Summary Table of Study Protocol

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
Protocol version identifier	1.0
Date of last version of the protocol	18 October 2016
EU Post Authorisation Study (PAS) Register No	Not yet available
Active Substance	Blinatumomab
Medicinal Product	Blincyto
Product Reference	H0003731
Procedure Number	NA
Marketing Authorisation Holder(s)	**Amgen Europe B.V.** Minervum 7061 4817 ZK Breda The Netherlands
Joint PASS	No
Research Question and Objectives	The primary objectives of the study are to describe the receipt of the Blincyto brochures, and knowledge and behaviours outlined in the Blincyto brochures among physicians, nurses and pharmacists. The secondary objectives of the study are: - To describe the level of understanding of key safety messages in the Blincyto brochures, among physicians, nurses and pharmacists. - To describe usage of the Blincyto brochures, among physicians, nurses and pharmacists.
Country(-ies) of Study	France, Germany, Italy, Spain, United Kingdom

Author	[redacted]

Marketing Authorisation Holder

Marketing authorisation holder(s)	**Amgen Europe B.V.** Minervum 7061 4817 ZK Breda The Netherlands
MAH Contact	[redacted]

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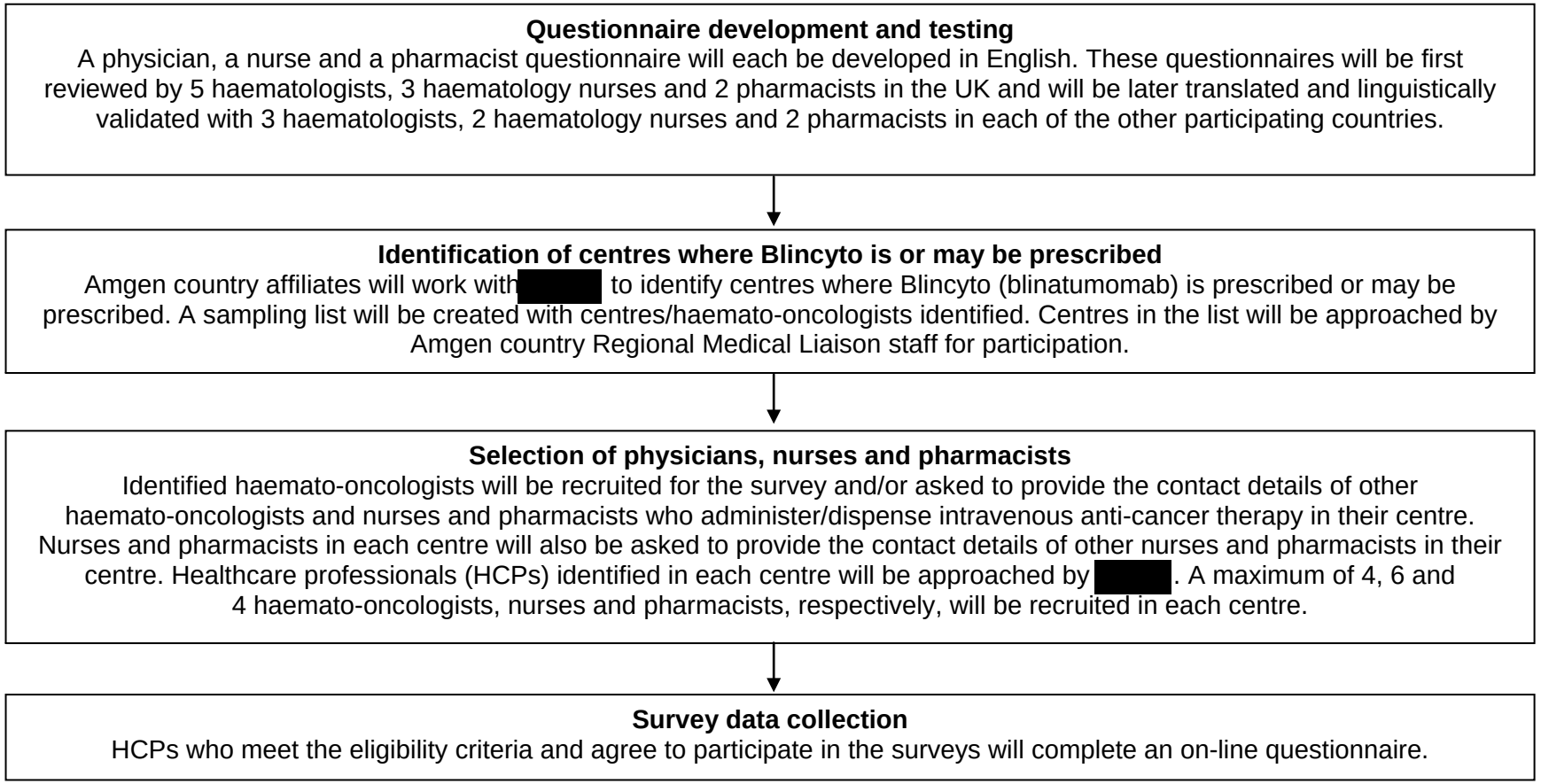
Investigator's Agreement

I have read the attached protocol entitled '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', dated 18 October 2016, and agree to abide by all provisions set forth therein.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

Signature	
Name of Investigator	Date (DD Month YYYY)

Study Design Schema



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2. List of Abbreviations

ADR	Adverse Drug Reaction
ALL	Acute Lymphoblastic Leukaemia
aRMM	additional Risk Minimisation Measure
CIOMS	Council for International Organizations of Medical Sciences
eDC	Electronic Data Capture
EMA	European Medicines Agency
EU	European Union
GVP	Good Pharmacovigilance Practice
HCP	Healthcare Professional
HSCT	Stem cell transplantation
MAH	Marketing Authorisation Holder
ME	Medication Error
MedDRA	Medical Dictionary for Regulatory Activities
OS	Overall Survival
PASS	Post-Authorisation safety Study
Ph-	Philadelphia chromosome–negative
RML	Regional Medical Liaison
RMP	Risk Management Plan
R/R	Relapsed/Refractory

3. Responsible Parties

MAH	Amgen is the MAH which oversees MAH activities and facilitates Competent Authority submissions [redacted]
MAH Representative	The MAH representative for this study is [redacted], a Clinical Research Organisation (CRO) delegated to serve as the study coordinating centre. [redacted] will conduct the study on behalf of Amgen. The MAH representative is responsible for overall conduct, deliverables and timelines for the study and communication with Amgen. [redacted]

4. Abstract

- **Study 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.

- **Study Background and Rationale:**

Blincyto® (blinatumomab) is indicated for the treatment of adults with Philadelphia chromosome–negative (Ph-) relapsed or refractory (R/R) B-precursor acute lymphoblastic leukaemia (ALL) as a continuous infusion. Due to the seriousness and rarity of the indication, and the lack of alternative medicinal products for the subset of patients with Ph- disease, Blincyto was designated by the European Medicines Agency (EMA) as an orphan medicinal product. The product was approved in November 2015 and is due to become available throughout the EU according to country-specific timelines.

During the marketing authorisation application, two important safety risks were identified to require additional risk minimisation measures (aRMMs): neurological events and the potential for medication errors (MEs).

A condition to the marketing authorisation for the safe and effective use of Blincyto is the implementation of aRMMs consisting of educational materials targeting healthcare

professionals (HCPs; physicians, pharmacists, nurses), as well as patients/caregivers. Educational materials for HCPs include brochures for physicians, nurses and pharmacists.

In line with regulatory guidance (eg, EMA GVP XVI and GVP VIII) a survey of physicians, nurses and pharmacists is herein presented to help 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. A survey of patients/caregivers is also proposed but described in a separate protocol.

- **Research Question and Objective(s)**
  - Primary Objectives
    The primary objectives of the study are to describe the receipt of the Blincyto brochures, and 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
    - To describe usage of the Blincyto brochures, among physicians, nurses and pharmacists.
  - Hypothesis(es)/Estimation
    This study is descriptive and therefore no formal hypothesis will be tested.

This study will help indicate if the aRMMs are successful if a majority of HCPs participating in the survey confirm receipt of the brochures and demonstrate knowledge and behavior of key safety messages. These results will be interpreted in context of the wider study including the secondary objectives and the results of individual questions, response rate and recruitment. In addition, any available information external to the study to help understand the experience of the HCP aRMMs will be considered to determine what action, if any, should be taken.

- **Study Design/Type**

This is an observational study consisting of three cross-sectional surveys of physicians, nurses and pharmacists to help evaluate the effectiveness of the educational brochures in minimising the risk of MEs and neurological events. The distribution of the three HCP surveys is planned to start 12 to 18 months after each country-specific launch to allow time for uptake of Blincyto and familiarity and use of the materials by the HCPs.

- **Study Population or Data Resource**

The surveys are planned to be conducted in France, Germany, Italy, Spain and the UK. However, if recruitment of subjects is slower than anticipated other countries may be added to meet the study timeline.

Haematology centres where Blincyto is prescribed or expected to be prescribed after its launch will be selected to participate. Identified haemato-oncologists will be recruited for the survey and/or asked to provide the contact details of other haemato-oncologists and nurses and pharmacists who administer/dispense intravenous anti-cancer therapy in their centre. Nurses and pharmacists in each centre will also be asked to provide the contact details of other nurses and pharmacists in their centre. HCPs identified in each centre will be approached by [redacted]. Haemato-oncologists, nurses and pharmacists will be invited to participate until a cap is reached in each centre of 4, 6 and 4, respectively.

