Summary Table of Study Protocol

Summary Table of Study Protocol	A Cross-sectional Survey of Patients and Caregivers Receiving Blincyto in Routine Clinical Practice in Europe to Evaluate the Effectiveness of Additional Risk Minimisation Measures
Protocol version identifier	1.0
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Active Substance	Blinatumomab
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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 research question is whether additional risk minimisation measures introduced for the safe and effective use of Blincyto® (blinatumomab) are effective in patients with Philadelphia chromosome-negative (Ph-) relapsed/refractory (R/R) B-precursor acute lymphoblastic leukaemia (ALL) and their caregivers. The primary objectives of the survey are to describe receipt of the educational materials and knowledge about key safety messages in the educational materials, among patients with Ph- R/R B-precursor ALL receiving Blincyto and their caregivers. The secondary objectives of the survey are: - To describe behaviours outlined in the educational materials, by patients with Ph-R/R B-precursor ALL receiving Blincyto and their caregivers. - To describe the level of understanding of key safety messages in the educational materials, among patients with Ph– R/R B-precursor ALL receiving Blincyto and their caregivers. - To describe usage of the educational materials, among patients with Ph– R/R B-precursor ALL receiving Blincyto and their caregivers.
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 'A cross-sectional survey of patients and caregivers receiving Blincyto in routine clinical practice in Europe to evaluate the effectiveness of additional risk minimisation measures', dated 18 October 2016, and agree to abide by all provisions set forth therein.

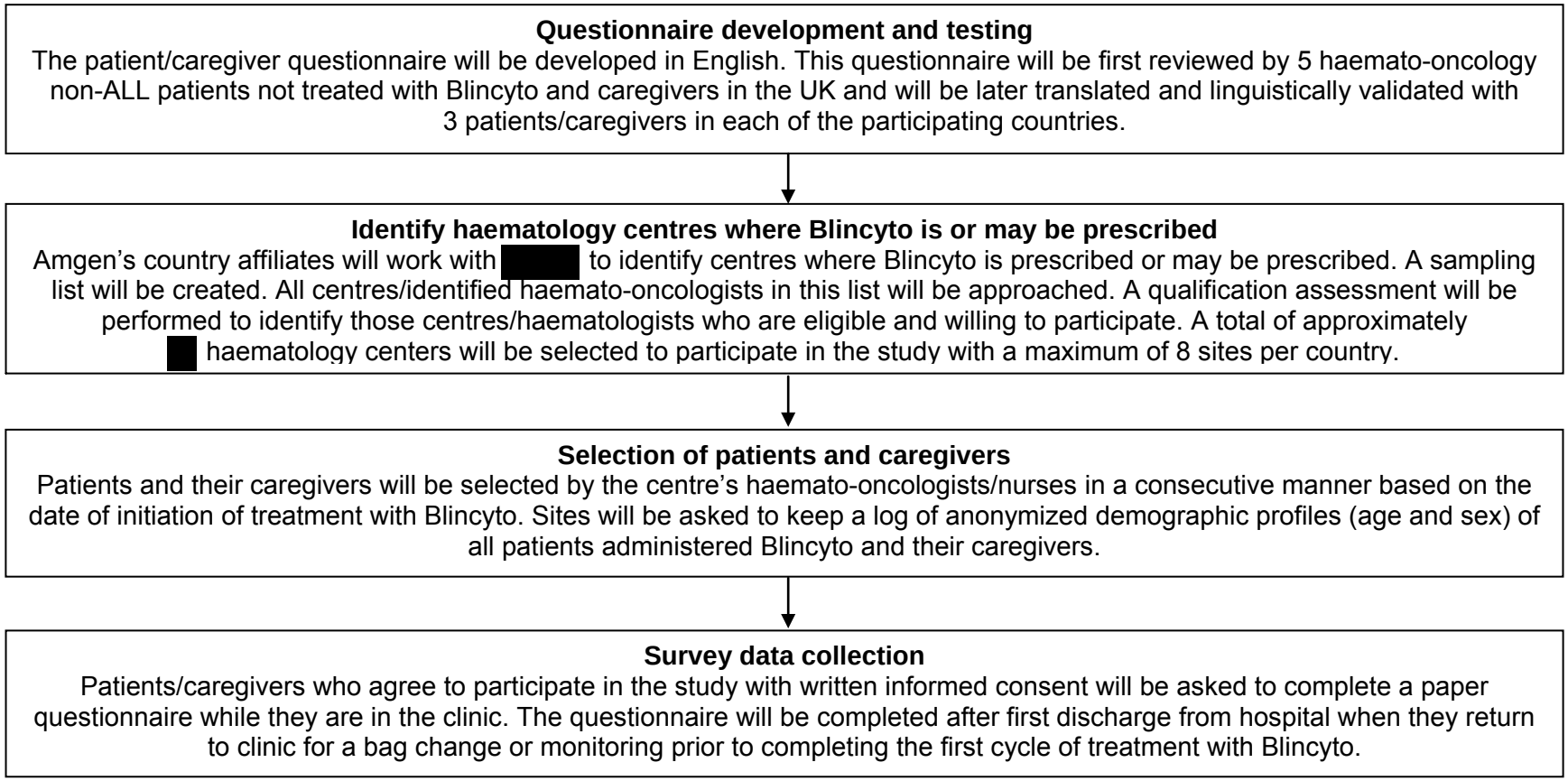
I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

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
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
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.
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:**

A cross-sectional survey of patients and caregivers receiving Blincyto in routine clinical practice in Europe to evaluate the effectiveness of additional risk minimisation measures.

