult and pediatric subjects in global clinical trials.

Safety Results: No subjects in either group had DLTs during the DLT evaluation period. The MTD was determined to be 9-28 µg/day in the adult population and 5-15 µg/m^2/day in the pediatric population. No events of interest were serious, fatal, or led to withdrawal of blinatumomab.

In the adult population, all 5 subjects had ≥ 1 adverse event; the most frequently reported event was cytokine release syndrome (4 of 5 subjects, 80.0%). Grade ≥ 3 adverse events were reported in 4 subjects (80%); the most frequently reported were neutropenia and febrile neutropenia (2 subjects each, 40%). No subject had adverse events leading to discontinuation of blinatumomab; no subjects had serious or fatal adverse events.

In the pediatric population, all 9 subjects had ≥ 1 adverse event; the most frequently reported event was pyrexia (7 subjects, 77.8%). Grade ≥ 3 adverse events were reported in all 9 subjects (100%); the most frequently reported was febrile neutropenia (5 subjects, 55.6%). One subject (11.1%) had extramedullary leukemic infiltration, which led to the subject's discontinuation of blinatumomab. One subject (11.1%) had a serious adverse event of hemorrhagic shock, which led to death; this was not considered related to blinatumomab.

Conclusions:

- Among the enrolled population of 5 adult Japanese subjects with relapsed/refractory Philadelphia-negative B-precursor ALL, the CR/CRh* rate within 2 cycles of blinatumomab treatment was 80.0% (4/5 subjects; 95% CI: 28.4% to 99.5%). For overall survival, 1 subject was alive at the time of the data cutoff and 4 subjects had died at 9.3, 10.2, 11.0, and 13.9 months. [redacted] No subjects had serious or fatal adverse events. One subject had treatment interrupted because of cytokine release syndrome.
- Among the enrolled population of 9 pediatric Japanese subjects with relapsed/refractory B-precursor ALL, the M1 remission rate within 2 cycles of blinatumomab treatment was 55.6% (5/9 subjects; 95% CI: 21.2% to 86.3%). For overall survival, 6 subjects were alive at the data cutoff date and 3 subjects had died at 0.9, 4.6, and 8.4 months. [redacted] One subject had a serious adverse event of hemorrhagic shock and died.

- Pharmacokinetics of blinatumomab was approximately linear and the blinatumomab exposure levels in Japanese subjects were generally within the range of those previously reported in non-Japanese subjects with relapsed/refractory B-precursor ALL in the global clinical trials.
- No DLTs were reported during the DLT evaluation period. The MTD and the recommended dose for the phase 2 portion of the study was determined to be 9-28 µg/day in the adult population and 5-15 µg/m^2/day in the pediatric population, which is consistent with the dosing regimens for adult and pediatric subjects in global studies. The safety profile of blinatumomab in Japanese subjects was consistent with that observed in non-Japanese subjects in the global clinical trials.