- **Summary of HCP Eligibility Criteria**

Inclusion criteria:

- Physician, nurse or pharmacist has managed, administered or prepared Blincyto for at least one adult patient with Ph- R/R B precursor ALL.

Exclusion criteria:

- Physician, nurse or pharmacist has been employed by Amgen (or delegate).
- Physician, nurse or pharmacist has participated in the pre-testing phase of the HCP survey.

- **Variables**

The questionnaire will assess the following key concepts related to the HCP brochures:

- Receipt of the brochures.
- Knowledge and understanding of key messages.
- Behaviors outined in the brochures including the distribution of educational brochures to patients/caregivers.
- Usage of the brochures.

- **Study Sample Size**

The study population will include approximately [redacted] physicians and [redacted] pharmacists to allow precisions of [redacted] and up to [redacted] nurses to allow precisions of [redacted] for correct responses of 60% and 90%, respectively, for the primary objective of receipt. For the score of correct responses to knowledge and behavior questions ranging from 0 to 10, when the estimated standard deviation ranges from [redacted], a sample size of [redacted] physicians and [redacted] pharmacists will produce a two-sided 95%

confidence interval with a distance from the mean to the limits ranging from [redacted], and a sample size of [redacted] nurses would produce a two-sided 95% confidence interval with a distance from the mean to the limits ranging from [redacted].

Surveyed HCPs will arise from approximately [redacted] centres however it may be more or less depending on recruitment.

- **Data Analysis**

Categorical data will be summarized by counts and percentages. Continuous data will be summarized using number, mean, standard deviation (SD), median, quartiles, minimum and maximum and in the case of non-normally distributed data, median, range and interquartile range. All 95% confidence intervals will be presented to three decimal places.

Analyses will be mainly descriptive for the overall study population and certain subgroups, such as those who read the material vs. those who did not. The statistical analysis will include a summary of the study conduct, a descriptive analysis and the analysis of the objectives.

Receipt will be described through the percentage of physicians, nurses and pharmacists who report having received the brochure.

Knowledge: A mean score will be created to summarise individual physician, nurse and pharmacist scores. An individual physician, nurse or pharmacist score is calculated as the proportion of all knowledge questions with correct responses.

Behaviour: A mean score will be created to summarise individual physician, nurse and pharmacist scores. An individual physician, nurse or pharmacist score is calculated as the proportion of all behavior questions with correct responses. For physicians and nurses, the score will also include the adequacy of the timing for the distribution of the card and brochure to patients/caregivers. Among physicians and nurses who do not distribute the materials to patients/caregivers, a categorical variable will describe the reasons for non-compliance.

Understanding: Among physicians, nurses and pharmacists who have read the educational material, an ordinal scale will describe the self-reported level of understanding.

Usage will be described with the percentage of physicians, nurses and pharmacists who have read the material. Among those physicians, nurses and pharmacists who have read the educational material, an ordinal scale will assess how often the material was

referred to. Among those who do not read the materials, a categorical variable will describe the reasons for not reading them.

Correlation of total scores for questions of knowledge and behaviour.

5. Amendments and Updates

None

6. Milestones

Milestone	Planned date
[redacted]	[redacted]
[redacted]	[redacted]
Start of data collection*	Feb 2017
[redacted]	[redacted]
Final report of study results	May 2019

[redacted]

7. Rationale and Background

7.1 Diseases and Therapeutic Area

Acute lymphoblastic leukaemia (ALL) is a malignant proliferation of lymphocytes at early stage of differentiation. ALL can affect patients of all ages but it mainly occurs in late adulthood and children aged 2 to 5 years (Katz et al. 2015). In the European Union (EU), more than 7,200 new incident cases are diagnosed annually (Gatta et al. 2011) with approximately 40% occurring in adults (Larson 2006). The prevalence of ALL is estimated to be 1.8 people in 10,000 (92,000 people in the EU). These figures qualify ALL as a rare disease in adults (Hoelzer et al. 2016).

The currently available front-line treatments, chemotherapies with severe side effects, often result in clinical remission. However, for many patients ALL remains a serious, life-threatening and incurable disease due to a high rate of relapse. Approximately 10% of patients are refractory to current chemotherapy regimens. Up to 90% of newly diagnosed patients with adult ALL will achieve initial clinical remission (Benjamin & Stein 2016), however, up to 50% of patients will relapse and need a second line of therapy (Linker et al. 2002; Gökbuget et al. 2009; Thomas et al. 1999). Patients who relapse a second time have a median Overall Survival (OS) of no more than 3 months (O'Brien et al. 2008). In the relapsed/refractory (R/R) adult population, the goal of therapy is to induce remission and proceed to allogeneic stem cell transplantation (HSCT), which is the only potentially curative option in adult patients with

R/R B precursor ALL, or to obtain long-term disease free survival and increase OS, if HSCT is not an option (Tavernier et al. 2007).

Blincyto® (blinatumomab) is indicated for the treatment of adults with Philadelphia chromosome–negative (Ph-) R/R B-precursor ALL as a continuous infusion. Due to the seriousness and rarity of the indication, and the lack of alternative medicinal products for the subset of patients with Ph- disease, Blincyto was designated by the European Medicines Agency (EMA) as an orphan medicinal product. The product was approved in November 2015 and is due to become available throughout the EU according to country-specific timelines.

Patients initially receive 2 cycles of treatment. Based on an individual benefit-risk assessment, 3 additional cycles of Blincyto consolidation treatment may be considered if complete remission has been achieved. A single cycle of treatment is 4 weeks of continuous infusion and each cycle of treatment is separated by a 2 week treatment-free interval.

Blincyto safety profile

During the marketing authorisation application, two important safety risks were identified to require additional risk minimisation measures (aRMMs): neurological events and the potential for medication errors (MEs).

Neurological events such as fits, problems with speech, alterations in consciousness, confusion and disorientation, problems with balance and coordination occur in approximately 50% of patients treated with Blincyto (Topp et al. 2015).

Blincyto is infused continuously using a pump device. Hospitalisation is recommended for initiation at a minimum for the first 9 days of the first cycle and the first 2 days of the second cycle. Blincyto may be administered at home after discharge with an ambulatory pump. Medication errors can occur at any time during the reconstitution, dilution and administration of Blincyto that may result in patients receiving a dose that is too high or too low. Mistakes in setting up the pump, or problems with the pump can also cause MEs. In the pivotal phase II trial that led to the approval of Blincyto in the EU, MEs were observed in 3.2% (6/189) of subjects (Topp et al. 2015). In the pooled safety dataset, which includes [redacted] patients exposed to Blincyto in [redacted] studies of different indications (not including the phase III trial), MEs were reported in [redacted] of subjects. [redacted] Overdoses were primarily due to infusion pump errors and Blincyto preparation errors. Most MEs did not result in an adverse

event. Of the ones associated with adverse events, most events were consistent with the known safety profile, mild in severity, and resolved.

Blincyto additional risk minimisation

As a requirement linked to the Blincyto Risk Management Plan (RMP), Amgen as the Marketing Authorisation Holder (MAH), shall ensure that in each member state where Blincyto is marketed all healthcare professionals (HCPs) who are expected to prescribe, dispense or administer the product, and patients/caregivers who are expected to use the product, be provided with the aRMMs presented in Table 1.

Table 1. Blincyto aRMMs in the European Union

Measure	Target population	Key messages
Educational brochure for nurses	Haematology Nurses	• Remarks on the importance of reporting adverse drug reactions (ADRs) • Description of the administration procedures of Blincyto • Description on patient's monitoring and management of early signs and symptoms of neurological events • Recommendation for patients not to drive while receiving Blincyto and to contact immediately the treating physician / nurse if they experience neurological symptoms
Educational brochure for physicians	Haematologist Oncologist	• Remarks on the importance of reporting ADRs • Information on treatment with Blincyto, administration and posology, duration of hospitalisation, interruption and/or permanent discontinuation of the treatment
Educational brochure for pharmacists	Hospital Pharmacists	• Remarks on the importance of reporting ADRs • Detailed description of the reconstitution and preparation procedures of Blincyto infusion solution for intravenous administration under aseptic conditions, using aseptic techniques
Educational brochure for patients/ caregivers	ALL patients receiving Blincyto and their caregivers	• Remarks on the importance of reporting ADRs • Description of the administration procedures of Blincyto and how to reduce the risk of MEs while using the infusion pump. • Description of the main signs and / or symptoms of neurologic events and the importance of notifying the treating physician or nurse immediately if symptoms occur • Recommendation for patients not to drive while receiving Blincyto
Patient Card	ALL patients receiving Blincyto and their caregivers	• Remarks on the importance of reporting ADRs • A warning message for HCPs treating the patient at any time, including emergency conditions, that the patient is using Blincyto • Contact details of the Blincyto prescriber • Blincyto treatment start date

Effectiveness of Blincyto educational tools

In line with regulatory guidance (eg, EMA Good Pharmacovigilance Practice [GVP] XVI) effectiveness of risk minimisation interventions requires an evaluation of the processes put in place to implement the aRMMs together with an assessment of relevant clinical and safety outcome(s).

A HCP survey was proposed to the EMA to describe receipt, knowledge and behaviour outlined in the aRMMs among physicians, nurses, and pharmacists. A patient/caregiver survey is also planned to describe receipt, knowledge, and behaviours outlined in the patient educational materials. The patient/caregiver survey is described in a separate protocol but the results of the two surveys should be interpreted together.

