1. ABSTRACT

- **Title**

Expanded access of Blincyto® in patients with acute lymphoblastic leukemia: a retrospective observational study (Neuf Study)

Date: 06 April 2020

Author: [redacted] Manager, Centre for Observational research, Amgen Limited, 1 Uxbridge Business Park, Sanderson Road, Uxbridge, UB8 1DH, United Kingdom

- **Keywords**

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

- **Rationale and Background**

Amgen has been providing Blincyto in an expanded access setting for patients with high unmet medical need since 2012. This study aimed to characterize the patient population with ALL and the specific subgroups receiving Blincyto in the expanded access setting not otherwise collected elsewhere and describe selected outcomes and Blincyto utilization.

- **Research Question and Objectives**

Primary objective:

To describe the clinical characteristics and treatment patterns of patients with B precursor ALL, having received Blincyto in the expanded access setting and identify clinically relevant subgroups.

Secondary objectives were as follows:

- describe the effectiveness of Blincyto within identified subgroups
- describe Blincyto utilization within identified subgroups

Hypothesis: This study was descriptive and no formal hypothesis was tested.

- **Study Design**

This was a retrospective, observational, multicenter study involving medical record review of patients who initiated Blincyto that was provided through an expanded access program.

- **Setting**

This study was conducted in 5 countries: France, Italy, Spain, United Kingdom, and Russia. Eligible patients included ALL patients who had initiated Blincyto in the expanded access setting from 01 January 2014 until 30 June 2017.

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

Inclusion criteria: B-precursor ALL patients who have initiated Blincyto through an expanded access program from 01 January 2014 until 30 June 2017.

Exclusion criteria were as follows:

- patients enrolled in Amgen expanded access Protocol 20130320
- patients who did not provide informed consent, where required per country regulations

- patient's medical chart was not available for data extraction

- **Variables and Data Sources**

Clinical and Treatment Characteristics:

- demographic and clinical characteristics (medullary and extramedullary involvement, immunophenotype, cytogenetics, and molecular biology) of patients at ALL diagnosis
- clinical characteristics of patients before Blincyto initiation (prior treatment history [chemotherapy and hematopoietic stem cell transplant {HSCT}]) and response, MRD results, mutation history
- clinical characteristics at Blincyto initiation (disease status, medullary and extramedullary involvement, immunophenotype, MRD results, cytogenetics, molecular biology, and comorbidities)
- concurrent ALL therapies during Blincyto treatment

Effectiveness:

- complete remission (CR)/CR with partial recovery of peripheral blood counts (CRh)/CR with incomplete recovery of peripheral blood counts (CRi)
- relapse-free survival (RFS): RFS time was calculated from the time of achieving CR/CRh/CRi (best response within first 2 cycles) until the date of relapse or M2 marrow or death, whichever occurred first.
- MRD response (molecular response defined as MRD < 1×10^{-4}; and complete molecular response defined as absence of detectible MRD with assay sensitivity ≥1×10^{-4})
- event-free survival (EFS; calculated from the time of Blincyto initiation until the date of relapse or M2 marrow after achieving a CR/CRh/CRi or death, whichever occurred first)
- disease-free survival (DFS; defined as time from initiation of Blincyto [for MRD positive patients] until date of relapse or M2 marrow or death, whichever occurred first)
- overall survival (OS; defined as time from Blincyto initiation until death because of any cause)
- receipt of allogeneic HSCT, incidence of graft versus host disease (GvHD), graft failure rate
- 100-day mortality after allogeneic HSCT
- subsequent immunotherapy or chemotherapy
- cluster of differentiation (CD)19 hematological relapse

Blincyto Utilization:

- duration of treatment
- number of cycles initiated
- dosing schedule (starting dose and subsequent doses)
- reasons for dose interruptions and reductions
- administration of dexamethasone

- reasons for discontinuation of Blincyto treatment
- number of days of hospitalization (treatment related, other)
- number of outpatient visits (treatment related, other)

Note: M1 = bone marrow blasts < 5%; M2 = bone marrow blasts between 5% and 25%; and M3 = bone marrow blasts ≥ 25%

Other Covariates:

In addition to the above secondary endpoint analyses, the proportion of patients who received allogeneic HSCT was summarized by response status, covariates, and clinical characteristics; the incidence of graft failure, and GvHD for such patients was also summarized. This analysis was limited to patients with CR/CRh/CRi who had allogeneic HSCT. The covariates for these analyses were as follows:

- HSCT conditioning regimen and donor type
- MRD level at HSCT
- age at HSCT

Mortality after allogeneic HSCT was investigated in patients who achieved CR/CRh/CRi at any time after Blincyto treatment and who were not treated with any other myelosuppressive therapy between Blincyto and HSCT: covariates in analysis investigating mortality independent of ALL and HSCT-related factors were relapse and death because of undocumented relapse.

Safety data were not collected in this study.