- **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 by the European Commission 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 patients/caregivers include a patient card and brochure.

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

- **Research Question and Objective(s)**
  - Primary Objectives

    The primary objectives of the survey are to describe receipt of the educational materials and knowledge about key safety messages in the educational materials, among patients with Ph- R/R B-precursor ALL receiving Blincyto and their caregivers.
  - Secondary Objectives
    - To describe behaviours outlined in the educational materials, by patients with Ph- R/R B-precursor ALL receiving Blincyto and their caregivers.
    - To describe the level of understanding of key safety messages in the educational materials, among patients with Ph– R/R B-precursor ALL receiving Blincyto and their caregivers.
    - To describe usage of the educational materials, among patients with Ph- R/R B-precursor ALL receiving Blincyto and their caregivers.
  - 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 patients and caregivers participating in the survey confirm receipt of the patient/caregiver brochure and card and have knowledge of key safety messages in the patient/caregiver brochure. 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 patient/caregiver aRMMs will be considered to determine what action, if any, should be taken.

- **Study Design/Type**

This is an observational cross-sectional survey of patients and caregivers to help evaluate the effectiveness of the patient/caregiver card and brochure in minimising the risk of MEs and neurological events. The distribution of the survey is planned to start no more than 18 months after each country-specific launch.

- **Study Population or Data Resource**

The survey is 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. Participating haemato-oncologists/nurses will include patients and caregivers who fulfil all selection criteria in a consecutive manner according to the date of initiation of treatment with Blincyto until reaching the target number of patients and caregivers to be recruited per centre. Patients and caregivers who agree to participate in the study with written informed consent will be asked to complete a paper questionnaire after first discharge from hospital when they return to the clinic for a bag change or monitoring.

- **Summary of Patient/Caregiver Eligibility Criteria**

Inclusion criteria:

- Patient/caregiver is 18 years of age or older.
- Patient and caregiver of a patient with Ph- R/R B-precursor ALL in the first cycle of treatment with Blincyto after first discharge from hospital, on the day of administration of the questionnaire.
- Patient/caregiver can read and understand the native language of the country in which the study is being conducted.

Exclusion criteria:

- Patient and caregiver of a patient who has only received Blincyto as an in-patient.
- Patient and caregiver of a patient who is in a clinical trial of Blincyto.
- Patient/caregiver is currently employed by Amgen/delegate.

- **Variables**

The questionnaire will assess the following key concepts related to the patient card and brochure:

- Receipt of the patient/caregiver brochure and card.
- Knowledge about key information in the patient/caregiver brochure.
- Behaviours outlined in the patient/caregiver brochure and card.
- Usage of the patient/caregiver brochure and card.
- Understanding of the patient/caregiver brochure and card.

- **Study Sample Size**

The study population will include approximately [redacted] patients and [redacted] caregivers to allow precisions of –[redacted] for correct responses of 60 and 90%, respectively, for the primary endpoint of receipt. For the score of correct responses to knowledge questions ranging from 0 to 10, when the estimated standard deviation ranges from [redacted] a sample size of [redacted] patients/caregivers will produce a two-sided 95% confidence interval with a distance from the mean to the limits ranging from [redacted]

- **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. 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 patients and caregivers who report having received the patient/caregiver card and/or brochure.

Knowledge: A mean score will be created to summarise individual patient and caregiver scores. An individual patient/caregiver score is calculated as the proportion of all knowledge questions with correct responses.

Behaviour: A mean score will be created to summarise individual patient and caregiver scores. An individual patient/caregiver score is calculated as the proportion of all behaviour questions with correct responses.

Understanding: Among patients and caregivers who have read the patient/caregiver brochure and/or card, an ordinal scale will describe the self-reported level of understanding.

Usage: A mean score will be created to summarise individual patient and caregiver scores. An individual patient/caregiver score will be calculated as the sum of the 'value' of responses to all usage questions (ordinal scale) divided by the maximum possible

score. Among patient and caregivers who have not read the materials, a categorical variable will describe the reasons for not reading them.

5. Amendments and Updates

None

6. Milestones

Milestone	Planned date
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Start of data collection**	Feb 2017
[redacted]	[redacted]
Final report of study results	Jul 2018

* [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 its high rate of relapse. Approximately 10% of patients are refractory to current chemotherapy treatment 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 (Gökbuget et al. 2009; Linker et al. 2002; Thomas et al. 1999). Patients who relapse a second time have a median 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 by the European Commission 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 [redacted] of subjects. In the pooled safety dataset, which includes [redacted] patients exposed to Blincyto in [redacted] studies of different indications, MEs were reported in [redacted] of subjects. The following MEs were reported: [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.

