1. ABSTRACT

- **Title:**

An Observational Study of Blinatumomab Safety and Effectiveness, Utilisation, and Treatment Practices

Date of the Abstract: 20 February 2025

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- **Keywords**

Relapsed or refractory (R/R), acute lymphoblastic leukaemia (ALL), drug utilisation, minimal residual disease positive (MRD+), Philadelphia chromosome-positive/negative (Ph+/-).

- **Rationale and Background**

At the time of approval for blinatumomab (Blincyto®), data were limited to the clinical study populations, with limited patient exposure, treatment duration, and follow-up, and to which strict exclusion criteria were applied. To further understand the benefit-risk of blinatumomab, more data on existing safety concerns in routine clinical practice and any data on exposure in yet unstudied populations were needed. This postauthorisation safety study was developed to assess the real-life safety and effectiveness of blinatumomab in the treatment of ALL in selected countries in Europe. This study also provided information on the frequency and type of medication errors that occurred in routine clinical practice.

- **Research Question and Objectives**

The research question was to characterise specific adverse events identified in patient charts (medical notes), and to estimate the frequency and type of medication errors identified in patient charts, among patients who received blinatumomab in routine clinical practice.

Primary objective of the study was to characterise the safety profile of blinatumomab in routine clinical practice in countries in Europe by characterising specified adverse events; these events included neurologic adverse events, opportunistic infections, and cytokine release syndrome (CRS). Additionally, to estimate the frequency and type of medication errors as identified in patient charts.

Secondary objectives were to estimate incidence of all adverse events collected in this study, and the incidence of both specified adverse events and all adverse events collected in this study among patient subgroups defined by demographic and clinical factors. Other secondary objectives were to evaluate effectiveness endpoints overall and among patient subgroups defined by demographic and clinical factors, and to describe blinatumomab utilisation and select healthcare resource use in routine clinical practice.

- **Study Design**

This multicentre study was an observational study involving a detailed retrospective medical record review of patients who initiated blinatumomab in a routine clinical setting. Because this study involved medical record review, it was anticipated that it would allow for the collection of routinely monitored safety and effectiveness outcomes while not having any effect on treatment practices.

- **Setting**

This study was conducted in cancer treatment centres with a focus on treating patients with ALL in selected countries in Europe. It was expected that larger centres were more likely to be recruited since the patient population eligible for blinatumomab was expected to be small, highly unique, and more likely to be treated in larger centres. However, an attempt was made to include smaller centres to aid representativeness of patients receiving blinatumomab in the real-world.

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

Medical records of patients initiating blinatumomab after country-specific reimbursement in routine clinical practice were eligible for abstraction.

Medical records of patients who met any of the following criteria were excluded: patients who had participated in blinatumomab clinical studies (unless the patient was receiving new blinatumomab treatment outside the clinical study), patients participating in other Amgen noninterventional prospective studies in which safety endpoints were collected, and patients who had received blinatumomab through an expanded access/compassionate use program. In addition, in countries where patient informed consent was required to access their medical records, any medical records of a patient who did not provide informed consent were excluded.

Approximately 300 adult patients treated with blinatumomab were planned to be enrolled in the study. The approximate duration of study was 7 years after the first patient was enrolled, at which point most of the patients would have been eligible to complete a minimum of 2 years of follow-up.

- **Data Sources and Methods**

All data (including exposure, outcomes, and covariates) were abstracted from the medical records by study centre staff at the treatment centre where blinatumomab was initiated. Abstracted data included demographics, comorbidities, primary disease characteristics and treatment, allogeneic haematopoietic stem cell transplantation (HSCT), concomitant medications, primary and secondary endpoints, and subgroup characteristics.

The enrolment period for this study was 5 years: the first patient was enrolled on 22 March 2017 and the last patient was enrolled on 22 March 2022. Chart abstractions continued for at least 2 years after the last patient identified at the study centre initiated blinatumomab. Baseline was defined as the start of infusion of the first cycle of blinatumomab. The total duration of study was approximately 7 years. The data were collected from 22 March 2017 to 20 March 2024.

