1. ABSTRACT

- **Title**

A Cross-Sectional Survey of Patients and Caregivers Receiving Blincyto in Routine Clinical Practice in Europe to Evaluate the Effectiveness of Additional Risk Minimisation Measures

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- **Keywords**

relapsed or refractory acute lymphoblastic leukaemia (ALL), survey, educational materials, risk minimisation measures, post-authorisation safety study (PASS)

- **Rationale and Background**

Evaluating the effectiveness of risk minimisation interventions is key to successful therapeutic risk management. The Blincyto® (blinatumomab) educational materials developed for the additional risk minimisation measure (aRMM) program were designed to increase awareness about the Blincyto safety profile and ensure its safe and effective use. The results of this study complement data from a separate survey of healthcare professionals (HCPs).

- **Research Questions and Objectives**

Research questions:

- Did key safety information contained in the patient/caregiver educational materials reach the target population?
- What was the level of knowledge and understanding of the target audience with regard to the key safety information described in the educational materials?
- What was the level of the behaviours outlined in the educational materials?
- Were the educational materials used as intended?

Primary objectives: to describe receipt and knowledge about the patient/caregiver educational materials among patients with Philadelphia chromosome-negative (hereinafter referred to as Philadelphia-negative) relapsed/refractory B-cell precursor ALL who had received Blincyto and their caregivers.

Secondary objectives: to describe behaviours outlined and the level of understanding of key safety messages in the patient/caregiver educational materials among patients with Philadelphia-negative relapsed/refractory B-cell precursor ALL who had received Blincyto and their caregivers, and to describe usage of the educational materials among patients with Philadelphia-negative relapsed/refractory B-cell precursor ALL who had received Blincyto and their caregivers.

- **Study Design**

An observational cross-sectional survey of patients and caregivers was planned in a selection of European Union (EU) countries. The final list of countries was dependent on country-specific factors including the timing of Blincyto launch and levels of usage. The survey was a self-administered paper questionnaire.

The timing of the patient/caregiver survey was sufficiently early in the product lifecycle to identify and promptly rectify any aspect of the educational program that might have needed to be modified.

- **Setting**

The study was undertaken on behalf of Amgen by an external research group, OXON Epidemiology. The surveys were conducted in France, Germany, Italy, and the UK. The selection of countries was made to allow for the completion of the study within the required timeframe and to support the external validity of the study findings by encompassing a wide range of healthcare systems. Spain was also a target country for the survey, but was not included in the study as Blincyto reimbursement had not been agreed in the country by the end of the study period (March 2019).

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

This study comprised cross-sectional surveys of patients and/or caregivers, which were considered as 2 strata for the analysis. Approximately 50 patients and 50 caregivers were planned to be recruited from approximately 25 centres.

These groups were eligible for inclusion: 1) patients with Philadelphia-negative relapsed/refractory B-cell precursor ALL who had received Blincyto as outpatients (≥ 18 years of age at Blincyto initiation) and who could read and understand the native language of the country in which the study was being conducted, and 2) caregivers (≥ 18 years of age) of such patients who could read and understand the native language of the country in which the study was being conducted.

Patients and/or caregivers of patients who had received Blincyto as inpatients only, who participated in Blincyto clinical studies, who had received Blincyto through a compassionate use program, or who were employed by Amgen/delegate when providing informed consent were excluded.

- **Variables and Data Sources**

Survey data were collected from a self-administered paper questionnaire developed specifically for patients and caregivers.

Each survey asked questions designed to examine the following key concepts related to the brochure and patient card: receipt of the brochure/card, knowledge and understanding of key messages, behaviours outlined in the brochure/card, and usage of the brochure/card (ie, whether the card was completed and shown to HCPs while on Blincyto treatment; and whether the brochure/card was read and referred to, including reasons for not reading them).

The primary endpoints for the patient/caregiver survey were:

- Receipt: a categorical variable was used to describe if patients and caregivers received the brochure and/or card.
- Knowledge: a mean score was created to summarise individual patient and caregiver scores; an individual patient/caregiver score was calculated as the proportion of all knowledge questions with correct responses.

The secondary endpoints for the patient/caregiver survey were:

- Behaviour: a mean score was created to summarise individual patient and caregiver scores; an individual patient/caregiver score was calculated as the proportion of all behaviour questions with correct responses.
- Understanding: among patients and caregivers who had read the patient/caregiver brochure and card, an ordinal scale was used to assess the self-reported level of understanding.
- Usage: a mean score was created to summarise individual patient and caregiver scores; an individual patient/caregiver score was calculated as the sum of the 'value' of responses to all usage questions (ordinal scale) divided by the maximum possible score. Among those who did not read the materials, a categorical variable was used to describe the reasons for not reading them.