This protocol focuses on the HCP survey. This study is classified as a Post-Authorisation Safety Study (PASS) and has been designed to meet the requirements of GVP module VIII: 'Post-authorization safety studies' (EMA 2016) and module XVI: 'Risk minimization measures - Selection of tools and effectiveness indicators' (EMA 2014) and to follow the recommendations provided by the Council for International Organizations of Medical Sciences (CIOMS) Working Group IX (CIOMS 2014). This protocol also takes into account the key elements of survey methodology described in GVP Module XVI (EMA 2014) in terms of sampling procedures and recruitment strategy; design and administration of the data collection instruments; analytical approach; as well as ethics, privacy, and overall study feasibility.

7.2 Rationale

Evaluating the effectiveness of risk minimisation interventions is key to successful therapeutic risk management. Such an evaluation is particularly valuable when risk minimisation measures are introduced in addition to those applied routinely (labelling, SmPC, prescription status, etc.). This is the case with Blincyto, since an aRMM programme targeting both HCPs and patients/caregivers has been introduced. The educational materials developed for the aRMM program were designed to increase awareness about the safety profile of the product and to ensure its safe and effective use.

The proposed survey is intended to describe 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 and distribution of materials to patients/caregivers by physicians, nurses and pharmacists.

The results of this survey will complement data from a twin patient/caregiver survey and should be interpreted in the context of the assessment of safety outcomes.

7.3 Statistical Inference (Estimation or Hypothesis[es])

This study is descriptive and therefore no formal hypothesis will be tested.

8. Research Question and Objectives

These surveys aim to address the following 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 physicians, nurses and pharmacists brochures and the distribution of educational materials to patients/caregivers?
- Are the physician, nurse and pharmacist brochures used as intended?

8.1 Primary

The primary objectives of the study are to describe the receipt of the Blincyto brochures, and knowledge and behaviours outlined in the Blincyto brochures among physicians, nurses and pharmacists.

8.2 Secondary

The secondary objectives of the study are:

- To describe the level of understanding of key safety messages in the Blincyto brochures, among physicians, nurses and pharmacists.
- To describe usage of the Blincyto brochures, among physicians, nurses and pharmacists.

This study will help indicate if the aRMMs are successful if a majority of HCPs participating in the survey confirm receipt of the brochures and demonstrate knowledge and behavior of key safety messages. These results will be interpreted in context of the wider study including the secondary objectives and the results of individual questions, response rate and recruitment. In addition, any available information external to the study to help understand the experience of the HCP aRMMs will be considered to determine what action, if any, should be taken.

9. Research Methods

9.1 Study Design

To meet the study objectives, three observational cross-sectional surveys of physicians, nurses and pharmacists are planned in France, Germany, Italy, Spain and the UK, after the introduction of Blincyto to the EU market.

The distribution of the surveys is planned to start 12 to 18 months after each country-specific launch to allow time for uptake of Blincyto and familiarity and use of the materials by the HCPs. The timing of this evaluation is sufficiently early in the product lifecycle to identify and rectify promptly any aspect of the educational program that might need to be modified.

9.2 Setting and Study Population

The surveys will be conducted in France, Germany, Italy, Spain and the UK. The selection of countries corresponds to the combination of expected product uptake and adequate timing of the product launch to allow for the completion of the study within the required timeframe. These countries have been selected to support the external validity of the study findings, as collectively they will encompass a wide range of healthcare systems: general practitioner-based gate-keeper function (UK, Spain and Italy), health insurance which is part of the social security system (Germany) and mixed (France).

This rationale is based on factors that may change as the study progresses (eg, planned country-specific launch schedule). Therefore, if recruitment of HCPs is slower than anticipated other countries may be added to meet the study timeline.

9.2.1 Study Period

The maximum planned period for data collection is 23 months. However, as product launch is planned in a staggered manner in Europe, this period is expected to be reduced in some countries.

As this is a one-wave cross-sectional design, data from HCPs will be collected at one point in time.

9.2.2 Selection and Number of Sites

Site selection and sampling strategy

The sampling frame will consist of haematology centres where Blincyto is prescribed or expected to be prescribed after its launch in each participating country. Potential sites for participation will be identified by Amgen country Regional Medical Liaison (RML)

staff. All centres in the list will be approached by RMLs to identify prescribers or potential prescribers willing to participate.

HCP selection and sampling strategy

The population for the HCP surveys will consist of haemato-oncologists, nurses and pharmacists working in haematology units. After at least one haemato-oncologist has been approached for participation, other haemato-oncologists, nurses and hospital pharmacists will be identified in the centre. Approcahed haemato-oncologists will also be requested to provide the name and contact details (email address or telephone number, after seeking their permission) of other haemato-oncologists, nurses who administer intravenous anti-cancer drugs and pharmacists who dispense intravenous anti-cancer drugs in their centre. In turn, identified nurses and pharmacists will be requested to provide the name and contact details of other nurses and pharmacists in their centre.

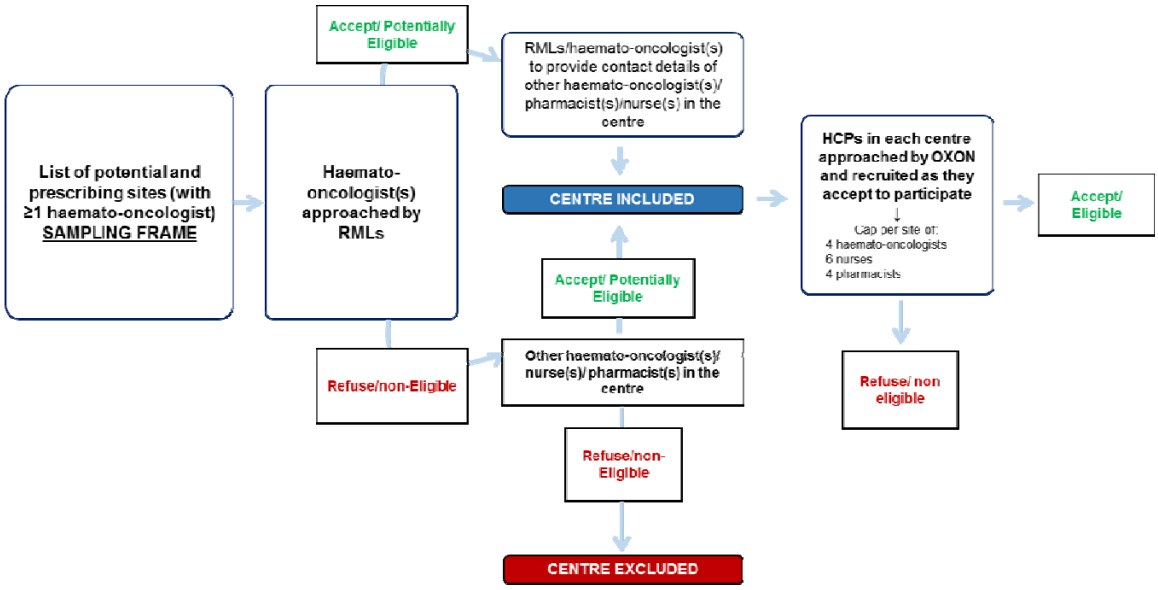
HCPs identified in each centre will be approached by [redacted] for participation in the surveys. Haemato-oncologists, nurses and pharmacists will be invited to participate until a cap is reached in each centre of 4 haemato-oncologists, 6 nurses and 4 pharmacists.

The number of eligible haemato-oncologists, nurses and pharmacists identified and contacted but not enrolled in the study, the number of non-respondents and the number eligible and willing to partcipate will be recorded.

An invitation letter will be sent by post or email with a link to the web-based questionnaire. Each invitation will include information on how to access the surveys online, and a unique participant code to ensure that the invitation is used only once. If the target level of HCPs is not reached after two emails or postal mailings, non-responding HCPs will be contacted by telephone.

The overall sampling strategy is depicted in Figure 1.

Figure 1. Illustration of Sampling Strategy



9.2.3 Healthcare Professional Eligibility

This study is comprised of cross-sectional surveys of physicians, nurses and pharmacists, which can be considered as three strata for the analysis.

9.2.3.1 Inclusion Criteria

- Physician, nurse or pharmacist has managed, administered or prepared Blincyto for at least one adult patient with Ph- R/R B precursor ALL.

9.2.3.2 Exclusion Criteria

- Physician, nurse or pharmacist has been employed by Amgen (or delegate).
- Physician, nurse or pharmacist has participated in the pre-testing phase of the HCP survey.

9.2.4 Baseline Period

This study consists of three cross-sectional surveys that do not involve any follow-up. Eligibility criteria will be assessed and HCP questionnaires will be completed at one point in time within the data collection period.

9.3 Variables

The surveys will examine the effectiveness of the educational materials targeting physicians, nurses and pharmacists about the risks associated with Blincyto treatment and the best course of action to undertake in order to minimise these risks.

Three questionnaires will contain multiple-choice questions with no free text fields.

The questionnaire will be structured as follows:

A. Acceptance to participate (date and signature)
B. Screening: eligibility, demographics
C. Main questionnaire domains

Section B (Screening) will collect socio-demographic characteristics (age group, gender and experience) about HCPs to explore factors associated with understanding and implementation of key messages. The questionnaire will be designed to take a maximum of 15 minutes to complete.