- **Results**

A total of 373 patients were enrolled and completed the end of follow-up. All patients are presented under following subgroups (stratified by age at Blincyto initiation: adult patients [age ≥ 18 years] and pediatric patients [age < 18 years]):

- R/R Ph- ALL (106 adult patients, 72 pediatric patients)
- R/R Ph+ ALL (34 adult patients, 2 pediatric patients)
- MRD-positive Ph- ALL (83 adult patients, 39 pediatric patients)
- MRD-positive Ph+ ALL (26 adult patients, 2 pediatric patients)

Table below provides the key demographic and baseline characteristics:

	R/R Ph- Patients		R/R Ph+ Patients		MRD+ Ph- Patients		MRD+ Ph+ Patients	
	Adults (N = 106) n (%)	Children (N = 72) n (%)	Adults (N = 34) n (%)	Children (N = 2) n (%)	Adults (N = 83) n (%)	Children (N = 39) n (%)	Adults (N = 26) n (%)	Children (N = 2) n (%)
Sex								
Male	56 (52.8)	43 (59.7)	18 (52.9)	2 (100)	44 (53.0)	23 (59.0)	20 (76.9)	2 (100)
Female	50 (47.2)	29 (40.3)	16 (47.1)	0 (-)	39 (47.0)	16 (41.0)	6 (23.1)	0 (-)
Age at Blincyto Initiation (years)								
Median	36.5	10.0	51.0	11.5	35.0	8.0	50.5	14.0
Q1, Q3	24.0, 52.0	5.0, 13.5	37.0, 64.0	9.0, 14.0	24.0, 56.0	5.0, 13.0	43.0, 55.0	11.0, 17.0
Time (months) from ALL diagnosis to Blincyto initiation								
Median	20.20	21.60	15.45	25.80	8.40	28.10	11.00	26.60
Q1, Q3	7.30, 39.40	9.10, 51.80	11.10, 23.60	25.00, 26.60	5.00, 26.10	6.60, 41.90	7.80, 31.80	21.00, 32.20
Any extramedullary involvement at Blincyto Initiation - n (%)								
Yes	20 (19.2)	10 (13.9)	5 (14.7)	0 (-)	0 (-)	0 (-)	0 (-)	0 (-)
No	84 (80.8)	62 (86.1)	29 (85.3)	2 (100)	82 (100)	38 (100)	26 (100)	2 (100)
Unknown	2	0	0	0	1	1	0	0
Bone marrow blasts at Blincyto Initiation								
≥ 50%	44 (45.8)	28 (39.4)	14 (50.0)	1 (50.0)	2 (2.8)	0 (-)	2 (8.7)	0 (-)
Patients with ≥ 1 HSCT before Blincyto								
Yes	43 (40.6)	28 (38.9)	12 (35.3)	1 (50.0)	9 (10.8)	8 (20.5)	8 (30.8)	0 (-)
No	63 (59.4)	44 (61.1)	22 (64.7)	1 (50.0)	74 (89.2)	31 (79.5)	18 (69.2)	2 (100)
Unknown	0	0	0	0	0	0	0	0

ALL = acute lymphoblastic leukemia; HSCT = hematopoietic stem cell transplant; MRD+ = minimal residual disease positive; Ph- = Philadelphia chromosome-negative; Ph+ = Philadelphia chromosome-positive; R/R = relapsed or refractory

A small proportion of MRD-positive patients (MRD status as determined by the treating physician) had percentage bone blasts ≥ 50% at Blincyto initiation (2.8%, N = 2 in Ph- adults and 8.7%, N = 2 in Ph+ adults). It is possible that these patients were MRD-positive with low percentage of bone blasts when the physician applied for the patients' entry into the expanded access program. However, the disease may have progressed between application and receipt of Blincyto, leading to bone blasts increasing to ≥ 50%. Since analysis was based upon an intention-to-treat approach, these patients remained in the MRD-positive groups.

Effectiveness Results

Results for CR/CRh/CRi are available for first and first 2 cycles of Blincyto treatment. However, this report limits the presentation to the results from the first 2 cycles, which better aligns with results reported from the TOWER study.

- R/R Ph- Patients:
  - In adult population, the rate of CR/CRh/CRi within the first 2 cycles of Blincyto treatment was 50.9% (54 of 106 patients; 95% CI: 41.0, 60.8); 49 patients (46.2%) achieved CR. In pediatric population, the rate of CR/CRh/CRi within the first 2 cycles of Blincyto treatment was 52.8% (38 of 72 patients; 95% CI: 40.7, 64.7); 35 patients (48.6%) achieved CR.
  - In the adult population, among the 33 patients who achieved CR/CRh/CRi within the first 2 cycles of Blincyto treatment and also had evaluable MRD, 28 patients (84.8%; 95% CI: 68.1, 94.9) had at least molecular response; of these, 12 patients (36.4%; 95% CI: 20.4, 54.9) had molecular response (defined as MRD $< 1 \times 10^{-4}$) and 16 patients (48.5%; 95% CI: 30.8, 66.5) had complete molecular response (defined as the absence of detectible MRD with assay sensitivity $\geq 1 \times 10^{-4}$). In the pediatric population, among the 29 patients who achieved CR/CRh/CRi within the first 2 cycles of Blincyto treatment and also had evaluable MRD, 25 patients (86.2%; 95% CI: 68.3, 96.1) had at least molecular response; of these, 8 patients (27.6%; 95% CI: 12.7, 47.2) and 17 patients (58.6%; 95% CI: 38.9. 76.5) had complete molecular response.
  - In the adult population, the median RFS time was 10.95 months (interquartile range [IQR]: 4.03, not estimable [NE]) with 30 events (death or relapse) occurring in 54 patients achieving CR/CRh/CRi during the first 2 cycles of Blincyto treatment (median follow-up time was 16.20 months (IQR: 9.54, 24.00). In the pediatric population, the median RFS time was 5.41 months (IQR: 1.67, NE) with 21 events (death or relapse) occurring in 38 patients achieving CR/CRh/CRi during the first 2 cycles of Blincyto treatment (median follow-up time was 14.39 months [IQR: 9.80, 20.10]). In an analysis censoring at time of HSCT, 15 events (relapse or death) occurred in 54 adult patients over a median follow-up of 3.93 months (IQR: 0.98, 12.95); median RFS was 10.95 months (IQR: 3.08, NE). In pediatric patients, median RFS was 4.85 months (IQR: 1.41, NE) when censoring at time of HSCT; 12 events (all relapses) occurred over a median follow-up of 1.21 months (IQR: 0.72, 8.89).
  - In the adult population, the median EFS time was 4.26 months (IQR: 0.46, 13.51) with 78 events (death, no CR/CRh/CRi response after $\geq$ 2 cycles of Blincyto, or relapse after Blincyto) occurring in 106 patients over a median follow-up time of 17.34 months (IQR: 10.79, 26.66). In the pediatric population, the median EFS time was 4.89 months (IQR: 1.87, 20.26) with 49 events (death, no CR/CRh/CRi response after $\geq$ 2 cycles of Blincyto, or relapse after Blincyto) occurring in 72 patients over a median follow-up time of 14.10 months (IQR: 9.87, 21.44).
  - In the adult population, the median overall survival (OS) was 12.16 months (IQR: 4.43, NE) with 55 events (deaths) occurring in 106 patients (median follow-up time was 17.25 months (IQR: 10.79, 23.61). In the pediatric population, the median OS was 8.20 months (IQR: 4.59, NE) with 39 events (death) occurring in 72 patients; median follow-up time was 15.34 months (IQR: 9.77, 22.16). In an analysis censoring at time of HSCT, OS in adult patients was 9.54 months (IQR: 4.39, 24.20) and in pediatric patients was