- **Results**

A total of 121 haematology centres comprised the reference population that was contacted for participation; of these, 3 sites (2.5%) were nonresponders (failed contacts). Of those with effective contacts, 75 sites (63.6%) were interested in participation. Relative to the 121 centres comprising the reference population, 33 sites (27.3%) met eligibility requirements and 23 sites (19.0%) were selected. Of the 23 participating sites, an approximately equal number were in France and Italy (10 sites [43.5%] and 9 sites [39.1%], respectively); and Germany and the UK (2 sites [8.7%] each). Nineteen (86.4%) of the 23 participating sites were academic centres; for 1 site, academic status was unknown. Overall, the rate of participating sites among the reference population (ie, effective recruitment rate) was 19.01%.

Results are summarised in Table 1.

Patients

Among the eligible set of 36 patients, the recruitment rate for the full analysis set was 72.2% (N = 26). A total of 26 patients completed the questionnaire and had valid responses to allow for the assessment of the primary objective and inclusion in the full analysis set. Among these, 13 (50.0%) were from Italy, 11 (42.3%) were from France, and 1 each (3.8%) was from Germany and the UK.

Of the 25 patients in the full analysis set with available data, 36.0% (N = 9) responded that they received or had access to either the patient card or brochure, 32.0% (N = 8) received or had access to neither, and 32.0% (N = 8) did not remember. The mean (SD) knowledge score for the 26 patients in the full analysis set was 86.9% (15.9%); most patients (88.5% [N = 23]) had a skilled level of knowledge (score $\geq$ 80%). Among all knowledge questions, patients were least familiar with the recommendation not to drive a car/use heavy machinery (65.4% answered the question correctly). The mean (SD) behaviour score for the 26 patients in the full analysis set was 77.6% (22.5%); most patients (53.8% [N = 14]) did not have a skilled level of behaviour (score $<$ 80%).

Among the 9 patients in the full analysis set who responded that they received some or all of the materials, 55.6% (N = 5) reported having read all of them, 22.2% (N = 2) read part of them, and 22.2% (N = 2) did not read them. Of the 7 patients who read all or part of the materials, 85.7% (N = 6) responded that they understood the information completely and 14.3% (N = 1) understood the information somewhat. For the 4 patients in the full analysis set with data available, the mean (SD) usage score was 55.6% (14.5%); no patients (0.0% [N = 0]) had a good level of usage (score $\geq$ 80%).

Caregivers

Among the eligible set of 20 caregivers, the recruitment rate for the full analysis set was 85.0% (N = 17). A total of 17 caregivers completed the questionnaire and had valid responses to allow for the assessment of the primary objective and inclusion in the full analysis set. Among these, 8 each (47.1%) were from Italy and France, 1 (5.9%) was from the UK, and 0 (0.0%) were from Germany.

Among the 17 caregivers in the full analysis set, 29.4% (N = 5) responded they received or had access to either the patient card or brochure, 35.3% (N = 6) received or had access to neither, and 35.3% (N = 6) did not remember. The mean (SD) knowledge score for the 17 caregivers in the full analysis set was 83.5% (19.0%); most caregivers 88.2% (N = 15) had a skilled level of knowledge (score ≥ 80%). Among all knowledge questions, caregivers were least familiar with the recommendation not to drive a car/use heavy machinery (68.8% answered the question correctly). The mean (SD) behaviour score for the 17 caregivers in the full analysis set was 87.7% (18.4%); most caregivers 64.7% (N = 11) had a skilled level of behaviour (score ≥ 80%).

Of the 4 caregivers in the full analysis set with available data who responded that they received some or all of the educational materials, 25.0% (N = 1) reported having read all of them, 50.0% (N = 2) read part of them, and 25.0% (N = 1) did not read them. Of the 3 caregivers who read all or part of the materials, 66.7% (N = 2) responded that they understood the information completely and 33.3% (N = 1) understood the information somewhat. For the 2 caregivers in the full analysis set with data available, the mean (SD) usage score could not be calculated; no caregivers (0.0% [N = 0]) had a good level of usage (score ≥ 80%).

Table 1. Patients and Caregivers: Summary of Receipt, Knowledge, Behaviour, Understanding, and Usage (Full Analysis Sets)

	Patients (N = 26)	Caregivers (N = 17)
Have you received or had access to the Blincyto educational materials?		
Yes, both the patient card and brochure	4 (16.0)	2 (11.8)
Yes, only the patient brochure	5 (20.0)	3 (17.7)
None of them	8 (32.0)	6 (35.3)
I do not remember	8 (32.0)	6 (35.3)
Missing - n	1	0
Received the educational materials - n	9	5
If received, have you read the Blincyto educational material?		
Yes, I read all of them	5 (55.6)	1 (25.0)
Yes, I read part of them	2 (22.2)	2 (50.0)
No, I did not read them	2 (22.2)	1 (25.0)
Missing - n	0	1
Knowledge score[a]		
N (n missing)	26 (0)	17 (0)
Mean (SD)	86.9 (15.9)	83.5 (19.0)
Skilled level of knowledge[a]		
Yes (score ≥ 80%) - n (%)	23 (88.5)	15 (88.2)
No (score < 80%) - n (%)	3 (11.5)	2 (11.8)