The questionnaire will assess the following key concepts related to each of the brochures:

- Receipt of the brochures.
- Knowledge and understanding of key messages.
- Behaviors outlined in the brochures including the distribution of educational brochures to patients/caregivers.
- Usage of the brochures ie, whether HCPs read and refer to the educatonal materials and reasons for not reading them.

9.3.1 Outcome Assessment

The primary endpoints for the HCP survey are:

- Receipt: A categorical variable will describe the proportion of physicians, nurses and pharmacists who report having received the brochure.
- Knowledge: A mean score will be created to summarise individual physician, nurse and pharmacist scores. An individual physician, nurse or pharmacist score is calculated as the proportion of all knowledge questions with correct responses.
- Behaviour: A mean score will be created to summarise individual physician, nurse and pharmacist scores. An individual physician, nurse or pharmacist score is calculated as the proportion of a ll behavior questions with correct responses. For physicians and nurses, the score will also include the adequacy of the timing for the distribution of the card and brochure to patients/caregivers. Among physicians and nurses who do not distribute the materials to patients/caregivers, a categorical variable will describe the reasons for non-compliance.

The secondary endpoints for the HCP survey are:

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

9.3.2 Covariate Assessment

For each HCP type, the following sociodemographic characteristics will be collected and used to describe the sample:

- Country
- Age group (<30, 31-45, 46-65, >65)
- Gender (male/female)
- Experience: years for physicians and in-training or not for all HCPs
- Time since last contact with a patient receiving Blincyto
- Participation in a Blincyto clinical trial

9.3.3 Validity and Reliability

Qualitative techniques will be used to ensure that the HCP questionnaires are readable, understandable and easy-to-use.

The questionnaires will be developed in English and conceptually reviewed by 5 haematologists, 3 haematology nurses and 2 pharmacists in the UK. The questionnaire will be subsequently translated and linguistically validated with 3 haematologists, 2 haematology nurses and 2 pharmacists in each of the participating countries.

During the linguistic validation interviews, trained interviewers will ask participants to complete the questionnaire while 'thinking aloud' and to describe their thinking and thought processes as they answer each question, each section and the questionnaire as a whole. The results will be used to optimize instructions, guidance, wording, response choices, as well as language.

A master version of each questionnaire will be generated following linguistic validation in the participating countries.

9.4 Data Sources

Data for this survey will be collected by means of three questionnaires developed especifically for physicians, nurses and pharmacists. Responses will be collected through an on-line electronic data capture (eDC) system that will be used to create the study database for analytical purposes.

The on-line questionnaire will be self-administered and can be completed at the participants' convenience. Although participants will be advised to complete the questionnaire in a timely manner, once they start the questionnaire, they will be able to stop at any point and, at a later time, pick up where they left off, if necessary.

Participants will not be able to go back and change answers to previous questions. This restriction minimizes the likelihood of the respondent using the web or other sources to influence answers to questions. Participants will also not be allowed to access the questionnaire once it has been submitted.

Additionally, a recruitment database with the feasibility to participate and the recruitment process will be compiled during the recruitment process and also used for the description of study conduct as described in Section 9.7.

9.5 Study Size

Based on precision calculations provided in Table 2 and Table 3, sample sizes for each survey are planned as follows:

- Physician and pharmacist surveys: the study aims to include approximately [redacted] physicians and [redacted] pharmacists to allow precisions of [redacted] for correct responses of 60% and 90%, respectively, for the primary endpoint question of receipt. For the score of correct responses to knowledge and behavior questions ranging from 0 to 10, a sample size of [redacted] would produce two-sided 95% confidence intervals with a distance from the mean to the confidence limits ranging from [redacted] when the estimated standard deviation ranges from [redacted], respectively.
- Nurse survey: the study aims to include up to [redacted] nurses to allow precision of [redacted] for correct responses of 60% and 90%, respectively, for the primary endpoint question of receipt For the score of correct responses to knowledge and behavior questions ranging from 0 to 10, a sample size of [redacted] would produce a two-sided 95% confidence interval with a distance from the mean to the limits ranging from [redacted] when the estimated standard deviation ranges from [redacted] respectively.

The approach to the study sample size for the HCP surveys is governed chiefly by the assumed percentage of HCPs who correctly respond to the questions, the acceptable precision around this assumed estimate and the degree of intra-class correlation. For practical reasons, we will aim to recruit more nurses than doctors and pharmacists as more nurses are expected to have contact with patients and are more likely to participate.

Table 2. Precision of Survey for [redacted] Nurses and [redacted] Physicians and Pharmacists According to a Range of Correct Response Rates to the Primary Endpoint Question of Receipt Using the Clopper-Pearson Method

Sample size	Correct Response	Lower Limit	Upper Limit
[redacted]	60%	[redacted]	[redacted]
	70%		
	80%		
	90%		
	60%		
	70%		
	80%		
	90%		
	60%		
	70%		
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	60%		
	70%		
	80%		
	90%		
	60%		
	70%		
	80%		
	90%		

Table 2. Precision of Survey for [redacted] Nurses and [redacted] Physicians and Pharmacists According to a Range of Correct Response Rates to the Primary Endpoint Question of Receipt Using the Clopper-Pearson Method

Sample size	Correct Response	Lower Limit	Upper Limit
[redacted]	60%	[redacted]	[redacted]
	70%		
	80%		
	90%		
	60%		
	70%		
	80%		
	90%		
	60%		
	70%		
	80%		
	90%		

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Table 3. Precision of Survey for [redacted] Nurses and [redacted] Physicians and Pharmacists According to Assumed Standard Deviations for the Mean Score of a Range of Correct Responses to Primary Endpoint Questions of Knowledge and Behaviour Using the Clopper-Pearson

Sample size	Expected SD around the mean score of correct responses	Precision (distance from mean to limits)
[redacted]	0.5	0.09
	1.5	0.28
	2.5	0.47
	3.5	0.66
	0.5	0.10
	1.5	0.29
	2.5	0.48
	3.5	0.68
	0.5	0.10
	1.5	0.30
	2.5	0.50
	3.5	0.69

Page 1 of 2

Table 3. Precision of Survey for 90 to 110 Nurses and 40 to 60 Physicians and Pharmacists According to Assumed Standard Deviations for the Mean Score of a Range of Correct Responses to Primary Endpoint Questions of Knowledge and Behaviour Using the Clopper-Pearson

Sample size	Expected SD around the mean score of correct responses	Precision (distance from mean to limits)
[redacted]	0.5	[redacted]
	1.5	
	2.5	
	3.5	
	0.5	
	1.5	
	2.5	
	3.5	
	...	
	0.5	
	1.5	
	2.5	
	3.5	
	0.5	
	1.5	
	2.5	
	3.5	
	0.5	
	1.5	
	2.5	
	3.5	
	0.5	
	1.5	
	2.5	
	3.5	
	0.5	
	1.5	
	2.5	
	3.5	

Approximately [redacted] physicians, [redacted] nurses and [redacted] pharmacists will be recruited across all participating countries from approximately [redacted] centres. The number of centres may be more or less depending on recruitment.

9.6 Data Management

A data management plan (DMP) will be written to guide of all aspects of data handling. It will include all data forms and annotations, testing documentation and summaries, database documentation, merging of datasets and transfer of files into SAS for statistical analysis.

Data managers and other staff at [redacted] will perform user acceptance testing before the eDC questionnaires and eCRF are released to study participants.

All data collected during the survey will be held confidentially. As discussed in Section 10.3 the identities of HCPs taking part in the survey will be controlled by the use of unique identification codes. These source ID numbers will be held securely, and these data will be used solely for the purpose of identifying whether the HCP has completed the survey.

9.6.1 Obtaining Data Files

Survey responses will be collected in the online eDC system. The study database will be transferred to SAS for analysis.

9.6.2 Linking Data Files

In addition to the online questionnaires, the feasibility and recruitment process will be registered in a excel database and managed by the study operations staff involved in the recruitment of participants. As described in Section 10.3, a unique code will be assigned to each HCP, which will be used to link the questionnaire with the recruitment database which will be kept by [redacted]

9.6.3 Review and Verification of Data Quality

This study is only intended to collect HCPs opinion through an on-line survey questionnaire and not clinical data, it is not planned to generate queries in the study.

9.7 Data Analysis

Statistical analyses will be mainly descriptive. A detailed statistical analysis plan (SAP) will be developed before final database lock and will include methods of analysis and presentation and table shells. All analyses will be performed using SAS 9.3 (or higher) statistical software (SAS, Cary, North Carolina, USA).

9.7.1 Planned Analyses

9.7.1.1 Primary Analysis

The primary analysis will be performed at one point in time, once the database is locked for analysis, and will address all the study objectives as described below.

9.7.2 Planned Method of Analysis

The study endpoints will be addressed using descriptive statistics.

9.7.2.1 General Considerations

Categorical data will be summarized by counts and percentages. Continuous data will be summarized using number, mean, standard deviation (SD), median, quartiles, minimum and maximum and in the case of non-normally distributed data, median, range and interquartile range. Corresponding 95% confidence intervals will be reported as appropriate. No adjustment will be made for multiple comparisons or for multiple analyses. All figures will be presented to three decimal places.

The statistical analysis will include a summary of the study conduct, an assessment of HCP representativeness, a descriptive analysis and the analysis of the objectives. Site characteristics (type of centre ie, academic/non-academic) will be described.