6.00 months (IQR: 3.34, NE). The median follow-up for adult patients was 6.59 months (IQR: 3.51, 15.54) with 39 deaths and for pediatric patients was 4.36 months (IQR: 1.70, 9.87) with 23 deaths.

- Median time to allogeneic HSCT after achieving CR/CRh/CRi (at any time after Blincyto treatment) for adult patients was 4.62 months (IQR: 1.05, NE) and was 1.97 months (IQR: 0.72, NE) for pediatric patients: median follow-up time was 8.43 months (IQR: 4.43, 12.95) and 7.21 months (IQR: 5.97, 10.00) respectively.
- In the adult population, 26 patients (42.6%) relapsed among the 63 patients who achieved CR/CRh/CRi at any time after Blincyto treatment (2 patients had missing data and were excluded). Among 22 relapsed patients who underwent CD19 assessment, 21 patients were CD19 positive. In the pediatric population, 19 patients (50%) relapsed among the 38 patients who achieved CR/CRh/CRi any time after Blincyto treatment. Among 12 relapsed patients who underwent CD19 assessment, 7 patients were CD19 positive.
- In an analysis of mortality after HSCT, with relapse and death because of undocumented relapse treated as completing risk, the Kaplan-Meier (KM) estimate for mortality (not because of relapse) in adult patients at 12 months was 19.3% (95% CI: 8.3, 45.2) and for pediatric patients was 4.8% (95% CI: 0.6, 37.3). Analyses were restricted to patients who proceeded to HSCT after achievement of CR/CRh/CRi at any time after Blincyto treatment, and did not receive any other myelosuppressive regimens between Blincyto and HSCT (29 adult patients; 23 pediatric patients).
- In the adult population, the median (min, max) cumulative dose of Blincyto was 700 (18, 4358.3) μg. In the pediatric population, the median (min, max) cumulative dose of Blincyto was 368.4 (78.3, 2001) μg.
- In total, 105 adult patients (99.1%) and 72 pediatric patients (100%) were hospitalized. Most hospitalizations occurred for Blincyto administration.

- R/R Ph+ Patients:
  - In the adult population, the rate of CR/CRh/CRi within the first 2 cycles of Blincyto treatment was 42.4% (14 of 33 patients; 95% CI: 25.5, 60.8) with 1 other patient being excluded because of missing response data; all 14 patients (42.4%) achieved CR. In the pediatric population, the rate of CR/CRh/CRi within the first 2 cycles of Blincyto treatment was 50% (1 of 2 patients; 95% CI: 1.3, 98.7); this 1 patient (50%) achieved CR.
  - In the adult population, among the 10 patients who achieved CR/CRh/CRi within the first 2 cycles of Blincyto treatment and also had evaluable MRD, 6 patients (60%; 95% CI: 26.2, 87.8) had at least molecular response; of these, 2 patients (20.0%; 95% CI: 2.5, 55.6) had molecular response and 4 subjects (40.0%; 95% CI: 12.2, 73.8) achieved complete molecular response. In the pediatric population, 1 patient achieved CR/CRh/CRi within the first 2 cycles of Blincyto treatment and had evaluable MRD, this patient had molecular response (100%; 95% CI: 2.5, 100).
  - In the adult population, the median RFS time was 6.66 months (IQR: 3.25, 18.16) with 10 events (relapse or death) occurring in 14 patients achieving CR/CRh/CRi during the first 2 cycles of Blincyto treatment (median follow-up time was 21.74 months (IQR: 12.03, 25.61). In the pediatric population, the median RFS time was not estimable as no event occurred in the 1 patient achieving

CR/CRh/CRi during the first 2 cycles of Blincyto treatment; this patient had a follow-up of 7.08 months.

