Title: Healthcare Providers' Awareness of the risks and safe use conditions associated with BLINCYTO®: A REMS Assessment Survey

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1. BACKGROUND AND RATIONALE

BLINCYTO® (blinatumomab) is indicated for the treatment of Philadelphia chromosome-negative (Ph-) relapsed or refractory (R/R) B-cell precursor acute lymphoblastic leukemia (ALL). A Risk Evaluation and Mitigation Strategy (REMS) with goals to mitigate the risks of cytokine release syndrome (CRS), neurologic toxicities, and preparation and administration errors, were identified at the time of approval of the biological license application (BLA). The REMS communication plan consists of REMS letters for healthcare providers (HCPs, including physicians and nurses), hospital and home healthcare pharmacists, and professional societies, a REMS Fact Sheet for healthcare providers, dissemination of REMS information at scientific meetings, and a REMS program website. The rationale for this survey of HCPs is to assess HCP awareness and knowledge of risks highlighted in the REMS communication plan.

2. OBJECTIVES

To determine the level of awareness on the risks and safe use conditions associated with BLINCYTO therapy and certain aspects of the BLINCYTO REMS Program among healthcare providers (HCPs) who have used BLINCYTO for patients in the treatment of Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL). Specifically the objectives are to

- Evaluate healthcare providers' awareness and understanding of the risks of cytokine release syndrome, neurologic toxicity, and preparation and administration errors associated with BLINCTYO use among prescribers who have prescribed BLINCTYO, pharmacists who have prepared BLINCTYO, and nurses who have administered BLINCTYO.
- Evaluate healthcare providers' awareness and understanding of the BLINCTYO indication among prescribers who have prescribed BLINCTYO, pharmacists who have prepared BLINCTYO, and nurses who have administered BLINCTYO.
- Evaluate healthcare providers' awareness and use of the BLINCTYO Prescribing Information and the REMS materials.

3. STUDY POPULATION/SAMPLE SIZE/STATISTICAL ANALYSES PLANS

Study Design

Cross-sectional surveys will be conducted in HCPs who have prescribed, dispensed, prepared and/or administered BLINCYTO in the US in the past 12 months outside the clinical trial setting. Surveys were conducted at 18 months, and will be conducted at 3

years and 7 years after the launch of BLINCYTO. This cross-sectional survey is being conducted 3-years after the launch of BLINCYTO in the US, and learnings from this survey may be incorporated into the 7-year assessment.

Study Population

Inclusion criteria include HCPs, defined as prescribers [MDs, DOs, Physician Assistants (PAs), Nurse Practitioners (NPs)], nurses (RNs, BSNs), and hospital and/or home healthcare pharmacists who have prescribed, dispensed, prepared and/or administered BLINCYTO therapy to patients outside of the clinical trial setting in the past 12 months. HCPs or their immediate family members (e.g. spouse, children, and/or parent) who are or were employed by Amgen, vendor, or the FDA will be excluded from participation.

A list of HCPs targeted by the REMS Program will be matched to the survey vendor's Physician Panels and/or other target sources to determine a list of respondents. In addition, customer/prescriber lists or secondary prescribing data will be used to increase the number of survey respondents. All HCPs that are identified via these sources will be invited to participate in this survey. Participation in consecutive waves (i.e. at 18 months, 3 years and 7 years after the launch of BLINCYTO) by an HCP is acceptable.

Survey Pre-testing

Through an independent provider, Amgen plans to conduct telephone assisted online pilot surveys with appropriate HCPs (e.g. approximately 5 each of oncologists, oncology nurses, hospital-based pharmacists) on the proposed survey questions. Pre-tests will be used to assess the survey research instrument for each of the following:

Directionality: Confirm that all questions are clearly understood by pre-test respondents.

Completeness: Confirm that the response options provided are exhaustive and that no reasonable response options are omitted from closed-ended list questions.

Question order effects: Determine whether there are question order effects (influence of previous question text or response on a following question) that can be controlled for by re-ordering questions.

Survey Methodology

Healthcare providers will be initially invited to participate in the survey by email (recruitment material, Appendix 2). Both online and telephone surveys will be offered. For those HCPs that opt for responding by telephone, the survey will be administered using computer-assisted telephone interviewing (CATI). In addition, direct mail

invitations to participate in the online survey and/or hard copy surveys may be used to reach our target of completed surveys.

Screening questions will be placed at the beginning of the survey in order to determine whether HCPs are eligible to take part in a study. HCPs deemed ineligible by these questions are then terminated from the survey.

Additional questions on key risk message domains will be included in order to evaluate risk messages specific to certain types of HCPs.