HCP representativeness: HCPs approached for enrollment, whose demographic profile information has been collected in the recruitment database (age and gender), will be divided into:

- HCPs who agree to participate in the study
- HCPs who refuse to participate in the study after being approached
- HCPs who do not respond to invitations to participate in the study

9.7.2.2 Missing or Incomplete Data and Lost to Follow-up

Responses to questions in the HCP questionnaires may be missing. They will be dealt with in two ways:

- In the primary analysis, missing data will be ignored.
- As a sensitivity analysis, a conservative assumption will be made in which missing values will be considered as incorrect or worst responses.

For questions without a correct or best response, missing data will be ignored in the analysis.

9.7.2.3 Descriptive Analysis

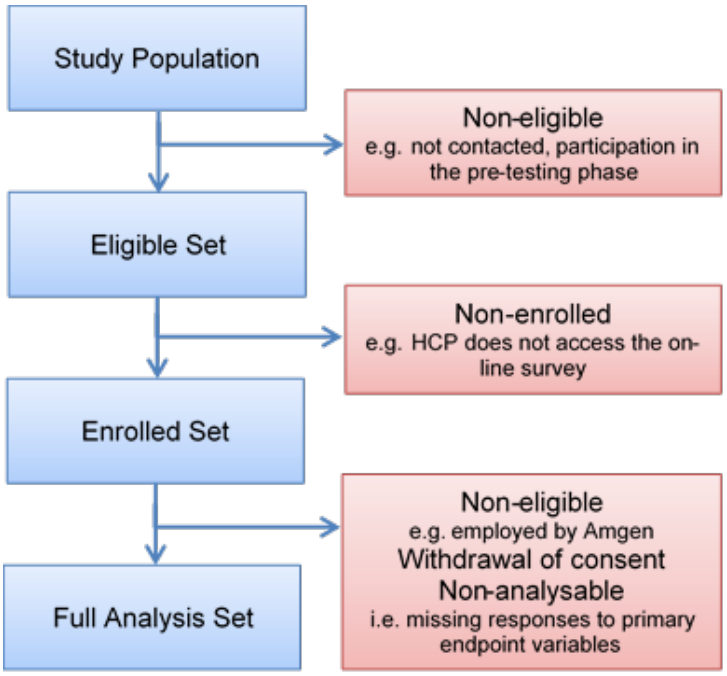
9.7.2.3.1 Description of Study Enrollment

The study populations as identified in the recruitment process for each of the HCP surveys will be described. Recruitment rates and a description of the number of subjects in the study and analysis populations will be provided.

Analysis sets: As shown in Figure 2, datasets for analysis will be further described in the SAP and will include:

- Study population: Physicians, nurses and pharmacists identified and potentially willing/eligible to participate.
- Eligible Set: All physicians, nurses and pharmacists who fulfill the eligibility criteria.
- Enrolled Set: All eligible physicians, nurses and pharmacists who agree to participate in the study and access the electronic survey.
- Full Analysis Set: All physicians, nurses and pharmacists who complete the questionnaire of their corresponding survey and have valid responses to allow for the assessment of the primary objective.

Figure 2. Study Population and Datasets Flow-chart



9.7.2.3.2 Description of Physicians, Nurses and Pharmacists Characteristics

For each survey, the following sociodemographic characteristics will be summarized: age group, gender, country and experience. Participation in Blincyto clinical trials and time since last contact with a patient receiving Blincyto will also be described.

9.7.2.4 Analysis of the Primary, Secondary and Exploratory Endpoint(s)

The primary analysis for each survey will be performed for the endpoints below described, and will include the total number of HCPs with valid responses to all relevant questions and the percentage of HCPs with a positive response for the endpoint:

- **Receipt** will be described through the percentage of physicians, nurses and pharmacists who report having received the brochure.
- A mean **knowledge** score will be created to summarise individual physician, nurse and pharmacist scores. An individual physician, nurse or pharmacist score is calculated as the proportion of all knowledge questions with correct responses.
- A mean **behaviour** score will be created to summarise individual physician, nurse and pharmacist scores. An individual physician, nurse or pharmacist score is calculated as the proportion of all behavior questions with correct responses. For physicians and nurses, the score will also include the adequacy of the timing for the distribution of the card and brochure to patients/caregivers. Among those who do not distribute the materials to patients/caregivers, a categorical variable will describe the reasons for non-compliance.
- Correlation of total scores for questions of knowledge and behaviour.

The secondary analyses are:

- Among physicians, nurses and pharmacists who have read the educational materials, an ordinal scale will describe the self-reported level of **understanding**.
- **Usage** will be assessed with the percentage of physicians, nurses and pharmacists who have read the material. Among those physicians, nurses and pharmacists who have read the brochure, an ordinal scale will assess how often the material was referred to. Among those who do not read the materials, a categorical variable will describe the reasons for not reading them.

9.7.2.5 Sensitivity Analysis

9.7.2.5.1 Subgroup Analysis

The results will be presented overall and by country, whether the materials were read or not, time since last contact with a patient receiving Blincyto and participation in Blincyto clinical trials.

9.8 Quality Control

Standard operating procedures will be applied to ensure quality to all aspects of the study conduct, data management and statistical analysis.

In addition, data generated by these surveys must be available for inspection upon request by representatives of national and/or local health authorities, sponsor monitors, representatives, and collaborators, as appropriate. The investigator must notify Amgen promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to Amgen.

9.9 Limitations of the Research Methods

HCPs who refuse to participate may limit the representativeness of the HCP survey. Selection of nurses and pharmacists will be dependent on the cooperation of physicians in centres.

HCP responses may be biased by referral to the brochures as they complete the questionnaire. This may be minimized by explaining that responses should be based on assessing what they currently know and that they should not refer to the brochures.

Measures to minimize HCP response bias with online questionnaires are: all questions are programmed to ensure that they are presented in an appropriate sequence, questions must be answered in sequence, skipping ahead to later questions is not permitted, questions cannot be changed once submitted, and skip patterns to questions are clearly indicated.

Self-reporting of actions and behavior may be biased towards positive values. The development of a questionnaire carefully pre-tested before actual study starts aims to minimize such a bias. Non-response of items should be minimized due to the rigorous process of questionnaire development, validation and testing.

Recall bias is an inherent limitation of questions asking about the past. This will be assessed by time since last contact with a patient receiving Blincyto, or its preparation.

The size of the study populations will allow an acceptable level of precision (considering the rarity of the disease) for the study primary endpoints. However, subgroup analyses will be exploratory and may be unreliable due to the small number of patients.

10. Protection of Human Subjects

10.1 Informed Consent

Consent for the surveys will be obtained online before completing the questionnaire. Those who decline to participate will not be able to access the questionnaire.

10.2 Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

Local approvals from ethics committees are not required as only data from HCPs and not clinical data from patients, will be collected.

10.3 Subject Confidentiality

For the purposes of protecting a HCPs identity, a unique code will be assigned to each HCP, such as a series of numbers and/or letters (for example, CA180330-0001-00001). The data that are recorded with the HCP's assigned code a called “key-coded data”.

Key-coded study data will be managed by the sponsor and/or its delegates in a study-specific electronic database (the "study database"). Only the investigator and the site staff have access to the link between HCP's assigned code and the identity. Data that could directly identify the HCPs will not be collected in the "study database".

The HCP's personal data which may be included in the recruitment and study databases will be treated in compliance with all local applicable laws and regulations. When archiving or processing personal data pertaining to the HCPs, all appropriate measures to safeguard and prevent access to this data by any unauthorized third party will be taken.

11. Collection of Safety Information and Product Complaints

As the questionnaire is on-line with no free-text questions, very few reports of adverse events and medication errors for Blincyto are expected.

11.1 Definition of Safety Events

11.1.1 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 the HCP's responsibility to evaluate whether an adverse event is related to Blincyto prior to reporting the adverse event to Amgen.

11.1.2 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 subject 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 subject 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.

11.1.3 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).

11.1.4 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.

11.2 Safety Reporting Requirements

[redacted] 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 and

submitted as individual case safety reports to Amgen via the applicable Amgen Safety Reporting Form (paper form) within 1 business day of awareness.

See Appendix C for sample Safety Report Form(s), Appendix D for Additional Safety Reporting Information regarding the adverse event grading scale used in this study, and Appendix E 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 the medical records.

11.2.1 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.

12. Administrative and Legal Obligations

12.1 Protocol Amendments and Study Termination

Amgen may amend the protocol at any time. If Amgen amends the protocol, written agreement from the Investigator must be obtained where applicable per local governing law and/or regulations.

Amgen reserves the right to terminate the study at any time. Both Amgen and the Investigator reserve the right to terminate the Investigator's participation in the study according to the contractual agreement.

13. Plans for Disseminating and Communicating Study Results

The protocol, study status updates and report(s) will be included in regulatory communications according to the risk minimisation plan, periodic benefit-risk evaluation reports and other regulatory milestones and requirements.

This study will be registered on the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) website before the start of data collection, and the study summary results will be posted on this public website no later than 12 months after study termination (defined as 'database lock').

A final study report will be developed and submitted to PRAC, and will serve as a basis for the development of publications and presentations in scientific journals, and press releases.

Abstracts, summaries, presentations and manuscripts will be prepared in line with dissemination guidelines of the International Committee of Medical Journal Editors (International Committee of Medical Journal Editors) and Guidelines for Good Pharmacoepidemiology Practice (International Society for Pharmacoepidemiology 2008) to help ensure the quality and integrity of pharmacoepidemiological research and to provide adequate documentation of research methods and results.