- In the adult population, the median OS was 16.33 months (IQR: 4.59, NE) with 15 events (deaths) occurring in 34 patients (median follow-up time was 12.95 months (IQR: 11.11, 20.07). In the pediatric population, the median OS was not reached; 1 patient had an event among the 2 patients. In an analysis censoring at time of HSCT, median OS in adult patients was 16.33 months (IQR: 4.59, 16.33) with 13 events (death) occurring in 34 patients over a median follow-up time 8.72 months (IQR: 4.79, 12.03); median OS in pediatric patients could not be estimated (1 patient had an event among the 2 patients).
- Median time to allogeneic HSCT from achieving CR/CRh/CRi (at any time after Blincyto treatment) for adult patients was not reached (median follow-up time was 8.39 months [IQR: 5.38, 9.48]); 6 adult patients (35.3%) underwent allogeneic HSCT. A single pediatric patient underwent HSCT after CR/CRh/CRi; time to event was 0.52 months.
- In the adult population, 8 patients (50%) relapsed among the 17 patients who achieved CR/CRh/CRi at any time after Blincyto treatment (1 patient was excluded from the analysis because of missing data). Among 5 relapsed patients who underwent CD19 assessment, all were CD19 positive. In the pediatric population, 1 patient achieved CR/CRh/CRi at any time after Blincyto treatment; this patient did not relapse after Blincyto treatment.
- In the adult population, the median (min, max) cumulative dose of Blincyto was 735 (36, 896) μg. In the pediatric population, the median (min, max) cumulative dose of Blincyto was 339.7 (265, 414.5) μg.
- A total of 34 adult patients (100%) and 2 pediatric patients (100%) were hospitalized. Most hospitalizations occurred for Blincyto administration.

- MRD-positive Ph- Patients:
  - In the adult population, among the 64 patients who were in CR/CRh/CRi at the start of Blincyto treatment and also had evaluable MRD, 57 patients (89.1%; 95% CI: 78.8, 95.5) had at least molecular response within 2 cycles of Blincyto treatment; of these, 12 patients (18.8%; 95% CI: 10.1, 30.5) had molecular response and 45 patients (70.3%; 95% CI: 57.6, 81.1) had complete molecular response. In the pediatric population, among the 32 patients who had CR/CRh/CRi at the start of Blincyto treatment and also had evaluable MRD, 23 patients (71.9%; 95% CI: 53.3, 86.3) had at least molecular response within 2 cycles of Blincyto treatment; of these, 9 patients (28.1%; 95% CI: 13.7, 46.7) had molecular response and 14 patients (43.8%; 95% CI: 26.4, 62.3) had complete molecular response.
  - Among the 83 adult patients with available data, median DFS was 25.74 months (IQR: 7.38, NE); 37 patients had events (relapse or death), and median follow-up time was 18.56 months (IQR: 14.03, 31.08). Thirty-nine pediatric patients had available data with 18 patients had events (relapse or death); median DFS was 13.57 (IQR: 6.72, NE) and median follow-up time was 12.39 months (IQR: 8.85. 15.93). In an analysis censoring at time-of-HSCT, median DFS was not reached in adult patients; among the 83 patients, 13 patients had events (death or relapse) over a median follow-up of 3.31 months (IQR: 2.26, 9.77). Among the 39 pediatric patients, 7 patients had

events over a median follow-up of 1.84 months (IQR: 1.44, 4.33) and median DFS (censored at the time of HSCT) was 9.11 months (IQR: 7.31, 16.23).

- In the adult population, the median OS was not reached; 28 events (deaths) occurring in 83 patients over a median follow-up time was 18.75 months (IQR: 14.03. 31.08). In the pediatric population, the median OS was not reached; 10 events (death) occurring in 39 patients over a median follow-up time of 12.49 months (IQR: 8.82, 17.84). Median OS censored at time of HSCT was not reached in adult patients; over a median follow-up time of 3.57 months (IQR: 2.33, 10.13), 7 out of 83 patients had events (death). Median OS censored at time of HSCT, was 19.31 months (IQR: 7.31, 19.31) in pediatric patients; 4 out of 39 patients had the events over a median follow-up of 2.03 months (IQR: 1.61, 7.31).
- Median time to allogeneic HSCT among the 76 adult patients in CR/CRh/CRi at, and any time after Blincyto treatment was 2.26 months (IQR: 0.93, NE) and for pediatric patients (of whom 36 patients were in CR/CRh/CRi at any time after Blincyto) was 1.02 months (IQR: 0.59, NE). Median follow-up time was 13.87 months (IQR: 9.21, 21.97) for adult patients and 9.51 months (IQR: 5.97, 17.87) in pediatric patients.
- Seventy-six adult patients and 36 pediatric patients were in CR/CRh/CRi at, and any time after Blincyto treatment; of these, 1 pediatric patient was excluded from analysis of subsequent relapse because of missing data. In the adult population, 27 patients (35.5%) relapsed after Blincyto treatment. Among 20 relapsed patients who underwent CD19 assessment, 17 patients were CD19 positive. In the pediatric population, 15 patients (42.9%) relapsed after Blincyto treatment. Among 11 relapsed patients who underwent CD19 assessment, 6 patients were CD19 positive.
- In an analysis of mortality after allogeneic HSCT, where death and death because of undocumented relapse were treated as competing risk, in adult patients who were in CR/CRh/CRi at, and any time from Blincyto treatment (and who did not receive any other myelosuppressive treatment between Blincyto and HSCT), the KM estimate for probability of survival at 12 months was 9% (95% CI: 3.8, 21.6). No pediatric patient had an event (death not because of relapse) during follow-up; no estimates of probability of mortality could be calculated.
- In the adult population, the median (min, max) cumulative dose of Blincyto was 772 (9, 1352.5) μg. In the pediatric population, the median (min, max) cumulative dose of Blincyto was 424.7 (18.6, 787.7) μg.
- Eighty-one adult patients (98.8%) and 35 pediatric patients (97.2%) were hospitalized. Most hospitalizations occurred for Blincyto administration.

