1. ABSTRACT

- **Title**

Survey of Physicians, Pharmacists, and Nurses Involved in the Prescribing, Preparation and Administration of Blincyto® in Europe to Evaluate the Effectiveness of Additional Risk Minimization 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**

In the European Union (EU), Blincyto (blinatumomab) has been approved for the treatment of adults with Philadelphia chromosome-negative (hereafter referred to as Philadelphia-negative) relapsed or refractory B-precursor ALL, adults with Philadelphia-negative minimal residual disease (MRD) B-precursor ALL, and paediatric patients with Philadelphia-negative relapsed or refractory B-precursor ALL.

To provide for the safe and effective use of Blincyto, Amgen implemented additional risk minimisation measures (aRMMs) consisting of educational materials for healthcare professionals (HCPs; physicians, pharmacists, nurses) and patients/caregivers. These educational materials 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. Amgen provides the relevant aRMM to all HCPs who are expected to prescribe, dispense, or administer Blincyto. Two surveys were developed to assess whether the processes put in place for the Blincyto educational efforts are effective in achieving a sufficient level of receipt of the materials, and knowledge and behaviour around key messages in the materials. The results of the HCP surveys are the focus of this report; the results of the patient/caregiver survey (Study 20150228) will be summarised in a separate report. The results of the HCP and patient/caregiver surveys should not be interpreted in isolation of one another.

- **Research Question and Objectives**

Research questions:

- Have the additional educational brochure materials for physicians, nurses, and pharmacists reached their target population?
- What is the level of knowledge and understanding of the target audience for key safety information described in the physician, nurse, and pharmacist brochures?
- What is the level of behaviours outlined in the physician, nurse, and pharmacist brochures and the distribution of educational materials to patients/caregivers?
- Are the physician, nurse, and pharmacist brochures used as intended?

Primary objectives: to describe the receipt of the Blincyto (blinatumomab) brochures, and to describe the knowledge and behaviours outlined in the Blincyto brochures among physicians, nurses, and pharmacists.

Secondary objectives: to describe the level of understanding of key safety messages in the Blincyto brochures among physicians, nurses, and pharmacists; and to describe usage of the Blincyto brochures among physicians, nurses, and pharmacists.

- **Study Design**

To meet the study objectives, 3 observational cross-sectional surveys of physicians, nurses, and pharmacists were planned in a selection of EU countries after the introduction of Blincyto to the EU market based on reimbursement dates and anticipated usage. The surveys used online self-administered questionnaires.

The distribution of the surveys was planned to start 3 months after each country-specific launch to allow sufficient time for uptake of Blincyto and familiarity and use of the materials by the HCPs. The timing of this evaluation was sufficiently early in the product lifecycle to identify and rectify promptly any aspect of the educational program that might need to be modified.

- **Setting**

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, however Spain was not included in the study as reimbursement had not been agreed in the country by the end of the study period (December 2018).

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

This study comprised cross-sectional surveys of physicians, nurses, and pharmacists, which were considered as 3 strata for the analysis.

Physicians, nurses, or pharmacists who have managed, administered, or prepared Blincyto for at least 1 adult patient (≥ 18 years of age at Blincyto initiation) with Philadephia chromosome-negative relapsed or refractory B-precursor ALL were eligible for inclusion. HCPs who participated in Blincyto studies were eligible for participation.

Physicians, nurses, or pharmacists who have been employed by Amgen (or delegate) or who participated in the pretesting phase of the HCP survey were excluded.

- **Variables and Data Sources**

Survey data were collected from the 3 self-administered questionnaires developed specifically for physicians, nurses, and pharmacists. Responses were collected through an online electronic data capture system, which was used to create the study database.

Each survey asked questions designed to examine the following key concepts related to each of the brochures: receipt of the brochures; knowledge and understanding of key messages; behaviours outlined in the brochures, including the distribution of educational brochures to patients/caregivers; and usage of the brochures (ie, whether HCPs read and referred to the educational materials and reasons for not reading them).

The primary endpoints for the HCP survey were:

- Receipt: a categorical variable was used to describe the proportion of physicians, nurses, and pharmacists who reported having received the brochure.
- Knowledge: a mean score was created to summarise individual physician, nurse, and pharmacist scores; an individual physician, nurse, and pharmacist score was calculated as the proportion of all knowledge questions with correct responses.
- Behaviour: a mean score was created to summarise individual physician, nurse, and pharmacist scores; an individual physician, nurse, or pharmacist score was calculated as the proportion of all behaviour questions with correct responses. For physicians and nurses, the score also included the adequacy of the timing for the distribution of the card and brochure to patients/caregivers. Among physicians and nurses who did not distribute the materials to patients/caregivers, a categorical variable was used to describe the reasons for noncompliance.