13.1 Publication Policy

The results of this study will be submitted for publication. Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors (ICJME) Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet conditions 1, 2, and 3 and 4.
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for corporate review. The vendor agreement will detail the procedures for, and timing of, Amgen's review of publications.

14. Compensation

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

15. References

Benjamin, J.E. & Stein, A.S., 2016. The role of blinatumomab in patients with relapsed/refractory acute lymphoblastic leukemia. *Therapeutic Advances in Hematology*, 7(3), pp.142–156.

CIOMS, 2014. *Practical approaches to risk minimisation for medicinal products: Report of CIOMS Working Group IX*, Geneva, Switzerland.

EMA, 2016. *Guideline on Good Pharmacovigilance Practices (GVP) Module VIII - Post-Authorisation Safety Studies (Revision 2)*, Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129137.pdf.

EMA, 2014. *Guideline on good pharmacovigilance practices (GVP) Module XVI - Risk minimisation measures: selection of tools and effectiveness (Revision 1)*, Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/02/WC500162051.pdf.

Gatta, G. et al., 2011. Rare cancers are not so rare: The rare cancer burden in Europe. *European Journal of Cancer*, 47(17), pp.2493–2511.

Gökbuget, N. et al., 2009. Treatment of Adult Acute Lymphoblastic Leukemia. *Seminars in Hematology*, 46(1), pp.64–75.

Hoelzer, D. et al., 2016. Acute lymphoblastic leukaemia in adult patients: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*, (February).

International Committee of Medical Journal Editors, Defining the role of authors and contributors. Available at: http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html.

International Society for Pharmacoepidemiology, 2008. Guidelines for Good Pharmacoepidemiology Practices (GPP). *Pharmacoepidemiology and Drug Safety*, 17, pp.200–208. Available at: http://pharmacoepi.org/resources/guidelines_08027.cfm.

Katz, A.J. et al., 2015. Acute lymphoblastic leukemia: an assessment of international incidence, survival, and disease burden. *Cancer causes & control : CCC*, 26(11), pp.1627–1642.

Larson, R., 2006. Management of acute lymphoblastic leukemia in older patients. *Semin Hematol*, 43(2), pp.126–133.

Linker, C. et al., 2002. Intensified and shortened cyclical chemotherapy for adult acute lymphoblastic leukemia. *Journal of Clinical Oncology*, 20(10), pp.2464–2471.

O'Brien, S. et al., 2008. Outcome of adults with acute lymphocytic leukemia after second salvage therapy. *Cancer*, 113(11), pp.3186–91.

Tavernier, E. et al., 2007. Outcome of treatment after first relapse in adults with acute lymphoblastic leukemia initially treated by the LALA-94 trial. *Leukemia*, 21(9), pp.1907–14.

Thomas, D.A. et al., 1999. Primary refractory and relapsed adult acute lymphoblastic leukemia: characteristics, treatment results, and prognosis with salvage therapy. *Cancer*, 86(7), pp.1216–30.

Topp, M.S. et al., 2015. Safety and activity of blinatumomab for adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia: a multicentre, single-arm, phase 2 study. *The Lancet Oncology*, 16(1), pp.57–66.

16. Appendices

Appendix A. List of Stand-alone Documents

No.	Title
1	*Physician questionnaire*
2	*Nurse questionnaire*
3	*Pharmacist questionnaire*

Appendix B. ENCePP Checklist for Study Protocols

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 3)

Adopted by the ENCePP Steering Group on 01/07/2016

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study 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

Study reference number:

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Comments:

This is a cross-sectional study and thus neither study progress reports nor interim progress reports are expected to be developed during the study conduct.

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	4, 7
2.1.2 The objective(s) of the study?	☒	☐	☐	4, 8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	4, 9.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

This study is descriptive and therefore no formal hypothesis will be tested.

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	4, 9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	4, 9.1
3.3 Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☐	☐	☒	
3.4 Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☒	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	4, 9.2.1
4.2.2 Age and sex?	☒	☐	☐	4, 9.2.3
4.2.3 Country of origin?	☒	☐	☐	4, 9.1, 9.2

ENCePP Checklist for Study Protocols (Revision 3)

Section 4: Source and study populations	Yes	No	N/A	Section Number
4.2.4 Disease/indication?	☒	☐	☐	4, 9.2.3
4.2.5 Duration of follow-up?	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☐	☐	☐	4, 9.2.2

Comments:

This is a cross-sectional design with no follow-up.

Section 5: Exposure definition and measurement	Yes	No	N/A	Section Number
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☐	☐	☒	
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☒	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	

Comments:

No exposure-outcome association will be assessed

Section 6: Outcome definition and measurement	Yes	No	N/A	Section Number
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	4, 9.3
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	4, 9.3
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	4, 9.3
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☐	☐	☒	

Comments:

This is a cross-sectional survey with no HEOR objectives

Section 7: Bias	Yes	No	N/A	Section Number
7.1 Does the protocol describe how confounding will be addressed in the study?	☐	☐	☒	

ENCePP Checklist for Study Protocols (Revision 3)

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1.1. Does the protocol address confounding by indication if applicable?	☐	☐	☒	
7.2 Does the protocol address:	☒	☐	☐	9.9
7.2.1. Selection biases (e.g. healthy user bias)	☒	☐	☐	9.9
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	9.9
7.3 Does the protocol address the validity of the study covariates?	☐	☒	☐	

Comments:

No strenght of association between exposure and outcome is measured

Section 8: Effect modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	9.7

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4
9.1.3 Covariates?	☒	☐	☐	9.4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.4
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.4
9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.4
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☒	☐	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☐	☒	☐	
9.3.3 Covariates?	☐	☒	☐	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	9.6.2

ENCePP Checklist for Study Protocols (Revision 3)

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☒	☐	☐	4, 9.7
10.2 Are descriptive analyses included?	☒	☐	☐	4, 9.7
10.3 Are stratified analyses included?	☒	☐	☐	4, 9.7
10.4 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	
10.5 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7.2.2
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	4, 9.5

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	13

Comments:

The Final Report will be sent to PRAC for approval.

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	9.2.2, 9.9

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☐	☐	☒	10

ENCePP Checklist for Study Protocols (Revision 3)

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	10
13.3 Have data protection requirements been described?	☒	☐	☐	10

Comments:

As explained in Section 10 of the protocol, this study (healthcare professional survey) does not require ethics approval.

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	13
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	13

Comments:

Name of the main author of the protocol: [redacted]

Date: 20/October/2016

Signature [redacted]

ENCePP Checklist for Study Protocols (Revision 3)

Appendix C. Sample Safety Reporting Form(s)

Project ID: 20150228	A	**Safety Reporting Form** Primary Data Collection	Date of Report:
		Fax reports to: Amgen Local Office <<populate LAO fax here or delete language>>	

1. Indicate event type: ☐ AE/Other safety finding ☐ AE/Other safety finding with Product Complaint ☐ Product Complaint only

2. Vendor Contact Details

name	phone	fax
address		
city	state/province	
postal code	country	

3. Reporter ID

Name or ID	phone	fax
address		
city	state/province	
postal code	country	

4. HCP Contact Details (if other than reporter)

name		
country		
address		
city	state/province	postal code
phone	fax	

5. Patient

Initials (optional)	Sex	Age (at time of event)	Was consent obtained to follow-up with HCP?
	☐ F ☐ M		☐ Yes ☐ No

Weight	Height	Race	Is patient also reporter?
☐ lbs ☐ kg	☐ in ☐ cm		☐ Yes ☐ No

6. Medical History (include primary diagnosis)

7. Suspect Product Information (include dosing details)

Product: _____

Indication: _____

	Start Date (day month year)	Stop Date (day month year)	Dose	Route	Freq

Pregnant? ☐ Yes ☐ No Lactating? ☐ Yes ☐ No

Allergy: _____

Prefilled Syringe? ☐ Yes ☐ No

Other Device _____

Lot # _____ ☐ Unknown

Serial # _____ ☐ Unavailable / Unknown

Vial size

8. AE, other safety finding, or product complaint information — **HCP ONLY**

Finding (List main event first; one event per line)	Onset Date (day month year)	Resolved Date (If patient died, list date of death) Cause of Death: (provide autopsy report) (day month year)	Hospitalization: Hospitalized? ☐ Yes ☐ No; Hospitalization Prolonged? ☐ Yes ☐ No; Admitting dx _____ (provide discharge summary); Date Admitted (day month year); Date Discharged (day month year)	Serious Criteria: 01 Fatal; 02 Immediately life-threatening; 03 Required hospitalization; 04 Prolonged hospitalization; 05 Persistent or significant disability /incapacity; 06 Congenital anomaly / birth defect; 07 Other significant medical hazard	Action Taken: 1=none; 2=dose reduced; 3=dose increased; 4=drug withdrawn; 5=Drug rechallenge (state outcome)	Outcome: 1=resolved; 2=resolved w/ sequelae; 3=resolving	Severity: 1=mild; 2=moderate; 3=severe	Relationship to Product/ Device: Is there a reasonable possibility that this event may have been caused by the Product / Device? Product	Device
								Y N	Y N
								Y N	Y N
								Y N	Y N

9. Description: chronological summary of symptoms or product complaint from above (signs, diagnosis, treatment, concomitant medications including those used to treat event.)