- MRD-positive Ph+ Patients:
  - In the adult population, among the 16 patients who were in CR/CRh/CRi at the start of Blincyto treatment and also had evaluable MRD, 9 patients (56.3%; 95% CI: 29.9, 80.2) had molecular response within the first 2 cycles of Blincyto treatment; of these, 6 patients (37.5%; 95% CI: 15.2, 64.6) had molecular response and 3 patients (18.8%; 95% CI: 4.0, 45.6) had complete molecular response. In the pediatric population, 1 patient had CR/CRh/CRi at the start of Blincyto treatment and also had evaluable MRD; this patient achieved molecular response within 2 cycles of Blincyto treatment.

- Among the 26 adult patients, median DFS was not reached; 9 patients had events (death or relapse) over a median follow-up-time of 16.23 months (IQR: 13.70, 20.59). In an analysis censoring at time of HSCT, median DFS was not reached; 4 events (death or relapse) occurred over a median follow-up time of 3.34 months (IQR: 1.48, 5.80). One of the 2 pediatric patients had an event (death) over a median follow-up time of 6.20 months; thus, median DFS could not be estimated. Similarly, median OS in pediatric patients where analyses were censored at time of HSCT could not be estimated (the median follow-up time in this analysis was 2.28 months (IQR: 1.44, 3.11).
- In the adult population of 26 patients, the median OS was not reached; 5 events (death) occurring in 26 patients during a median follow-up time of 16.49 months (IQR: 8.39, 22.33). Similarly, median OS was not reached when censoring at time of HSCT; 2 events (death) occurred over a median follow-up time of 5.57 months (IQR: 3.51. 18.03). In the pediatric population of 2 patients, the median OS was not estimable in both analyses; 1 patient died over a follow-up of 7.31 months. When censoring at time of HSCT, no event occurred over a median follow-up of 3.36 months (IQR: 1.87, 4.85).
- Median time to allogeneic HSCT for patients in CR/CRh/CRi at, and any time after Blincyto treatment for adult patients was 15.97 months (IQR: 1.21, NE). The 11 adult patients (52.4%) who underwent allogeneic HSCT had a median follow-up time 14.82 months (IQR: 5.77, 20.89). One pediatric patient met the criteria for analysis (allogeneic HSCT and in CR/CRh/CRi at, and any time after Blincyto treatment with no intervening anticancer therapy); this patient underwent HSCT after 0.46 months of response.
- In an analysis of mortality after HSCT in patients who underwent HSCT and were in CR/CRh/CRi at, and any time after Blincyto treatment (with no intervening other myelosuppressive therapy between Blincyto and HSCT) with relapse and death because of documented relapse as competing risk, the KM estimate for probability of mortality in adult patients at 12 months was 18.1% (95% CI: 3.7, 88.0). A similar analysis could not be undertaken for pediatric patients as no patient met the criteria for the analysis.
- Among the 20 adult patients with data available, 6 patients (30%) relapsed after Blincyto treatment. Among 3 relapsed patients who underwent CD19 assessment, all were CD19 positive. In the pediatric population, no patient relapsed or underwent CD19 assessment.
- In the adult population, the median (min, max) cumulative dose of Blincyto was 784 (268, 968) μg. In the pediatric population, the median (min, max) cumulative dose of Blincyto was 479.5 (171.2, 711.2) μg.
- All patients were hospitalized; most hospitalizations occurred for Blincyto administration.

- **Discussion**

This retrospective chart review study characterizes data collected for 373 patients with ALL who received Blincyto as part of the expanded access setting. Most patients were enrolled from Italy (133 patients [35.66%]), followed by Russia (108 patients [28.95%]), Spain (64 patients [17.16%]), France (59 patients [15.82%]), and United Kingdom (9 patients [2.41%]). Key results are discussed under following subgroups.

Relapsed/Refractory Philadelphia-negative Patients:

Of the 178 patients enrolled in the R/R Ph- subgroup, most were adult patients (N = 106).

Adult Patients:

The median age was 36.5 (IQR: 24.0, 52.0) years with male preponderance (N = 56 [52.8%]). The median (min, max) time from ALL diagnosis to Blincyto treatment was 20.20 (1.3, 179.0) months. Before the initiation of Blincyto, 43 patients (40.6%) underwent ≥ 1 HSCT. At Blincyto initiation, 44 patients (45.8%) had ≥ 50% bone marrow blasts and 20 patients (19.2%) had extramedullary disease. The median (min, max) cumulative dose of Blincyto was 700 (18, 4358.3) μg. The median number of cycles started and completed was 2 (IQR: 1, 3).