- **Results**

<u>Participants</u>

- Overall, 279 patients were enrolled across 74 study centres in 13 countries. Of these, 264 patients were included in the full analysis set (FAS).
  End-of-blinatumomab treatment data were available for all 264 patients in the FAS; the primary reasons for ending blinatumomab were proceeding to HSCT (44.3%, 117 of 264), disease progression (24.6%, 65 of 264), treatment completion (15.5%, 41 of 264), adverse event (9.1%, 24 of 264), others (3.0%, 8 of 264), requirement for alternative therapy (2.3%, 6 of 264), death (0.8%, 2 of 264), and subject request (0.4%, 1 of 264).

- End-of-study data were available for all 264 patients; the reasons for the end of study were death (50.0%, 132 of 264), study completion (43.6%, 115 of 264), lost to follow-up (5.3%, 14 of 264), and withdrawal of consent from the study (1.1%, 3 of 264).
- Among the 264 patients in the FAS, 52.7% (n = 139) were males and 47.3% (n = 125) were females. At baseline, the median age was 46.5 (range: 17 to 81) years. Among the 264 patients, 0.4% (n = 1) were in the ≥ 12 to < 18 years age group, 33.0% (n = 87) were in the ≥ 18 to < 35 years age group, 31.1% (n = 82) were in the ≥ 35 to < 55 years age group, 22.0% (n = 58) were in the ≥ 55 to < 65 years age group, and 13.6% (n = 36) were ≥ 65 years of age. As per the planned analyses, results are provided for subgroups with ≥ 15 patients (Adult R/R Ph- ALL subgroup, Adult R/R Ph- ALL LFR subgroup, and Adult MRD+ Ph- subgroup):
  - *Adult R/R Ph- ALL subgroup (N = 183)*: The median age at ALL diagnosis was 44.0 (range: 0.2 to 79.0) years. At blinatumomab initiation, the disease status was primary refractory in 12.6% (23 of 183) of patients and refractory to salvage therapy in 18.0% (33 of 183) of patients. At baseline, the percentage of bone marrow blasts was ≤ 5% in 37 patients (20.2%), > 5% to ≤ 10% in 21 patients (11.5%), > 10% to ≤ 25% in 24 patients (13.1%), > 25% to ≤ 50% in 13 patients (7.1%), and > 50% in 47 patients (25.7%). At the time of ALL diagnosis, 59.0% (108 of 183) of patients had a white blood cell count < 30 000/μL. At the time of blinatumomab treatment, 82.5% (151 of 183) of patients were eligible for HSCT. Overall, 20.8% (38 of 183) of patients had received previous allogeneic HSCT and 0.5% (1 of 183) of patients had received previous autologous HSCT. The median time from previous HSCT to start of blinatumomab treatment was 10.85 (range: 2.4 to 137.7) months. All patients in the Adult R/R Ph- ALL subgroup had previous treatment with at least 1 anticancer therapy for the current malignancy before starting blinatumomab. Patients had various numbers of lines of anticancer therapies before blinatumomab treatment: 59.0% (108 of 183) of patients had frontline chemotherapy, and 24.0% (44 of 183) of patients had frontline chemotherapy and first salvage chemotherapy.
  - *Adult R/R Ph- ALL LFR subgroup (N = 60)*: The median age at ALL diagnosis was 32.0 (range: 15.0 to 79.0) years in adult patients with R/R Ph- ALL LFR. At baseline, the percentage of bone marrow blasts was ≤ 5% in 18 patients (30.0%), > 5% to ≤ 10% in 7 patients (11.7%), > 10% to ≤ 25% in 3 patients (5.0%), > 25% to ≤ 50% in 5 patients (8.3%), and > 50% in 16 patients (26.7%). At the time of ALL diagnosis, 55.0% (33 of 60) of patients had a white blood cell count < 30 000/μL. At the time of blinatumomab treatment, 85.0% (51 of 60) of patients were eligible for HSCT. Overall, 28.3% (17 of 60) of patients had received previous allogeneic HSCT and no patient received previous autologous HSCT. The median time from previous HSCT to start of blinatumomab treatment was 17.34 (range: 8.5 to 77.1) months. All 60 patients in the Adult R/R Ph- ALL LFR subgroup had previous treatment with at least 1 anticancer therapy for the current malignancy before starting blinatumomab. Patients had various numbers of lines of anticancer therapies before blinatumomab treatment: 78.3% (47 of 60) of patients had frontline chemotherapy, and 8.3% (5 of 60) of patients with R/R Ph- ALL LFR had frontline chemotherapy and first salvage chemotherapy.