Reporter Signature: _____ Page 1 of ____

The data provided by you will be transferred as a report to Global Safety at Amgen Inc (USA) and will be exclusively used for safety and quality purposes
For vendor surveys of Health Care Professionals

FORM-067756 Ver. #: 3.0 Effective date: 07-Jul-2014 Page 1 of 1 *ADR Form Created: DD-MMM-YYYY*

Appendix D. Additional Safety Reporting Information

Adverse Event Severity Scoring System

Grade	Amgen Standard Adverse Event Severity Scoring System
1	MILD: Aware of sign or symptom, but easily tolerated
2	MODERATE: Discomfort enough to cause interference with usual activity
3	SEVERE: Incapacitating with inability to work or do usual activity

Appendix E. Pregnancy and Lactation Notification Worksheets

AMGEN® Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX#

1. Case Administrative Information

Protocol/Study Number: _____

Study Design: ☐ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ Site # _____

Phone (___) _____ Fax (___) _____ Email _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ Subject Gender: ☐ Female ☐ Male Subject DOB: mm / dd / yyyy

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm/dd/yyyy

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm/dd/yyyy

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Pregnancy Information

Pregnant female's LMP mm / dd / yyyy ☐ Unknown

Estimated date of delivery mm / dd / yyyy ☐ Unknown ☐ N/A

If N/A, date of termination (actual or planned) mm / dd / yyyy

Has the pregnant female already delivered? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If yes, provide date of delivery: mm / dd / yyyy

Was the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

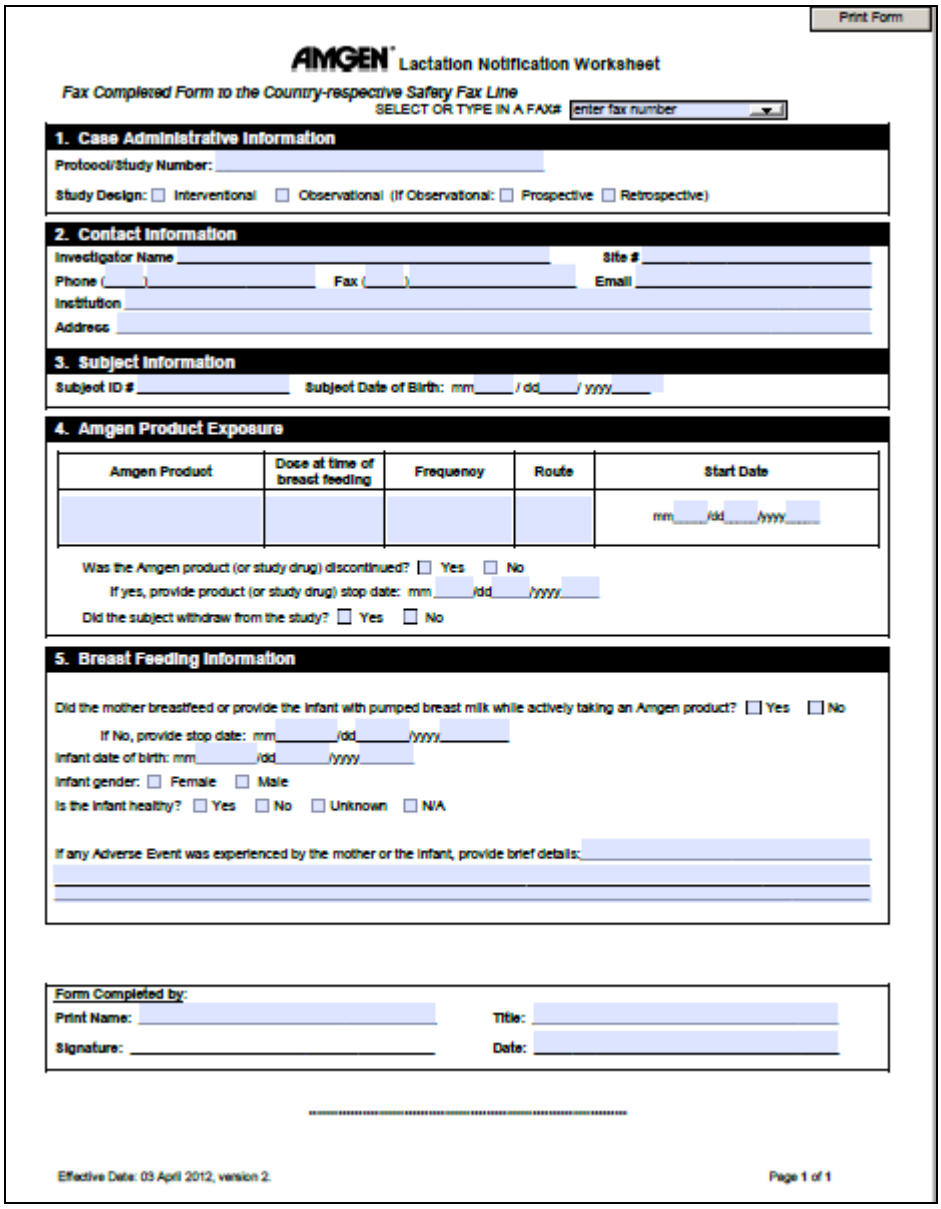
If any Adverse Event was experienced by the infant, provide brief details: _____

Form Completed by:

Print Name: _____ Title: _____

Signature: _____ Date: _____

Effective Date: March 27, 2011 Page 1 of 1



Print Form

AMGEN Lactation Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line
SELECT OR TYPE IN A FAX# enter fax number

1. Case Administrative Information

Protocol/Study Number: _____

Study Design: ☐ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ Site # _____

Phone (____)_____ Fax (____)_____ Email _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ Subject Date of Birth: mm____ / dd____ / yyyy____

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm____/dd____/yyyy____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐ Yes ☐ No

If No, provide stop date: mm_____/dd_____/yyyy_____

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

Is the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the mother or the infant, provide brief details: _____

Form Completed by:

Print Name: _____ Title: _____

Signature: _____ Date: _____

Effective Date: 03 April 2012, version 2. Page 1 of 1

Appendix F. Educational Brochures for Physicians, Nurses and Pharmacists

Bincyto Educational Brochure for Physicians

BLINCYTO® ▼ (blinatumomab)

Important Risk Minimisation Information for Physicians

This educational brochure contains important information regarding the administration of BLINCYTO and the risks of medication errors and neurologic events

This educational material is essential to ensure the safe and effective use of the product and appropriate management of the important selected risks and therefore it is advised to be read carefully before prescribing and administering the medicinal product

If you have any questions about the administration and the adverse events of BLINCYTO ,refer to the Summary of Product Characteristics (SmPC), provided with this brochure

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 of the SmPC for how to report adverse reactions.

BLINCYTO™ (blinatumomab)

This guide has been developed as part of a Risk Management Plan (RMP) for prescribers involved in the care of patients treated with BLINCYTO, to provide you with further information about some of the risks (neurologic events and medication errors) associated with the use of BLINCYTO.

What is BLINCYTO™?

BLINCYTO is a bispecific T-cell engager antibody construct that binds specifically to CD19 expressed on the surface of cells of B-lineage origin and CD3 expressed on the surface of T-cells. It is indicated for the treatment of adults with Philadelphia chromosome negative relapsed or refractory B-precursor acute lymphoblastic leukaemia (ALL).

Overview of BLINCYTO treatment

Patients will receive BLINCYTO by continuous intravenous infusion .

- Hospitalisation is recommended for initiation at a minimum for
  - the first 9 days of the first cycle
  - the first 2 days of the second cycle
- Supervision by healthcare professional or hospitalisation is recommended for all subsequent cycle starts and reinitiation (e.g. if treatment is interrupted for 4 or more hours)

- In patients with a history or presence of clinically relevant central nervous system (CNS) pathology (see section 4.4 of the SmPC), hospitalisation is recommended at a minimum for the first 14 days of the first cycle. In the second cycle, hospitalisation is recommended at a minimum for 2 days, and clinical judgment should be based on tolerance to blinatumomab in the first cycle. Caution should be exercised as cases of late occurrence of first neurological events in the second cycle have been observed.

A single treatment cycle consists of 4 weeks of continuous BLINCYTO infusion. Each cycle of treatment is separated by a 2-week treatment-free interval. Patients may receive 2 cycles of treatment. Patients who have achieved complete remission (CR/CRh) after 2 treatment cycles

may receive up to 3 additional cycles of BLINCYTO for consolidation treatment, based on an individual benefit-risk assessment.

Table 1. Recommended dose (for patients at least 45 kg in weight)

Cycle 1		2 week-treatment free interval Days 29-42	Cycle 2 and subsequent cycles (days 1-28)
Starting dose (days 1-7)	Subsequent dose (days 8-28)		
9 mcg/day via continuous infusion	28 mcg/day via continuous infusion		28 mcg/day via continuous infusion

Patients will receive continuous intravenous infusion of BLINCYTO. Discuss the infusion duration with your patients as there is a choice of bag change frequency. However, the target therapeutic dose of BLINCYTO delivered does not change.

