1. ABSTRACT

- **Title**

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Title:

Long-term Follow-up of Adult Philadelphia Chromosome-negative Acute Lymphoblastic Leukemia Relapsed Refractory Patients Enrolled in Study 00103311

- **Keywords**

long-term follow-up; Kaplan-Meier probability, overall survival, relapsed or refractory acute lymphoblastic leukaemia, Study 00103311

- **Rationale and Background**

Blinatumomab received accelerated approval from the Food and Drug Administration for the treatments of adults and children with relapsed/refractory Philadelphia chromosome-negative (Ph-) B-cell acute lymphoblastic leukaemia (ALL) in 2014; this was converted to full approval in 2017. The European Medicines Agency (EMA) granted conditional approval to blinatumomab for the treatment of adults with relapsed/refractory Ph- B-cell ALL in November 2015, with conditional approval converted to full approval in June 2018 based on the results of a phase 3, randomised study that demonstrated longer median overall survival (OS: 7.7 months versus 4.0 months) in subjects treated with blinatumomab compared with standard of care (SOC) chemotherapy (Study 00103311, TOWER study) (Kantarjian et al, 2017). This phase 3 study was planned to end early if the OS, the primary efficacy endpoint of the study, was met at the interim analysis. As a part of the conversion to full approval of the relapsed/refractory ALL indication in the European Union (EU), the Pharmacovigilance Risk Assessment Committee (PRAC) requested Amgen to conduct an additional final OS assessment of subjects who were alive at last follow-up in the phase 3 study.

The purpose of this study (20180138) was to conduct a one-time survival status assessment on subjects who were alive at the last follow-up and still participating in the phase 3 Study 00103311.

- **Research Question and Objectives**

The objective of this study was to update the OS Kaplan-Meier (KM) probability estimates and the plot last reported in the randomised phase 3 blinatumomab Study 00103311.

- **Study Design**

This study was a one-time follow-up/survival status assessment on subjects who were alive at the last follow-up and still participating in the phase 3 Study 00103311 at the end of that study.

- **Setting**

The data source for collecting survival status of the subjects was the study centres/subjects from existing blinatumomab Study 00103311 using medical charts, national registries, subject contact, next of kin contact, or other available means per local regulation. For subjects in the SOC chemotherapy group, any blinatumomab use after the end of the Study 00103311 was also evaluated.

- **Subjects and Study Size, Including Dropouts**

The population for the study included the 108 subjects who were alive and still participating in Study 00103311 at the end of that study.

- **Variables and Data Sources**

The endpoint in this study was OS. The single output from this study effort was to generate an updated OS KM probability estimates and KM plot. The data collection/source for collecting survival status was the study centres/subjects from existing blinatumomab Study 00103311.

- **Results**

Participants:

- At the last follow-up in Study 00103311, 108 subjects were alive and still participating at the end of that study. Of these, a total of 75 eligible subjects (69.4%) were assessed for survival status in Study 20180138 and completed this study. Subject enrollment was not achieved for 33 subjects (30.6%).
- In the SOC chemotherapy group, 19 of 31 subjects (61.3%) were assessed; 11 of the 19 subjects (57.9%) were alive and 8 subjects (42.1%) had died. In the blinatumomab group, 56 of 77 subjects (72.7%) were assessed; 28 of the 56 subjects (50.0%) were alive and 28 subjects had died (50.0%).
- The demographics and other characteristics measured at the baseline of Study 00103311 were no longer balanced between the 2 treatment groups enrolled and assessed in Study 20180138. A slightly higher percentage of subjects in the SOC chemotherapy group were men compared with blinatumomab group (63.2% versus 53.6%). Subjects in the SOC chemotherapy group were younger compared with subjects in blinatumomab group (median age of 29.0 years versus 37.5 years). There was over twice the percentage of subjects over the age of 65 in the blinatumomab group than in the SOC chemotherapy group (12.5% versus 5.3%).
- Subjects in the SOC chemotherapy group had more favourable baseline characteristics than subjects in the blinatumomab group. A higher percentage of subjects in the SOC chemotherapy group had an Eastern Cooperative Oncology Group performance status of 0 at baseline than subjects in the blinatumomab group (68.4% versus 55.4%). A higher percentage of subjects in the SOC chemotherapy group was minimal residual disease-negative after first-line treatment than subjects in the blinatumomab group (42.1% versus 23.2%). A lower percentage of subjects in the SOC chemotherapy group was refractory to salvage treatment than subjects in the blinatumomab group (5.3% versus 17.9%). A lower percentage of subjects in the SOC chemotherapy group was in second or greater relapse than subjects in the blinatumomab group (5.3% versus 16.1%). A lower percentage of subjects in the SOC chemotherapy group had relapsed