All possible answers for each survey question (not including screening questions) will be randomized. Participants will not be allowed to return to questions or be allowed to skip ahead during the survey administration. The correct answer choices will be provided on a screen at the end of the online survey. If the survey is completed by telephone, the correct answer choices will be provided by mail.

Survey Questions – Key Messages and Domains

Survey questions will be categorized into 6 total domains, with 3 domains for the key risk messages (the risk of cytokine release syndrome, the risk of neurologic toxicity, and the risk of preparation and administration errors). The domains are as follows:

a. HCPs understanding of the risk of cytokine release syndrome associated with use of BLINCYTO
b. HCPs understanding of the risk of neurologic toxicity associated with use of BLINCYTO
c. HCPs understanding of the risk of preparation and administration errors associated with use of BLINCYTO
d. HCPs understanding of the appropriate use of BLINCYTO
e. HCPs awareness and utilization of REMS materials
f. Screening and demographics

The questionnaire in Appendix 1 includes the survey questions, as well as the domains corresponding to each question.

Endpoints

- HCP is aware of the risk of cytokine release syndrome associated with use of BLINCYTO
- HCP is aware of the risk of neurologic toxicity associated with use of BLINCYTO

- HCP is aware of the risk of preparation and administration errors associated with use of BLINCYTO
- HCP is aware of the indication for BLINCYTO

Sample Size

Given the relatively small patient population, the total number of HCPs involved in their care is anticipated to be small. At least 150 completed surveys will be targeted per wave, including at least 50 prescribers, 50 nurses, and 50 hospital and/or home healthcare pharmacists.

Assuming an 80% knowledge threshold score (defined in the Descriptive Analysis section), the 95% confidence intervals (CIs), calculated using Wilson intervals, are presented in **Table 1** below. For a sample size of 50 of a specific type of HCP, the 95% CI for an 80% knowledge threshold score ranges from 70.0% to 88.8%. For a sample size of 150 pooled HCPs, the 95% CI for an 80% knowledge threshold score ranges from 72.9% to 85.6%.

Table 1. **95% confidence intervals (CIs) for an 80% threshold knowledge score by varying sample sizes**

Sample size	95% confidence intervals (CIs) for an 80% threshold knowledge score
50	70.0%, 88.8%
75	69.6%, 87.5%
100	71.1%, 86.7%
150	72.9%, 85.6%

Descriptive Analyses

In general, analyses will be performed for prescribers, nurses, and pharmacists separately, as well as for the pooled group of HCPs to assess the effectiveness of the entire REMS communication plan of BLINCYTO. Demographics and other characteristics of the HCPs will be summarized using proportions. For each survey question, the proportion and 95% CI of each response option including ‘not sure’ will be reported. For each knowledge question, the proportion of HCPs selecting the correct response and corresponding 95% CI will be calculated. Analyses for each of the objectives are described in detail below.

For objective 1 (evaluate awareness and understanding of the risks of cytokine release syndrome, neurologic toxicity, and preparation and administration errors), analyses will be conducted separately for each of the 3 key risk message domains (cytokine release syndrome, neurologic toxicity, and preparation and administration errors). Results will be presented for each HCP type separately, as well as pooled. Specifically, knowledge for each of the domains will be assessed as follows:

1) Key risk domain: Risk of cytokine release syndrome

   - Prescribers: Must correctly identify cytokine release syndrome as a risk in at least one of Questions 9 and 10 to have knowledge
   - Nurses: Must correctly identify cytokine release syndrome as a risk in at least one of Questions 9 and 10 to have knowledge
   - Pharmacists: Must correctly identify cytokine release syndrome as a risk in Question 10 to have knowledge

2) Key risk domain: Risk of neurologic toxicity

   - Prescribers: Must correctly identify neurologic toxicity as a risk in at least one of Questions 9 and 10 to have knowledge
   - Nurses: Must correctly identify neurologic toxicity as a risk in at least one of Questions 9 and 10 to have knowledge
   - Pharmacists: Must correctly identify neurologic toxicity as a risk in Question 10 to have knowledge

3) Key risk domain: Risk of preparation and administration errors

   - Prescribers: Must correctly identify approximately 70% of the preparation and administration error items in Questions 9 and 13 (i.e. 3 out of 4 items) to be considered to have knowledge
   - Nurses: Must correctly identify approximately 70% of the preparation and administration error items in Questions 9, 11, 14, and 15 (i.e. 6 out of 9 items) to be considered to have knowledge
   - Pharmacists: Must correctly identify approximately 70% of the preparation and administration error items in Questions 12, 14, and 15 (i.e. 6 out of 8 items) to be considered to have knowledge

A threshold knowledge score for each of the key risk messages and corresponding 95% CI will be estimated as the proportion of HCPs (by type and overall) having knowledge of the key risk messages. The percentage of respondents above and below the threshold knowledge score for each key risk message domain will be also be calculated. Responses for Questions 16 and 17 will be described with proportions and 95% CIs for each response option.