- *Adult MRD+ Ph- subgroup (N = 46)*: The median age at ALL diagnosis was 42.50 (range: 17 to 70) years. At baseline, the percentage of bone marrow blasts was ≤ 5.0% in 31 patients (67.4%), > 25% to ≤ 50.0% in 1 patient (2.2%), and > 50% in 2 patients (4.3%). Overall, 8.7% (4 of 46) of patients had received previous allogeneic HSCT; and 2.2% (1 of 46) of patients had received previous autologous HSCT. The median time from previous HSCT to start of blinatumomab treatment was 10.66 (range: 4.2 to 53.9) months. All 46 patients had previous treatment with at least 1 anticancer therapy for the current malignancy before starting blinatumomab. Patients had various numbers of lines of anticancer therapies before blinatumomab treatment: 60.9% (28 of 46) had frontline chemotherapy, and 19.6% (9 of 46) of adult patients had frontline chemotherapy and first salvage chemotherapy.

Safety

- *Overview of Adverse Events:* Overall, 90.9% (240 of 264) of patients in the FAS had a treatment-emergent adverse event (defined as adverse events with an onset between the beginning of blinatumomab infusion and 30 days after the end of the last infusion; hereafter referred to as adverse events). The adverse events reported for ≥ 5% of patients by preferred terms were pyrexia (47.3%), headache (18.2%), CRS (14.8%), neutropenia (12.9%), febrile neutropenia (9.5%), tremor (7.2%), alanine aminotransferase increased (6.8%), anaemia (6.4%), and neurotoxicity (6.1%).

  Grade ≥ 3 adverse events were reported for 58.0% (153 of 264) of patients, and grade ≥ 4 events were reported for 26.9% (71 of 264) of patients. Serious adverse events were reported for 52.7% (139 of 264) of patients. Fatal adverse events were reported for 7.6% (20 of 264) of patients. Eighty-three patients (31.4%, 83 of 264) had adverse events leading to interruption of blinatumomab and 26 patients (9.8%, 26 of 264) had adverse events leading to discontinuation of blinatumomab.

  Adverse events considered by the investigator (ie, treating physician) to be related to blinatumomab were reported for 68.9% (182 of 264) of patients. The treatment-related adverse events reported for ≥ 5% of patients by preferred terms were pyrexia (27.7%), CRS (14.4%), headache (11.4%), neutropenia (8.7%), neurotoxicity, and tremor (each in 5.7%).

  Treatment-related grade ≥ 3 adverse events were reported for 34.5% (91 of 264) of patients, and grade ≥ 4 events were reported for 11.7% (31 of 264) of patients. The overall patient incidence of adverse events was similar between 2 main disease subgroups (92.9% [170 of 183] in Adult R/R Ph- ALL subgroup versus 90.0% [54 of 60] in Adult R/R Ph- ALL LFR subgroup). In this study, fatal adverse events were reported for 8.2% (15 of 183) of patients in the Adult R/R Ph-ALL subgroup, 1.7% (1 of 60) of patients in the Adult R/R Ph- ALL LFR subgroup, and 6.5% (3 of 46) of patients in the Adult MRD+ Ph- subgroup. One patient (0.5%; 1 of 183) in the Adult R/R Ph-ALL subgroup and 1 (2.2%; 1 of 46) in Adult MRD+ Ph- subgroup had treatment-related fatal adverse event.

- *Incidence of Specified Adverse Events:* Neurological events were identified using the "central neuropsychiatric events due to direct neurotoxicities" Amgen Medical Dictionary for Regulatory Activities Queries (AMQ) narrow search strategy. Overall, 41.7% (110 of 264) of patients had adverse events under the specified event category of neurological events (fatal in 0.4% [n = 1], grade ≥ 3 in 10.6% [n = 28], grade ≥ 4 in 1.5% [n = 4], serious in 9.8% [n=26], and led to interruption and

discontinuation of blinatumomab in 11.7% [n = 31], and 3.0% [n = 8] respectively). The neurological events reported for ≥ 5% of patients by preferred terms were headache (18.2%, n = 48), tremor (7.2%, n = 19), and neurotoxicity (6.1%, n = 16).