The secondary endpoints for the HCP survey were:

- Understanding: among physicians, nurses, and pharmacists who read the educational materials, an ordinal scale was used to assess the self-reported level of understanding.
- Usage: a categorical variable was used to describe the proportion of physicians, nurses, and pharmacists who report having read the brochure. Among physicians, nurses, and pharmacists who read the educational material, an ordinal scale was used to assess how often the material was referred to. Among those who do not read the materials, a categorical variable was used to describe the reasons for not reading them.
- **Results**

Results are summarised in Table 1.

Physicians

A total of 50 physicians 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, 27 (54.0%) were from Italy, 13 (26.0%) were from France, 7 (14.0%) were from the UK, and 3 (6.0%) were from Germany. In addition, 7 (14.0%) had < 3 years of experience managing patients with ALL, 10 (20.0%) had 3 to 5 years of experience, 9 (18.0%) had 6 to 10 years of experience, and 24 (48.0%) had > 10 years of experience. Overall, the rate of participating physicians among their sampling frame (ie, effective recruitment rate) was 12.35%.

Among the 50 physicians in the full analysis set, 78.0% (N = 39) responded that they received the Blincyto educational materials, 12.0% (N = 6) did not, and 10.0% (N = 5) did not remember. The mean (SD) knowledge score was 74.3% (23.1%); overall, 44.0% (N = 22) physicians had a skilled level of knowledge (score ≥ 80%) while 56.0% (N = 28) did not (score < 80%). The mean (SD) behaviour score for 49 physicians in the full analysis set was 76.9% (17.5%); overall, 49.0% (N = 24) physicians had a skilled level of behaviour (score ≥ 80%) and 51.0% (N = 25) did not (score < 80%).

Among the 39 physicians in the full analysis set who responded that they received the materials, 87.2% (N = 34) reported having read them, 7.7% (N = 3) did not, and 5.1% (N = 2) did not remember. Of those who read the materials, 79.4% (N = 27) responded that they understood the material completely, 11.8% (N = 4) did not

understand some information, and 8.8% (N = 3) did not remember. For the 37 physicians in the full analysis set with data available, the mean (SD) usage score was 73.6% (27.0%); most physicians (67.6% [N = 25]) did not have a good level of usage (score < 80%).

Nurses

Overall, 48 nurses 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, 23 (47.9%) were from Italy, 16 (33.3%) were from France, 6 (12.5%) were from the UK, and 3 (6.3%) were from Germany. Overall, the effective recruitment rate for nurses was 7.22%.

Among the 48 nurses in the full analysis set, 56.3% (N = 27) reported that they received the Blincyto educational materials, 33.3% (N = 16) did not, and 10.4% (N = 5) did not remember. The mean (SD) knowledge score for the 48 nurses in the full analysis set was 70.3% (17.2%); most nurses (77.1% [N = 37]) did not have a skilled level of knowledge (score < 80%). The mean (SD) behaviour score for the 48 nurses in the full analysis set was 65.6% (20.7%); most nurses (66.7% [N = 32]) did not have a skilled level of behaviour (score < 80%).

Among the 27 nurses who responded that they received the materials, most (88.9% [N = 24]) reported having read them, while 7.4% (N = 2) did not, and 3.7% (N = 1) did not remember. Of those who read the materials, 66.7% (N = 16) reported that they understood the material completely, 16.7% (N = 4) did not understand some information, and 16.7% (N = 4) did not remember. For the 26 nurses in the full analysis set with data available, the mean (SD) usage score was 70.2% (25.0%); most nurses (80.8% [N = 21]) did not have a good level of usage (score < 80%).

Pharmacists

A total of 50 pharmacists 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, 19 (38.0%) were from the UK, 15 (30.0%) were from France, 11 (22.0%) were from Germany, and 5 (10.1%) were from Italy. Overall, the effective recruitment rate was 5.97% for pharmacists.

Among the 50 pharmacists in the full analysis set, 60.0% (N = 30) indicated that they received the Blincyto educational materials, 24.0% (N = 12) responded that they did not, and 16.0% (N = 8) did not remember. The mean (SD) knowledge score for the 50 pharmacists in the full analysis set was 68.0% (26.3%); most pharmacists (74.0% [N = 37]) did not have a skilled level of knowledge (score < 80). The mean (SD) behaviour score for 49 pharmacists in the full analysis set was 69.8% (28.6%). Approximately half (53.1% [N = 26]) of pharmacists had a skilled level of behaviour (score ≥ 80%).

Among the 30 pharmacists who responded that they received the materials, most (96.7% [N = 29]) reported having read them, while 3.3% (N = 1) did not remember. Of those who read the materials, 82.8% (N = 24) indicated that they understood the material completely, 13.8% (N = 4) did not understand some information, and 3.5% (N = 1) did not remember. For the 29 pharmacists in the full analysis set with data available, the mean (SD) usage score was 86.2% (15.1%); overall, 51.7% (N = 15) had a good level of usage (score ≥ 80%) and 48.3% (N = 14) did not have a good level of usage (score < 80%).