Overall, the rate of CR/CRh/CRi within the first 2 cycles of Blincyto treatment was 50.9% (54 of 106 patients; 95% CI: 41.0, 60.8); 49 patients (46.2%) achieved CR. Among the 36 patients achieving CR/CRh/CRi in the first 2 cycles and who also had evaluable MRD, 28 patients (84.8%) had at least molecular response. Twenty-six patients (42.6%) relapsed after having achieved CR/CRh/CRi at any time after Blincyto treatment. Among 22 relapsed patients who underwent CD19 assessment, 21 patients were CD19 positive. The median RFS time was 10.95 months (IQR: 4.03, NE) with 30 events (death or relapse) occurring in 54 patients achieving CR/CRh/CRi during the first 2 cycles of Blincyto treatment; after censoring patients at the time of HSCT, the median RFS time was 10.95 months (IQR: 3.08, NE) with 15 events (relapse or death) occurring in 54 patients. The median OS was 12.16 months (IQR: 4.43, NE) with 55 events (death) occurring in 106 patients. In an analysis censoring at the time of HSCT, median OS was 9.54 months (IQR: 4.39, 24.20). The KM estimate of probability of OS was 55.8% (95% CI: 32.5, 73.8) at 1 year. Median time to allogeneic HSCT after achieving CR/CRh/CRi was 4.62 months (IQR: 1.05, NE); 33 patients (52.4%) underwent allogeneic HSCT. The median EFS time was 4.26 months (IQR: 0.46, 13.51) with 78 events occurring in 106 patients. After censoring patients at the time of HSCT, the median EFS time was 3.41 months (IQR: 0.46, 16.59) with 61 events (death, no CR/CRh/CRi response after ≥ 2 cycles of Blincyto, or relapse after Blincyto) occurring in 106 patients. In an analysis of mortality after HSCT, the KM estimate for probability of survival at 12 months was 19.3% (95% CI: 8.3, 45.2) with 29 patients included in analysis and 5 patients having the event; 14 patients were censored (alive without relapse) and 10 patients had the competing risk (8 patients relapsed, 2 patients died because of undocumented relapse). TKIs were used as comedication in 1 patient (0.9%), which included dasatinib and nilotinib. A total of 105 patients (99.1%) were hospitalized, mostly because of Blincyto administration.

Pediatric Patients:

Seventy-two pediatric patients with R/R Ph- ALL were included in the study. The median age was 10.0 (IQR: 5.0, 13.5) years with male preponderance (N = 43 [59.7%]). The median (min, max) time from ALL diagnosis to Blincyto treatment was 21.60 (2.9, 135.3) months. Before the initiation of Blincyto, 28 patients (38.9%) underwent ≥ 1 HSCT. At Blincyto initiation, 28 patients (39.4%) had ≥ 50% bone marrow blasts and 10 patients (13.9%) had extramedullary disease. The median (min, max) cumulative dose of Blincyto was 368.4 (78.3, 2001) μg. The median number of cycles started was 1 (IQR: 1, 2) and completed was 1 (IQR: 1, 1).

Overall, the rate of CR/CRh/CRi within the first 2 cycles of Blincyto treatment was 52.8% (38 of 72 patients; 95% CI: 40.7, 64.7); 35 patients (48.6%) achieved CR. Among the 31 patients achieving CR/CRh/CRi in the first 2 cycles and who also had

evaluable MRD, 25 patients (86.2%) had at least molecular response. Nineteen patients (50%) relapsed after achieving CR/CRh/CRi at any time after Blincyto treatment. Among 12 relapsed patients who underwent CD19 assessment, 7 patients were CD19 positive. The median RFS time was 5.41 months (IQR: 1.67, NE) with 21 events (death or relapse) occurring in 38 patients achieving CR/CRh/CRi during the first 2 cycles of Blincyto treatment; after censoring patients at the time of HSCT, the median RFS time was 4.85 months (IQR: 1.41, NE) with 12 events (relapse) occurring in 38 patients. The median OS was 8.20 months (IQR: 4.59, NE) with 39 events (death) occurring in 72 patients. In an analysis censoring at the time of HSCT, median OS was 6.00 months (IQR: 3.34, NE). The KM estimate of probability of OS was 75.9% (95% CI: 51.3, 89.3) at 1 year. Median time to allogeneic HSCT after achieving CR/CRh/CRi was 1.97 months (IQR: 0.72, NE); 25 patients (65.8%) underwent allogeneic HSCT. In an analysis of mortality after HSCT, the KM estimate for probability of survival at 12 months was 4.8% (95% CI: 0.6, 37.3) with 23 patients included in analysis and 1 patient having the event; 14 patients were censored (alive without relapse), and 8 patients had the competing risk (6 patients relapsed, 2 patients died because of undocumented relapse). TKIs were not used as comedication. Seventy-two patients (100%) were hospitalized, mostly because of Blincyto administration.

Relapsed/Refractory Philadelphia-positive Patients:

Of the 36 patients enrolled in the R/R Ph+ subgroup, most were adult patients (N = 34).

Adult Patients:

The median age was 51.0 (IQR: 37.0, 64.0) years with male preponderance (N = 18 [52.9%]). The median (min, max) time from ALL diagnosis to Blincyto treatment was 15.45 (5.7, 42.5) months. Before the initiation of Blincyto, 12 patients (35.3%) underwent ≥ 1 HSCT. At Blincyto initiation, 14 patients (50%) had ≥ 50% bone marrow blasts and 5 patients (14.7%) had extramedullary disease. The median (min, max) cumulative dose of Blincyto was 735 (36, 896) μg. The median number of cycles started was 2 (IQR: 1, 4) and completed was 1 (IQR: 1, 4).