Opportunistic infection events were identified using opportunistic infections Standardised Medical Dictionary for Regulatory Activities Queries (SMQ) and opportunistic infections blinatumomab AMQ narrow search strategies.

Using opportunistic infections blinatumomab AMQ (narrow) search strategy, no adverse events were reported under the specified event category of opportunistic infections. Using the opportunistic infections SMQ (narrow) search strategy, opportunistic infections events were reported for 3.4% (n = 9) of patients. These events were considered serious in 2.7% (n = 7) of patients and fatal in 0.4% (n=1) of patients. The opportunistic infections reported by preferred terms were bronchopulmonary aspergillosis, cytomegalovirus infection reactivation, systemic candida (0.8% each; n=2); cytomegalovirus viraemia, hepatic infection fungal, and pneumonia fungal (0.4% each; n=1).

Cytokine release syndrome events were identified using CRS AMQ narrow search strategy. Overall, 14.8% (39 of 264) of patients had adverse events under the specified event category of CRS (no fatal events, grade ≥ 3 in 3.8% [n = 10], serious in 9.5% [n=25], and led to interruption of blinatumomab in 5.3% [n = 14]).

The incidence of specified adverse events (neurological events, opportunistic infections, and CRS) was consistent across disease subgroups.

- *Time to Onset of First Specified Adverse Events:* The median time to onset of first event from first dose of blinatumomab for the specified event category of neurological events (narrow) was 10.0 (range: 1 to 462) days overall and in the Adult R/R Ph- ALL subgroup, 7.0 (range: 1 to 243) days in the Adult R/R Ph- ALL LFR subgroup, and 8.0 (range: 2 to 87) days in the Adult MRD+ Ph- subgroup.

  Time to onset of event was not reported for opportunistic infections as no adverse events were reported under this category using opportunistic infections blinatumomab AMQ (narrow) search strategy.

  The median time to onset of first event from first dose of blinatumomab for the specified event category of CRS (narrow) was 2 (range: 1 to 97) days overall, 2.0 (range: 1 to 97) days in the Adult R/R Ph- ALL subgroup, 2.5 (range: 1 to 97) days in the Adult R/R Ph- ALL LFR subgroup, and 2.0 (range: 1 to 44) days in the Adult MRD+ Ph- subgroup.

- *Duration of Specified Adverse Events*:

  Neurological events: Overall, 107 of 264 patients (40.5%) with any resolved neurological events (narrow) had 231 resolved neurological events. The median duration of any resolved neurological events was 9.0 days (range: -2 to 833 days; [The negative duration is because of imputing the date value from the partial date for one of the subjects in the adverse event data]). This result was consistent across disease subgroups. Seven of 264 patients (2.7%) with neurological events had 7 unresolved neurological events.

  Duration of event was not reported for opportunistic infections as no adverse events were reported under this category using opportunistic infections blinatumomab AMQ (narrow) search strategy.

Cytokine release syndrome: Overall, 39 of 264 patients (14.8%) with CRS (narrow) had 52 resolved CRS events. The median duration of any resolved CRS events was 5.0 (range: 1 to 35) days. No patients had unresolved CRS events.

- *Medication Errors:* Total of 31 medication errors were reported for 26 subjects (9.8%, 26 of 264). Of these, there were 22 patients with 1 medication error each, 3 patients with 2 medication errors each, and 1 patient with 3 medication errors. Medication errors occurred during inpatient visits (51.6%, 16 of 31), at home (29.0%, 9 of 31), and at outpatient clinics (19.4%, 6 of 31). The most frequently reported type of medication error was administration errors (71.0%, 22 of 31). Of the 31 medication errors, 29 medication errors reached the patient (5 errors led to overdoses, 12 errors led to underdoses, and 12 errors led to neither overdose nor underdose).