Footnotes are defined on next page of table

Table 1. Patients and Caregivers: Summary of Receipt, Knowledge, Behaviour, Understanding, and Usage (Full Analysis Sets)

	Patients (N = 26)	Caregivers (N = 17)
Behaviour score[a]		
N (n missing)	26 (0)	17 (0)
Mean (SD)	77.6 (22.5)	87.7 (18.4)
Skilled level of behaviour[a]		
Yes (score ≥ 80%) - n (%)	12 (46.2)	11 (64.7)
No (score < 80%) - n (%)	14 (53.9)	6 (35.3)
Read the educational materials - n	7	3
If read, how well did you understand the information in the educational materials?		
Completely - n (%)	6 (85.7)	2 (66.7)
Somewhat - n (%)	1 (14.3)	1 (33.3)
Received the educational materials - n	9	5
Usage score[a]		
N (n missing)	4 (5)	2 (3)
Mean (SD)	55.6 (14.5)	-
Good level of usage[a]		
Yes (score ≥ 80%) - n (%)	0 (0.0)	0 (0.0)
No (score < 80%) - n (%)	4 (100.0)	2 (100.0)

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[a] Scoring percentages of overall level of correct responses. Scores ranged from 0 to 100, with the highest values representing the better achievement of the key concept in the dimension. The primary analysis considers missing, illegible, and responses 'I don't know', 'I'm not sure', or 'I don't remember' as missing values.
Source: Modified from Table 14-4.4 and Table 14-4.6

- **Discussion**

This observational research study report assesses to what extent the aRMM educational materials for patients and caregivers were effective in achieving a sufficient level of receipt and usage of the educational materials, knowledge and understanding of key messages, and behaviours in terms of safe and appropriate use of the medication. The countries included in the study were France, Italy, Germany, and the UK. Overall, 26 patients and 17 caregivers were included in the full analysis set.

Limitations include the potential for recall bias, selection bias within centres, and non-participation. Self-reporting of actions and behaviour may be biased towards positive values. The number of patients and caregivers willing/able to participate was lower than anticipated (27 patients and 17 caregivers were enrolled versus 50 planned for each type of respondent). In addition, for 2 of the 4 countries surveyed (Germany and the UK), the number of patients participating was very low compared with the number of patients participating in France and Italy. Only approximately one-third of patients and caregivers received the educational materials; thus, receipt of educational materials by patients and caregivers was limited by the behaviours of physicians and nurses in distribution of the educational materials. Finally, subgroup analyses were exploratory, and results may be unreliable due to small numbers of subjects in each subgroup.

The diversity of countries, study centres, and patients/caregivers should have allowed a broad overview of how the Blincyto aRMM educational material may perform in Europe;

however, results were mostly limited to 2 countries and low sample numbers make it challenging to draw conclusions. Management of ALL is undertaken according to the protocols and recommendations of their respective ALL working groups (eg, Gruppo Italiano Malattie Ematologiche dell'Adulto [Italian Group of Haematological Diseases in Adults; GIMEMA], Group for Research on Adult ALL [France, Belgium, Switzerland; GRAALL], German Multicentre Study Group for Adult ALL [GMALL], European Working Group for ALL [EWALL], and Spanish Programme for the Study and Treatment of Haematological Malignancies [PETHEMA]). The participating countries, Italy, France, Germany, and the UK, cover most of the relevant ALL working groups in Europe. Because of the low sample numbers for patients and caregivers in both Germany and the UK, it cannot be firmly concluded that the participating countries appropriately represent Europe and the European standard of care overall.

In summary, approximately one-third of patients and caregivers received the educational materials (36.0% and 29.4%, respectively). Among the patients and caregivers who received some or all of the materials, most (77.8% of patients and 75% of caregivers) reported having read all or part of them. For patients and caregivers who read the materials, 85.7% and 66.7%, respectively, understood them completely. The overall mean knowledge and behaviour scores for patients were > 75% and the overall mean knowledge and behaviour scores for caregivers were > 80%. Among all knowledge questions, both patients and caregivers were least familiar with the recommendation not to drive a car/use heavy machinery (65.4% and 68.8%, respectively, answered the question correctly). In general, results suggest that distribution of the educational materials was a limiting factor for receipt and usage by patients.

The European Medicines Agency has identified neurological events and medication errors as events of interest in patients treated with Blincyto. These events are monitored on an ongoing basis and reported in the Periodic Benefit-Risk Evaluation Report (PBRER). Based on the PBRER for the reporting period of 23 November 2015 to 02 June 2019, there have been no identified patterns or increases in severity reported in these events, the evaluation of safety data for these events has not detected any new risks for Blincyto, and the overall benefit-risk balance of Blincyto remains favourable. This study focuses on evaluation of the aRMM educational materials for patients and caregivers, which were designed to increase awareness about the risks of neurological events and potential for medication errors with Blincyto and to ensure its safe and effective use.

- **Marketing Authorization Holder**

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- **Names and Affiliations of Principal Investigators**

Not applicable.

- A list of all collaborating institutions will be made available upon request.