For objective 2 (to evaluate awareness and understanding of the BLINCTYO indication), HCPs must correctly identify ALL as the indication in Question 18. The proportion of HCPs (by type and overall) who responded correctly will be estimated along with 95% CIs.

For objective 3 (to evaluate awareness and use of the BLINCTYO Prescribing Information and the REMS materials), responses for Questions 19-37 will be described with proportions and 95% CIs for each response option.

4. ADVERSE EVENTS

In the event that an adverse event is reported, these will be reported to Amgen Safety consistent with standard practices

4.1 Definition of Safety Events

4.1.1 Adverse Events

An adverse event is any untoward medical occurrence in a subject/patient administered a pharmaceutical product(s) irrespective of a causal relationship with this treatment.

An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a product(s), whether or not considered related to the product(s). The definition of an adverse event includes:

- Worsening of a pre-existing condition or underlying disease
- Events associated with the discontinuation of the use of a product(s), (eg, appearance of new symptoms)

It is vendor's responsibility to report the adverse event to Amgen.

4.1.2 Serious Adverse Events

A serious adverse event is any adverse event as defined above that meets at least one of the following serious criteria:

- is fatal
- is life threatening (places the patient at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an “other significant medical hazard” that does not meet any of the above criteria

A hospitalization meeting the regulatory definition for “serious” is any in-patient hospital admission that includes a minimum of an overnight stay in a healthcare facility.

“Other significant medical hazards” refer to important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events could include allergic bronchospasm, convulsions, and blood dyscrasias, drug-induced liver injury, events that necessitate an emergency room visit, outpatient surgery, or other events that require other urgent intervention.

4.1.3 Other Safety Findings

Other Safety Findings (regardless of association with an adverse) include:

- Medication errors, overdose, whether accidental or intentional, misuse, or abuse, , involving an Amgen product,
- Pregnancy and lactation exposure,
- Transmission of infectious agents,
- Reports of uses outside the terms for authorized use of the product including off-label use,
- Occupational exposure,
- Any lack or loss of intended effect of the product(s).

4.1.4 Product Complaints

Product Complaints include any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a product or device after it is released for distribution to market or clinic by either Amgen or by distributors and partners for whom Amgen manufactures the material. This includes any drug(s) or device(s) provisioned and/or repackaged /modified by Amgen. Drug(s) or device(s) includes investigational product.

4.2 Safety Reporting Requirements

Vendor is responsible for ensuring that safety events (adverse events, product complaints and other safety findings), reported by the HCP or interviewer that occur in patients treated with BLINCYTO after study enrollment through the final study contact, are recorded in the HCP's study documentation. Safety events must be submitted as individual case safety reports to Amgen via the applicable Amgen Safety Reporting Form (paper or electronic form) within 1 business day of awareness.

See Appendix 3 for Safety Report Form, Appendix 4 for Additional Safety Reporting Information regarding the adverse event grading scale used in this study, and Appendix 5 for sample Pregnancy and Lactation Notification Worksheets.

The HCP may be asked to provide additional information for any event submitted, which may include a discharge summary or extracts from the medical record. Information provided about the event must be consistent with medical records.

4.2.1 Safety Reporting Requirement to Regulatory Bodies

Amgen will report safety data as required to regulatory authorities, Investigators/institutions, IRBs/IECs or other relevant ethical review board(s) in accordance with Pharmacovigilance guidelines and in compliance with local regulations. The Investigator is to notify the appropriate IRB/IEC or other relevant ethical review board of Serious Adverse Events in accordance with local procedures and statutes.

5. SUBJECT CONFIDENTIALITY

This study will comply with all applicable laws regarding subject privacy. No direct subject contact or collection of additional subject data will occur. Study results will be in tabular form and aggregate analyses that omits subject identification. Any reports will not include subject identifiers.

6. PUBLICATION INTENT

There is no intent to publish the results of these analyses.

7. COMPENSATION

Healthcare professionals will receive payment for their participation in the surveys. This compensation will be based on a Fair Market Value (FMV) assessment (eg, time and effort).

Appendix 1. Questionnaire

Removed to allow unbiased data collection.

Appendix 2. Recruitment Materials

Removed due to document size restriction.

Appendix 3. Safety Reporting Form

Removed due to document size restriction.

Appendix 4. Additional Safety Reporting Information

Removed due to document size restriction.

Appendix 5. Pregnancy and Lactation Notification Worksheets

Removed due to document size restriction.