Effectiveness

- Complete remission (CR), CR with partial recovery of peripheral blood counts (CRh*), or CR with incomplete recovery of peripheral blood counts (CRi) within the first 2 cycles of treatment (ie, CR/CRh*/CRi), was achieved in 82.0% (150 of 183; 95% CI: 75.6, 87.2) of adult patients with R/R Ph- ALL, and 88.3% (53 of 60; 95% CI: 77.4, 95.2) of adult patients with R/R Ph- ALL LFR. Of these, CR was achieved in 67.8% (124 of 183; 95% CI: 60.5, 74.5) of adult patients with R/R Ph- ALL and 85.0% (51 of 60; 95% CI: 73.4, 92.9) of adult patients with R/R Ph- ALL LFR.
- Among 183 adult patients with R/R Ph- ALL, 150 achieved CR/CRh*/CRi within 2 cycles of blinatumomab treatment and had an evaluable postbaseline MRD assessment of which 53 patients were in the Adult R/R Ph- ALL LFR subgroup. During the first 2 cycles of blinatumomab treatment, MRD response was achieved in 75.4% (95 of 126; 95% CI: 66.9, 82.6) of adult patients with R/R Ph- ALL, and 79.5% (35 of 44; 95% CI: 64.7, 90.2) of adult patients with R/R Ph- ALL LFR. The MRD response during the first cycle of treatment was achieved in 72.6% (85 of 117; 95% CI: 63.6, 80.5) of adult patients with R/R Ph- ALL and 75.0% (30 of 40; 95% CI: 58.8, 87.3) of adult patients with R/R Ph- ALL LFR. Among 46 adult patients with MRD+ Ph- ALL, 42 achieved CR/CRh*/CRi within first 2 cycles of blinatumomab treatment and had an evaluable postbaseline MRD assessment. The MRD response was achieved in 81.8% (27 of 33; 95% CI: 64.5, 93.0) of adult patients with MRD+ Ph- ALL during the first 2 cycles of blinatumomab treatment.
- In the Adult R/R Ph- ALL subgroup of patients who achieved CR/CRh*/CRi during the first 2 cycles of blinatumomab treatment, 60.0% (90 of 150) of patients had relapse-free survival (RFS) events: 40.7% (61 of 150) of patients had relapse and 19.3% (29 of 150) of patients had died. In the Adult R/R Ph- ALL LFR subgroup, 45.3% (24 of 53) of patients had RFS events: 35.8% (19 of 53) of patients had relapse and 9.4% (5 of 53) of patients had died. The median RFS was 15.9 (95% CI: 8.7 to 41.3) months in the Adult R/R Ph- ALL subgroup and not evaluable (NE) (95% CI: 11.3 to NE) months in the Adult R/R Ph- ALL LFR subgroup. The median time to censoring was 65.4 (95% CI: 52.7 to 67.5) months in the Adult R/R Ph- ALL subgroup and 65.4 (95% CI: 51.1 to 67.5) months in the Adult R/R Ph- ALL LFR subgroup. The 24-month Kaplan-Meier (KM) estimate for RFS was 43.0% (95% CI: 35.0% to 51.0%) in the Adult R/R Ph- ALL subgroup and 58.0% (95% CI: 43.0% to 70.0%) in the Adult R/R Ph- ALL LFR subgroup.
- In disease-free survival (DFS) analysis, 50.0% (23 of 46) of patients had DFS events (18 patients [39.1%] had relapse and 5 patients [10.9%] had died). The median time

to DFS was 31.2 (95% CI: 5.9 to NE) months in MRD+ Ph- subgroup. The median time to censoring was 47.3 (95% CI: 35.1 to 52.4) months in the Adult MRD+ Ph- subgroup. The 24-month KM estimate for DFS was 54.0% (95% CI: 39.0% to 67.0%) in the Adult MRD+ Ph- subgroup.