Table 1. Physicians, Nurses, and Pharmacists: Summary of Receipt, Knowledge, Behaviour, Understanding, and Usage (Full Analysis Sets)

	Physicians (N = 50)	Nurses (N = 48)	Pharmacists (N = 50)
Have you received or had access to the Blincyto educational materials			
Yes – n (%)	39 (78.0)	27 (56.3)	30 (60.0)
No – n (%)	6 (12.0)	16 (33.3)	12 (24.0)
I don't remember – n (%)	5 (10.0)	5 (10.4)	8 (16.0)
Received the educational materials - n	39	27	30
If received, have you read the Blincyto educational material?			
Yes – n (%)	34 (87.2)	24 (88.9)	29 (96.7)
No – n (%)	3 (7.7)	2 (7.4)	0 (0.0)
I don't remember – n (%)	2 (5.1)	1 (3.7)	1 (3.3)
Knowledge score[a]			
N (n missing)	50 (0)	48 (0)	50 (0)
Mean (SD)	74.3 (23.1)	70.3 (17.2)	68.0 (26.3)
Skilled level of knowledge[a]			
Yes (score ≥ 80%) – n (%)	22 (44.0)	11 (22.9)	13 (26.0)
No (score < 80%) – n (%)	28 (56.0)	37 (77.1)	37 (74.0)
Behaviour score[a]			
N (n missing)	49 (1)	48 (0)	49 (1)
Mean (SD)	76.9 (17.5)	65.6 (20.7)	69.8 (28.6)
Skilled level of behaviour[a]			
Yes (score ≥ 80%) – n (%)	24 (49.0)	16 (33.3)	26 (53.1)
No (score < 80%) – n (%)	25 (51.0)	32 (66.7)	23 (46.9)
Read the educational materials - n	34	24	29
If read, how well did you understand the information in the educational materials?			
Completely - n (%)	27 (79.4)	16 (66.7)	24 (82.8)
Some information not understood - n (%)	4 (11.8)	4 (16.7)	4 (13.8)
I don't remember - n (%)	3 (8.8)	4 (16.7)	1 (3.5)
Received the educational materials - n	39	27	30
Usage score[a]			
N (n missing)	37 (2)	26 (1)	29 (1)
Mean (SD)	73.6 (27.0)	70.2 (25.0)	86.2 (15.1)
Good level of usage[a]			
Yes (score ≥ 80%) – n (%)	12 (32.4)	5 (19.2)	15 (51.7)
No (score < 80%) – n (%)	25 (67.6)	21 (80.8)	14 (48.3)

Source: Modified from Table 14-4.1.1, Table 14-4.2.1, Table 14-4.3.1, Table 14-4.4.1, Table 14-4.5.1, Table 14-4.6.1, Table 14-4.7.1, and Table 14-4.8

[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.

- **Discussion**

This observational research study report describes whether the aRMM educational materials for HCPs are effective in achieving a sufficient level of receipt of the materials, and knowledge and behaviour around key messages in the materials. The countries included in the study were France, Italy, Germany, and the UK. Overall, 50 physicians, 48 nurses, and 50 pharmacists were included in the full analysis set.

Limitations include the potential for HCP selection bias, missing information, and recall bias. Self-reporting of actions and behaviour may be biased towards positive values. Participation in the study was voluntary, and refusal to participate may have limited the representativeness of the HCP survey. In countries where recruitment proved challenging, additional recruitment strategies were used, however, there may be differences between HCPs recruited by the primary and alternative recruitment methods. 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 HCPs allows a global overview of how the Blincyto aRMM educational material may perform in Europe. Management of ALL is done according to the protocols and recommendations of their respective ALL working groups (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. Based on this, the participating countries appropriately represent Europe and the European standard of care overall.

In summary, a higher proportion of physicians received the brochure (78.0%) compared with nurses and pharmacists (56.3% and 60.0%, respectively). Among the HCPs who received the materials, most (87.2% to 96.7%) reported having read them. For physicians, the overall mean knowledge, behaviour, and usage scores were consistently > 70%, and 79% of the physicians who read the material understood it completely. For nurses, the overall mean scores for knowledge, behaviour, and usage were ≥ 65%, and 66% of the nurses who read the material understood it completely. For pharmacists, the mean overall scores for knowledge, behaviour, and usage were > 65%, and 82% of the pharmacists who read the material understood it completely.

In the blinatumomab program, neurologic events and medication errors are events of interest. 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 blinatumomab, and the overall benefit-risk balance of blinatumomab remains favourable. This study focuses on evaluation of the aRMM educational materials for HCPs, 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.