after receiving an allogeneic HSCT than subjects in the blinatumomab group (26.3% versus 35.7%).

- Subjects in the SOC chemotherapy group had more favourable postbaseline allogeneic haematopoietic stem cell transplantation (alloHSCT) status than subjects in the blinatumomab group. A higher percentage of subjects in the SOC chemotherapy group had received postbaseline alloHSCT than subjects in the blinatumomab group (84.2% versus 51.8%). A higher percentage of subjects in the SOC chemotherapy group had achieved a complete remission (CR)/complete remission with partial recovery of peripheral blood counts (CRh*)/complete remission with incomplete recovery of peripheral blood counts (CRi) within 12 weeks after treatment initiation and did not use any anticancer therapies before receiving an alloHSCT than subjects in the blinatumomab group (42.1% versus 35.7%).

Overall Survival:

- The median time to censoring in Study 20180138 updated OS analysis was approximately 60 months. The median OS was 4.0 months (95% CI: 2.9 to 5.5 months) in the SOC chemotherapy group compared with 7.6 months (95% CI: 5.6 to 9.4 months) in the blinatumomab group with a p-value = 0.086 (stratified log-rank test). The hazard ratio was 0.81 (95% CI: 0.63 to 1.03) in favour of the blinatumomab group.
- Of the 405 randomised subjects in Study 00103311, 310 deaths (76.5%) were reported: 98 (73.1%) in the SOC chemotherapy group and 212 (78.2%) in the blinatumomab group. A total of 95 subjects (23.5%) were censored: the 36 subjects (26.9%) in the SOC chemotherapy group and 59 subjects (21.8%) in the blinatumomab group.
- Of 134 subjects who received SOC chemotherapy in Study 00103311, 12 subjects (9.0%) switched over to blinatumomab treatment, 8 subjects were recorded in Study 00103311 and 4 subjects were recorded from Study 20180138. Overall, the median (range) time to blinatumomab use from randomisation was 6.7 months (1 to 30 months).

Safety:

- Safety data collection was performed in this study per protocol with the safety outcome of death reported in the aggregate within the updated OS curve and plot.

- **Discussion**

The long-term follow-up Study 20180138 conducted a one-time survival status assessment on 108 subjects with relapsed/refractory B-cell precursor ALL who were alive at the last follow-up and still participating in the phase 3 Study 00103311 at the end of that study. This phase 3 study was planned to end early if the OS, the primary endpoint of the study, was met at the interim analysis. Of 108 alive subjects, 75 eligible subjects were assessed for survival status; of these 39 subjects were alive and 36 subjects were deceased at the end of long-term follow-up.

This observational study (20180138) assessed OS with a follow-up of approximately 60 months from the time of randomisation in Study 00103311. The OS updated for additional follow-up, the main endpoint for this study (20180138), was descriptive in nature and still favoured subjects randomised to blinatumomab. The OS results from

this study were consistent with the OS results observed in Study 00103311. Although this observational study has some limitations, including lack of balanced baseline demographics and key disease characteristics for subjects entering the long-term follow-up study, the OS results were clinically meaningful, showing the benefit of blinatumomab over SOC chemotherapy for a difficult to treat patient population with few treatment options.

- **Marketing Authorization Holder**

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- **Names and Affiliations of Principal Investigators**

Principal investigators of study centres included in this study are provided in Section 3.