- In the Adult R/R Ph- ALL subgroup, 53.0% (97 of 183) of patients died because of any cause (ie, overall survival [OS] events); and in the Adult R/R Ph- ALL LFR subgroup, 31.7% (19 of 60) of patients died. The median OS was 29.9 (95% CI: 17.8 to NE) months in the Adult R/R Ph- ALL subgroup and was NE in R/R Ph- ALL LFR subgroup. The 24-month KM estimate for OS was 52.0% (95% CI: 44.0% to 59.0%) in the Adult R/R Ph- ALL subgroup, and 71.0% (95% CI: 58.0% to 81.0%) in the Adult R/R Ph- ALL LFR subgroup. In the Adult MRD+ Ph- subgroup, 37.0% (17 of 46) of patients died. The median OS was NE (95% CI: 36.0, NE). The 24-month KM estimate for OS was 67.0% (95% CI: 51.0% to 79.0%).
- The percentage of adult R/R Ph- patients who proceeded to allogeneic HSCT after blinatumomab treatment was 55.2% (101 of 183), of which 68.8% (64 of 93) proceeded after achieving CR/CRh*/CRi and were not exposed to other myelosuppressive therapy between response and transplant. Among R/R Ph- LFR adult patients, 65.0% (39 of 60) proceeded to allogeneic HSCT; the percentage of patients that proceeded to allogeneic HSCT without exposure to any other myelosuppressive therapy after achieving CR/CRh*/CRi was 79.4% (27 of 34). Among adult patients with MRD+ Ph-, 71.7% (33 of 46) proceeded to allogeneic HSCT after blinatumomab treatment, of which 84.8% (28 of 33) proceeded after achieving CR/CRh*/CRi and without exposure to other myelosuppressive therapy between response and transplant.
- The median time to allogeneic HSCT after achieving CR/CRh*/CRi was 2.4 (95% CI: 2.1 to 3.0) months in the Adult R/R Ph- ALL subgroup, 2.6 (95% CI: 1.9 to 3.2) months in the Adult R/R Ph- ALL LFR subgroup, and 2.4 (95% CI: 1.4 to 3.4) months in the MRD+ Ph- ALL subgroup. The median time to censoring (ie, median follow-up time) was 22.8 (95% CI: 13.6 to 48.3) months in the Adult R/R Ph- ALL subgroup, 17.3 (95% CI: 7.6 to 48.3) months in the Adult R/R Ph- ALL LFR subgroup, and 37.2 (95% CI: 22.0 to NE) months in the MRD+ Ph- ALL subgroup.
- Among 64 adult patients with R/R Ph- ALL, 27 adult patients with R/R Ph- ALL LFR and 28 adult patients with MRD+ Ph- ALL who proceeded to allogeneic HSCT after achieving CR/CRh*/CRi and without receiving treatment with additional anticancer therapies, the patient incidences of mortality and relapse after allogeneic HSCT were as follows:
    - Twenty-two (34.4%) in the Adult R/R Ph- ALL subgroup, 6 patients (22.2%) in the Adult R/R Ph-LFR subgroup, and 5 patients (17.9%) in the Adult MRD+ Ph- subgroup died. The median time to event was not reached in all the 3 subgroups.
    - Sixteen patients (25.0%) in the Adult R/R Ph- ALL subgroup, 8 patients (29.6%) in the Adult R/R Ph-LFR subgroup, and 6 patients (21.4%) in the Adult MRD+ Ph- subgroup had relapse. The median time to event was not reached in all the 3 subgroups.