Planned bag change frequency	Infusion rate
Every 24 hours	10 ml/hr
Every 48 hours	5 ml/hr
Every 72 hours	3.3 ml/hr
Every 96 hours	2.5 ml/hr

Dose adjustment

Neurologic events

In the pivotal clinical study (n=189), neurologic events ocurred approximately in 52% of subjects. The most common neurologic adverse reactions (≥10% of patients) reported were dizziness and tremor . Some other common neurologic adverse reactions (≥1% and <10%) included encephalopathy, aphasia, paresthesia, convulsion, cognitive disorder, confusional state, disorientation, and memory impairment. Serious neurologic events occurred in approximately 16% of subjects. Elderly patients experienced a higher rate of neurologic events. Patients with a medical history of neurologic signs and symptoms may experience a higher rate of neurologic events when receiving BLINCYTO.
There is limited experience with BLINCYTO in patients with documented active ALL in the central nervous system (CNS) or cerebrospinal fluid (CSF). Consider treating these patients after clearance of CSF blasts with CNS directed therapy (such as intrathecal chemotherapy).

There is also limited experience in patients with a history or presence of clinically relevant central nervous system CNS pathology. In particular, caution should be exercised as they may be at higher risk of neurological events (i.e. tremor, dizziness, confusional state, encephalopathy and ataxia). The median time to onset of a neurologic event in this population was 12 days .

Assess patients for signs and symptoms of neurological events (e.g. confusion, disorientation, dizziness, tremor, seizure) prior to and throughout the treatment cycle. Consider using a writing test periodically to assist with monitoring for neurological events during BLINCYTO treatment.

In case of seizure, consider using an appropriate anticonvulsant.

Consider to interrupt or discontinue the infusion of BLINCYTO temporarily as appropriate in case of grade 3 or 4 neurological toxicity. Please see table below.

Neurological toxicity	Convulsion	Discontinue BLINCYTO permanently if more than one convulsion occurs.
	Grade 3	Interrupt BLINCYTO until no more than grade 1 (mild) and for at least 3 days, then restart BLINCYTO at 9 mcg/day. Escalate to 28 mcg/day after 7 days if the toxicity does not recur. For re-initiation, pre-medicate with a 24 mg dose of dexamethasone. Then reduce

	dexamethasone step-wise over 4 days. If the toxicity occurred at 9 mcg/day, or if the toxicity takes more than 7 days to resolve, discontinue BLINCYTO permanently.
Grade 4	Discontinue BLINCYTO permanently.

It is essential to counsel patients regarding the potential neurologic effects:

- Not to drive, operate heavy machines or engage in hazardous activities while receiving BLINCYTO
- To contact you if they experience neurological symptoms

An observational study will be conducted in selected countries within the European region/zone, to gather data on the real-world use of BLINCYTO. The primary objective of this study is to characterize the safety profile of BLINCYTO in routine clinical practice including medication errors. In addition, a patient survey is being conducted to assess, in patients or caregivers, knowledge of the potential for neurologic events and medication errors and to enquire of their awareness of the BLINCYTO patient educational materials.

Please inform your patients of these studies and encourage their participation.

In the pivotal clinical study (n=189), less than 1.4% of patients treated with BLINCYTO tested positive for binding and neutralizing anti-blinatumomab antibodies. If formation of anti-blinatumomab antibodies with a clinically significant effect is suspected, contact the Marketing Authorisation Holder to discuss antibody testing. Contact details are provided in section 6 of the package leaflet.

Bincyto Educational Brochure for Nurses

Version 1.0 BLINCYT® ▼ (blinatumomab) Approved: September- 2015

Educational Brochure for Nurses

BLINCYTO® ▼ (blinatumomab)

Important Risk Minimisation Information for Nurses

This educational brochure contains important information regarding the administration of BLINCYTO and the risks of medication errors and neurologic events

This educational material is essential to ensure the safe and effective use of the product and appropriate management of the important selected risks and therefore it is advised to be read carefully before administering the medicinal product.

If you have any questions about the administration and the adverse events of BLINCYTO, refer to the Summary of Product Characteristics (SmPC), provided with this brochure

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 of the SmPC for how to report adverse reactions.

1

Version 1.0 BLINCYT® ▼ (blinatumomab) Approved: September- 2015

Educational Brochure for Nurses

Important Information Regarding BLINCYTO

The following actions should be taken to prevent or minimize the risk of medication errors and to provide important counseling information on neurologic events

Administration	IV lines	• Do not flush the infusion lines into the patient, as it will cause an inadvertent bolus of BLINCYTO to be administered. BLINCYTO should be infused through a dedicated lumen.
	Pump specifications and settings	• Only program the pump based on the printed infusion rate on the label attached to the infusion bag. • Do not calculate the infusion rate yourself. • Lock the pump and make sure the battery is adequately charged with each bag change. • Instruct patients not to unlock the pump. • If the pump does not appear to perform properly (for example: alarm goes off) at any time, instruct patients and caregivers not to try to fix the pump and tell them to get help from the treating physician or from you immediately. • Instruct patients not to change any pump settings on purpose (with the exception of stopping the pump in case of emergency). • Remember to check if the remaining volume of infusion bag correlates with the set infusion rate prior to each bag change. If the remaining volume of infusion bag does not correlate with the set infusion rate prior to each bag change, please record discrepancy and contact the physician for further instruction.
	IV bag change	• The IV bag change must occur within 4 hours of the designated time regardless of the remaining volume in the existing infusion bag.
	Therapy interruption	• Healthcare professional supervision or hospitalisation is recommended in instances where treatment is being re-initiated following an interruption of 4 or more hours (see section 4.2 of the SmPC for more information).
	Catheter site care	• BLINCYTO solution is a preservative-free solution. Aseptic technique must always be adhered to when administering BLINCYTO. • Instruct the patients and/or caregivers on how to perform catheter site care as required.

Counseling	Neurologic events	• Assess patients for signs and symptoms of neurological events (e.g. confusion, disorientation, dizziness, tremor, seizure) prior to and throughout the treatment cycle (see section 4.4 of the SmPC for further information). Consider using a writing test periodically to assist with monitoring for neurological events during BLINCYTO treatment.
		• Elderly patients experience a higher rate of neurological events.
		• Counsel patients on the potential neurologic effects.
		• Advise patients:
		  • **Not to drive, use heavy machinery, or engage in hazardous activities while receiving BLINCYTO.**
		  • To contact you or the doctor if they experience neurological symptoms.

2

Bincyto Educational Brochure for Pharmacists

BLINCYTO®▼ (blinatumomab)

Important Risk Minimisation Information for Pharmacists

This educational brochure contains important information regarding the reconstitution and preparation procedures for blinatumomab. To ensure the safe and effective use of the medicinal product and appropriate management of the important selected risks, please carefully read this material before reconstituting and preparing of the medicinal product.

If you have any questions about the reconstitution and preparation of blinatumomab please refer to the Summary of Product Characteristics (SmPC), which is provided with this educational brochure.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 of the SmPC for how to report adverse reactions.

Version 2.0 BLINCYTO® ▼ (blinatumomab) Approved: April-2016

Educational Brochure for Pharmacists

Important information about the preparation of BLINCYTO intravenous administration

Table 1. Preparation of BLINCYTO infusion solution

Dose	Infusion duration	Normal Saline (250-ml bag)[a]	Solution (Stabiliser) Volume (mL)	Required Number of BLINCYTO vials	Reconstituted BLINCYTO solution (mL)	Infusion rate (mL/hr)
9 microgram/day	24 hours	1	5.5	1	0.83	10
	48 hours	1	5.5	1	1.7	5
	72 hours	1	5.5	1	2.5	3.3
	96 hours	1	5.5	2	3.3	2.5
28 microgram/day	24 hours	1	5.5	1	2.6	10
	48 hours	1	5.5	2	5.2	5
	72 hours	1	5.5	3	8	3.3
	96 hours	1	5.5	4	10.7	2.5

[a]Normal saline (0.9% Sodium Chloride)

Use only polyolefin, PVC non-di-ethylhexylphthalate (non-DEHP), or ethyl vinyl acetate (EVA) infusion bags/pump cassettes and Polyolefin, PVC non-DEHP, or EVA intravenous tubing with a sterile, non-pyrogenic, low protein-binding 0.2 µm in-line filter

Table 2. Steps to prepare BLINCYTO infusion solution under aseptic conditions using aseptic techniques

Step 1	• Transfer appropriate amount of Solution (stabiliser) to the Normal Saline (0.9% Sodium Chloride) infusion bag • Gently mix the contents of the bag to avoid foaming • Discard remaining Solution (stabiliser) vial if applicable
Step 2	• Reconstitute BLINCYTO powder for concentrate with 3 mL of Water for Injection • Do not reconstitute BLINCYTO with the Solution (stabiliser) • Do not shake • Gently swirl contents to avoid excess foaming • Reconstitute the required number of BLINCYTO vials (see table above). Visually inspect the reconstituted solution for particulate matter and to confirm colour. The solution should be clear to slightly opalescent, colourless to slightly yellow.
Step 3	• Transfer appropriate amount of reconstituted BLINCYTO solution into the Normal Saline (0.9% Sodium Chloride) infusion bag • Gently mix the contents of the bag to avoid foaming
Step 4	• Attach the intravenous tubing to the prepared BLINCYTO infusion solution bag with the sterile 0.2 µm in-line filter
Step 5	• Remove air from the prepared BLINCYTO infusion solution bag
Step 6	• Prime the intravenous infusion line with the prepared BLINCYTO infusion solution • Do not prime the intravenous infusion line with Normal Saline (0.9% Sodium Chloride) solution for injection
Step 7	• Store the prepared BLINCYTO infusion solution bag at 2°C to 8°C for a maximum of 10 days if not immediately used (for further information, please see section 6.3 of the SmPC)