Overall, the rate of CR/CRh/CRi within the first 2 cycles of Blincyto treatment was 42.4% (14 of 33 patients; 95% CI: 25.5, 60.8); 14 patients (42.4%) achieved CR. Among the 10 patients achieving CR/CRh/CRi in the first 2 Blincyto cycles and also had evaluable MRD, 6 subjects (60%) had at least MRD response. Eight patients (50%) relapsed after achieving CR/CRh/CRi at any time after Blincyto treatment. Among 5 relapsed patients who underwent CD19 assessment, all were CD19 positive. The median RFS time was 6.66 months (IQR: 3.25, 18.16) with 10 events (relapse or death) occurring in 14 patients achieving CR/CRh/CRi during the first 2 cycles of Blincyto treatment; after censoring patients at the time of HSCT, the median RFS time was 6.66 months (IQR: 3.25, 8.62) with 9 events (relapse or death) occurring in 14 patients. The median OS was 16.33 months (95% CI: 4.59, NE) with 15 events (death) occurring in 34 patients. In an analysis censoring at the time of HSCT, OS was 16.33 months (IQR: 4.59, NE). Median time to allogeneic HSCT after achieving CR/CRh/CRi was not estimable; 6 patients (35.3%) underwent allogeneic HSCT. TKIs were used as comedication in 14 patients (41.2%), which included imatinib, dasatinib, nilotinib, bosutinib, and ponatinib. Thirty-four patients (100%) were hospitalized, mostly because of Blincyto administration.

Pediatric Patients:

Two pediatric patients with R/R Ph+ ALL were included in the study. The median age was 11.5 (IQR: 9.0, 14.0) years; both patients were male. The median (min, max) time from ALL diagnosis to Blincyto treatment was 25.80 (25.0, 26.6) months. Before the

initiation of Blincyto, 1 patient (50%) underwent ≥ 1 HSCT. At Blincyto initiation, 1 patient (50%) had ≥ 50% bone marrow blasts and no patient had extramedullary disease. The median (min, max) cumulative dose of Blincyto was 339.7 (265, 414.5) μg. The median number of cycles started was 1 (IQR: 1, 1); no patient completed Blincyto treatment cycle.

Overall, the rate of CR/CRh/CRi within the first 2 cycles of Blincyto treatment was 50% (1 of 2 patients; 95% CI: 1.3, 98.7); 1 patient (50%) achieved CR and also had molecular response. No patient relapsed after Blincyto treatment. The median RFS time was not estimable as only 1 patient with a follow-up of 7.08 months was available for the analysis. The median OS was not estimable as only 1 event occurring in 2 patients. In an analysis censoring at the time of HSCT, OS was not reached. One patient underwent allogeneic HSCT after achieving CR/CRh/CRi after Blincyto treatment (at 0.52 months after response). TKIs were not used as comedication. Both pediatric patients (100%) were hospitalized because of Blincyto administration.

Minimal Residual Disease Positive Philadelphia-negative Patients:

Of the 122 patients enrolled in the MRD-positive Ph- subgroup, most were adult patients (N = 83).

Adult Patients:

The median age was 35.0 (IQR: 24.0, 56.0) years with male preponderance (N = 44 [53%]). The median (min, max) time from ALL diagnosis to Blincyto treatment was 8.40 (2.3, 204.9) months. Before the initiation of Blincyto, 9 patients (10.8%) underwent ≥ 1 HSCT. At Blincyto initiation, 2 patients (2.8%) had ≥ 50% bone marrow blasts and no patient had extramedullary disease. The median (min, max) cumulative dose of Blincyto was 772 (9, 1352.5) μg. The median number of cycles started was 2 (IQR: 1, 3) and completed was 2 (IQR: 1, 2).

Within the first 2 cycles of Blincyto treatment, 64 patients had evaluable MRD; among these patients, 89.1% (N = 57, 2 patients were excluded because of missing data) had at least molecular response. Twenty-seven patients (35.5%) relapsed after Blincyto treatment. Among 20 relapsed patients who underwent CD19 assessment, 17 patients were CD19 positive. The median OS was not reached; 28 events (death) occurring in 83 patients over a median follow-up time of 18.75 months (IQR: 14.03, 31.08). The KM estimate of probability of OS at 1 year was 76.4% (95% CI: 64.7, 84.7) after Blincyto initiation. Similarly, median OS was not reached when the analysis was censored at time of HSCT; 7 events (death) occurring in 83 patients over a median follow-up period of 3.57 months (IQR: 2.33, 10.13). Median time to allogeneic HSCT for patients in CR/CRh/CRi at, and any time after Blincyto treatment was 2.26 months (IQR: 0.93, NE); 54 patients (71.1%) underwent allogeneic HSCT over a median follow-up time of 13.87 month (IQR: 9.21, 21.97). The DFS, as estimated by KM methodology, was 54.1% (95% CI: 41.7, 65.0) at 24 months from Blincyto initiation; this increased to 54.0 months (95% CI: 30.2, 72.9) in analysis censoring at the time of HSCT. In an analysis of mortality after allogeneic HSCT, the KM estimate for probability of survival (with relapse and death because of undocumented relapse treated as a competing risk) at 12 months after Blincyto initiation in patients who achieved CR/CRh/CRi at any time (and who had no intervening myelosuppressive therapy between Blincyto and HSCT) was 9% (95% CI: 3.8, 21.6). TKI (dasatinib) was used as comedication for 1 patient (1.2%). Eighty-one patients (98.8%) were hospitalized, mostly because of Blincyto administration.

Pediatric Patients:

Thirty-nine pediatric patients with MRD-positive Ph- ALL were included in the study. The median age was 8.0 (IQR: 5.0, 13.0) years with male preponderance (N = 23 [59%]). The median (min, max) time from ALL diagnosis to Blincyto treatment was 28.10 (2.6, 139.3) months. Before the initiation of Blincyto, 8 patients (20.5%) underwent ≥ 1 HSCT. At Blincyto initiation, no patient had > 50% bone marrow blasts or extramedullary disease. The median (min, max) cumulative dose of Blincyto was 424.7 (18.6, 787.7) μg. The median number of cycles started and completed was 1 (IQR: 1, 2).