Blinatumomab Utilisation

- Of 264 patients who received blinatumomab treatment, the median cumulative dose received was 1463.0 μg (range: 54 to 6477 μg) blinatumomab. Regarding duration of use, the median number of cycles completed was 2.0 (range: 1 to 5) cycles. About 28.8% (76 of 264) of patients completed only 1 cycle of blinatumomab treatment, 36.4% (96 of 264) completed 2 cycles, 9.8% (26 of 264) completed 3 cycles, 7.6% (20 of 264) completed 4 cycles, and 3.8% (10 of 264) completed 5 cycles. Blinatumomab treatment had a median duration of 57 (range: 6 to 215) days across all treatment cycles.
- Among the 183 patients from the R/R Ph- ALL subgroup, the median cumulative dose received by the patients was 1453.0 μg (range: 54 to 6477) of blinatumomab. Regarding duration of use, the median number of cycles completed was 2.0 (range: 1 to 5) cycles. A total of 27.3% (50 of 183) of patients completed only 1 cycle of blinatumomab treatment, 35.5% (65 of 183) completed 2 cycles, 8.7% (16 of 183) completed 3 cycles, 7.7% (14 of 183) completed 4 cycles, and 4.9% (9 of 183) completed 5 cycles.
- Among the 60 patients from the R/R Ph- ALL LFR subgroup, the median cumulative dose received by the patients was 1500.0 μg (range: 231 to 5849 μg) of blinatumomab. Regarding duration of use, the median number of cycles completed was 2.0 (range: 1 to 5) cycles. A total of 23.3% (14 of 60) of patients completed only 1 cycle of blinatumomab treatment, 36.7% (22 of 60) completed 2 cycles, 11.7% (7 of 60) completed 3 cycles, and 10.0% (6 of 60) completed 4 cycles and 5 cycles.
- Among the 46 patients from the MRD+ Ph- subgroup, the median cumulative dose received by the patients was 1487.5 μg (range: 315 to 4900 μg) of blinatumomab. Regarding duration of use, the median number of cycles completed was 2.0 (range: 1 to 4) cycles. A total of 34.8% (16 of 46) of patients completed only 1 cycle of blinatumomab treatment, 39.1% (18 of 46) completed 2 cycles, 10.9% (5 of 46) completed 3 cycles, 4.3% (2 of 46) completed 4 cycles, and no patient reached up to 5 or more cycles.

Healthcare Resource Use

- Median number of intravenous infusion bags changed per patient was 16.0 (range: 1 to 142). These bags were changed in the hospitals (91.3%, 241 of 264 patients), in outpatient units/centres (71.2%, 188 of 264 patients), and at patients' home (4.2%, 11 of 264 patients).
- Among the adult patients with R/R Ph- ALL, the median number of bags changed per patient was 15.0 (range: 1 to 142). These bags were changed in the hospitals (94.0%, 172 of 183 patients), in outpatient units/centres (70.5%, 129 of 183 patients), and at patients' home (4.4%, 8 of 183 patients). Among the adult patients with R/R Ph- ALL LFR, the median number of bags changed per patient was 16.0 (range: 3 to 55). These bags were changed in the hospitals (95.0%, 57 of 60 patients), in outpatient units/centres (73.3%, 44 of 60 patients), and at patients' home (8.3%, 5 of 60 patients). Among the adult patients with MRD+ Ph-, median number of bags changed per patient was 16.0 (range: 4 to 57). These bags were changed in the hospitals (87.0%, 40 of 46 patients), in outpatient units/centres (80.4%, 37 of 46 patients), and at patients' home (2.2%, 1 of 46 patients).

- **Discussion and Conclusion**

  Safety

  In this study, neurological events were reported in 41.7% of patients, with headache, tremor, and neurotoxicity being the most frequently reported events. These findings generally align with those reported in prior clinical studies involving blinatumomab, with neurological events reported for approximately 60% to 70% of patients in the adult relapsed/refractory and MRD+ ALL clinical study population. In this study, opportunistic infections were infrequently reported (3.4%), and all were considered not related to blinatumomab treatment by the investigator. Cytokine release syndrome, a well-characterised risk of blinatumomab treatment was reported in 14.8% of patients. Cytokine release syndrome typically occurs during the early cycles of treatment and was reported at a frequency comparable to those in previous studies (14.0% in the pooled ALL clinical study population). Notably, the incidence of serious CRS in this study was 9.5%, which is higher than previously reported in interventional clinical studies of blinatumomab. Of note, in 12 patients, the reported CRS event was upgraded from nonserious to serious after a query referencing the inclusion of CRS in the EMA's important medical events list, a process utilised in this observational study but not in the prior blinatumomab interventional clinical studies. Overall, the CRS events reported in this study were consistent with the anticipated severity based on prior clinical experience, with the majority (42 of 52 events; 81.0%) of CRS events were of grade 1 or 2 in this study. All CRS events reported in the study resolved, and no life-threatening, or fatal (grade 4 or 5) CRS events occurred. Overall, no new safety concerns emerged based on the results of this study, and the benefit-risk profile of blinatumomab remains positive.