Within the first 2 cycles of Blincyto treatment, 32 patients had evaluable MRD; among these patients, 71.9% (N = 23) had at least molecular response. Fifteen patients (42.9%) relapsed after Blincyto treatment. Among 11 relapsed patients who underwent CD19 assessment, 6 patients were CD19 positive. The median OS was not reached; at 24 months after Blincyto initiation the KM estimate for probability of survival was 53.3% (95% CI: 18.9, 78.9). Similarly, median OS when censoring at time of HSCT was not reached; at 18 months after Blincyto initiation the KM estimate for probability of survival was 72.9% (95% CI: 35.9, 90.7). Median time to allogeneic HSCT after achieving CR/CRh/CRi (at any time after Blincyto treatment) in patients with no intervening myelosuppressive therapy between Blincyto and HSCT was 1.02 months (95% CI: 0.69, 2.26); 25 patients (69.4%) underwent allogeneic HSCT. Median DFS was 13.57 months (IQR: 6.72, NE); when censored at the time of HSCT, DFS was 9.11 months (IQR: 7.31, 16.23). TKIs were not used as comedication. Thirty-five patients (97.2%) were hospitalized, mostly because of Blincyto administration.

Minimal Residual Disease Positive Philadelphia-positive Patients:

Of the 28 patients enrolled in the MRD-positive Ph+ subgroup, most were adult patients (N = 26).

Adult Patients:

The median age was 50.5 (IQR: 43.0, 55.0) years with male preponderance (N = 20 [76.9%]). The median (min, max) time from ALL diagnosis to Blincyto treatment was 11.00 (3.7, 69.7) months. Before the initiation of Blincyto, 8 patients (30.8%) underwent ≥ 1 HSCT. At Blincyto initiation, 2 patients (8.7%) had ≥ 50% bone marrow blasts and no patient had extramedullary disease. The median (min, max) cumulative dose of Blincyto was 784 (268, 968) μg. The median number of cycles started was 2 (IQR: 1, 2) and completed was 1.5 (IQR: 1, 2).

Within the first 2 cycles of Blincyto treatment, 16 patients had evaluable MRD; among these patients, (56.3%) (N = 9) had at least molecular response. Six patients (30% of those where data were available) relapsed after Blincyto treatment. Among 3 relapsed patients who underwent CD19 assessment, all were CD19 positive. The median OS was not reached; 5 events (death) occurring in 26 patients over a median follow-up time of 16.49 months. The KM estimate of probability of OS at 1 year was 83.6% (95% CI: 62.0, 93.5). Similarly, median OS in analyses censored at time of HSCT was not reached (2 events [death] over a median follow-up time of 5.57 months). Median time to allogeneic HSCT after achieving CR/CRh/CRi at any time after Blincyto treatment was 15.97 months (IQR: 1.21, NE); 11 patients (52.4%) underwent allogeneic HSCT. The DFS, as estimated by KM methodology, was 57.7% (95% CI: 32.4, 76.4) at 24 months. TKIs were used as comedication in 12 patients (48%), which included imatinib, dasatinib, and ponatinib. Twenty-six patients (100%) were hospitalized, mostly because of Blincyto administration.

Pediatric Patients:

Two pediatric patients with MRD Ph+ ALL were included in the study. The median age was 14.0 (IQR: 11.0, 17.0) years; both the patients were male. The median (min, max) time from ALL diagnosis to Blincyto treatment was 26.60 (21.0, 32.2) months. Before the initiation of Blincyto, no patient underwent HSCT. At Blincyto initiation, no patient had extramedullary disease or ≥ 50% bone marrow blasts. The median (min, max) cumulative dose of Blincyto was 479.5 (171.2, 711.2) μg. The median number of cycles started was 2 (IQR: 1, 3) and completed was 1.5 (IQR: 1, 2).

Within the first 2 cycles of Blincyto treatment, 1 patient had evaluable MRD; this patient had complete molecular response (undetectable MRD). Data on relapse was available for 1 patient; this patient did not relapse after Blincyto treatment. The median OS and DFS was not estimable; as data were only available for 2 patients. Time to allogeneic HSCT after achieving CR/CRh/CRi in the single patient who met these criteria was 0.46 months. TKIs were used as comedication in 2 patients (100%), which included dasatinib. Both the patients (100%) were hospitalized because of Blincyto administration.

Interpretation:

Data generated in this study (Neuf) are largely consistent with previously published data in each indication, eg, the TOWER (adult R/R Ph- B-cell ALL), BLAST (adult MRD Ph-/Ph+ B-cell ALL) and RIALTO (pediatric R/R Ph- B-cell ALL) studies. However, results should be interpreted with caution because of the highly selected nature of patients (ie, those enrolled in the Blincyto expanded access program). Patients enrolled in such a program may be highly heterogeneous compared with other patients as there may be a proportion of sicker, more treatment-experienced patients, who may not be otherwise considered for Blincyto-related clinical pathways in routine clinical practice. Bearing these caveats in mind, this study provides compelling evidence for the real-world effectiveness of Blincyto.

- **Marketing Authorization Holder**

Amgen Europe B.V.
Minervum 7061
4817 ZK Breda
The Netherlands

- **Names and Affiliations of Principal Investigators**

[redacted],
Hospital Saint Louis,
1 Avenue Claude Vellefaux, 75010, Paris, France