  The patient incidence of medication errors was 9.8% with the most frequently reported type being administration error, accounting for 71.0% of all errors (22 out of 31). These administration errors were primarily related to operator use error (38.7%), and pump malfunction (22.6%). Medication errors reported in this study was higher than observed in the interventional TOWER (4.5%) and ALCANTARA (4.4%) studies. The observed difference may be partly because of different definitions of medication errors; the TOWER and ALCANTARA interventional studies derived medication errors entirely from reported adverse event data which specifically collected information related to overdoses. In contrast, this study used a broader definition of medication errors capturing all types of errors related to incorrect preparation and administration, including those without clinical sequelae as adverse events. Of the 29 medication errors that reached the patients, 5 were overdoses, 12 were underdoses, and 12 had no effect on the overall dosing, as they did not lead to either an overdose or underdose.

  Overall, the types of adverse events reported in this study were consistent with the established safety profile of blinatumomab, and no new safety concerns were identified.

  Effectiveness

  In this study, the response rate (CR, CRh*, CRi) for R/R Ph- ALL was 82.0% (95% CI: 75.6, 87.2). In line with more recently published real-world studies, this study had more patients receiving blinatumomab as first salvage therapy and fewer patients with prior transplant. Only 24.0% of patients had received prior first salvage therapy, 59.0% of patients had no prior salvage therapy, and 21.0% had prior transplant in this study. Given that this study included less pretreated population with more recent diagnosis, the observed increase in response rate among R/R Ph-

ALL patients was within the range of other recently published real-world studies. Moreover, the MRD response rates observed in this study were comparable to the wider literature, including those recently published and earlier Amgen-sponsored studies with 80.0% of MRD+ patients in BLAST and 83.0% of Ph- MRD-evaluable NEUF patients. In contrast to this study, response rates reported in other Amgen-sponsored earlier studies were lower, eg, the TOWER (44.0%) or the NEUF study (51.0% in Ph- patients, 41.0% in Ph+ patients), a retrospective observational study that evaluated clinical characteristics and treatment patterns in adult patients with B-cell ALL who received blinatumomab in the expanded access program. Both TOWER and NEUF patients received higher prior lines of therapy, and a larger proportion of patients had prior transplant before enrolling, which likely explains the lower response rates reported in these earlier Amgen-sponsored studies. While 42.0% of TOWER patients received prior first salvage therapy and 35.0% had prior transplant, 42.0% of NEUF patients had no prior salvage therapy and 20.0% had received prior first salvage therapy, 27.0% had prior greater than second line salvage therapy and 41.0% had prior transplant.

In the TOWER study, the median OS in patients receiving blinatumomab was 7.7 months. In NEUF, the median OS was 12.2 months for Ph- patients and 16.3 months for Ph+ patients. The OS observed in this study was 29.9 months is relatively longer compared to that reported in other interventional and observational studies. Nonetheless, other observational studies have reported OS between 1 to 2 years. Additionally, as more than half of the patients received blinatumomab as first salvage in this study and therefore, report higher CR/CRh*/CRi compared to other studies (82.0% in this study compared to 44.0% in TOWER and 51.0% in NEUF) and proceed more commonly to HSCT after blinatumomab use (55.0% in this study compared to 24.0% in TOWER and 41.0% in NEUF), it was very likely that OS was higher than in the TOWER and NEUF studies.

In this study, a higher proportion of R/R Ph- ALL patients proceeded to HSCT (55.0%) compared to the interventional TOWER study (24.0%), and these rates were slightly higher or comparable to other observational studies (41.0% in NEUF; 36.0% to 63.0% across other studies). The relatively higher response rates of this study likely contribute to the higher rates of HSCT. For MRD+ patients, the proportion of patients proceeding to HSCT was comparable to that observed in the interventional BLAST study (67.0%) and other observational studies (68.0% in NEUF; 63.0% to 100.0% across other studies).

Overall, this study showed comparable safety profile and clinical outcomes consistent with more recent studies involving patients who were earlier in their line of treatment for ALL.

- **Marketing Authorisation Holder**

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- **Names and Affiliations of Principal Investigators**

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