Examples of medication errors related to the wrong usage of Blincyto by patient/caregivers include overdose due to pump setting problems, infusion bag placed on the counter to warm it up and pump turned off when the pump alarms low battery.

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

This protocol focuses on the patient and caregiver 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 aRMMs 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 by patients and caregivers.

The results of this survey will complement data from a twin HCP 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

This survey aims to address the following research questions:

- Has key safety information contained in the patient/caregiver educational materials reached the target population?
- What is the level of knowledge and understanding of the target audience with regard to the key safety information described in the patient/caregiver educational materials?
- What is the level of the behaviours outlined in the educational materials?
- Are the patient/caregiver educational materials used as intended?

8.1 Primary

The primary objectives of the study are to describe receipt of the educational materials and knowledge about the patient/caregiver educational materials, among patients with Ph– R/R B-precursor ALL receiving Blincyto and their caregivers.

8.2 Secondary

The secondary objectives of the study are:

- To describe behaviours outlined in the patient/caregiver educational materials, among patients with Ph– R/R B-precursor ALL receiving Blincyto and their caregivers.
- To describe the level of understanding of key safety messages in the patient/caregiver educational materials, among patients with Ph– R/R B-precursor ALL receiving Blincyto and their caregivers.
- To describe usage of the educational materials, among patients with Ph– R/R B-precursor ALL receiving Blincyto and their caregivers.

This study will help indicate if the aRMMs are successful if a majority of patients and caregivers participating in the survey confirm receipt of the patient/caregiver brochure and card and have knowledge of key safety messages in the patient/caregiver brochure. 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 patient 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, an observational cross-sectional survey of patients and caregivers is planned in France, Germany, Italy, Spain and the UK, after the introduction of Blincyto to the EU market.

The distribution of the patient/caregiver survey is planned to start no more than 18 months after each country-specific launch. 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 survey 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: the General Practitioner 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 (ie. initial usage forecasts and planned launch schedule). Therefore, if recruitment of patients and caregivers is slower than anticipated other countries may be added to meet sample size goals within the study timeline.

9.2.1 Study Period

The maximum planned period for patient/caregiver recruitment and data collection is 12 months. However, as product launch is planned in a staggered manner in Europe and the time needed for regulatory/ethics approvals varies between countries, this period is expected to be reduced in some countries [redacted]

As this is a one-wave cross-sectional design, data from patients and caregivers 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 (and identified prescribers where available) where Blincyto is prescribed or expected to be prescribed after its launch in each participating country (data on file provided by Amgen). This list will be

assembled by working closely with Amgen's country affiliates to identify Blincyto prescribers or potential prescribers. Given the poor prognosis of R/R ALL and the complexities of allogenic HSCT and experience required to manage these patients, and the highly selective use of Blincyto, usage is expected to be mainly in tertiary haematological centres.

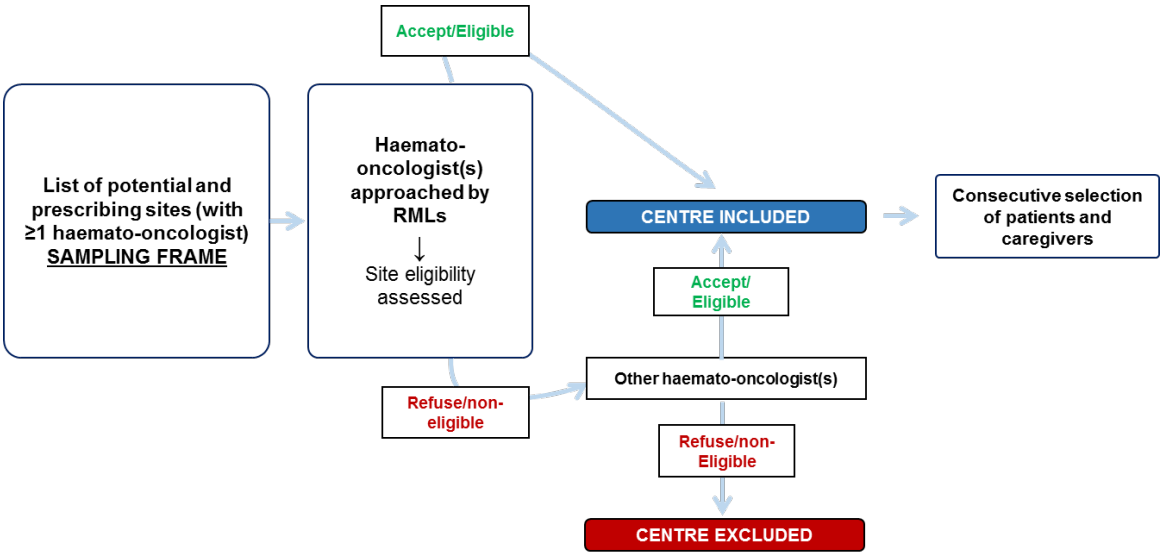
[redacted] As shown in Figure 1, all centres in the list will be approached (by mail, telephone, fax or email, as appropriate) to identify prescribers or potential prescribers willing to participate. During this initial contact, site eligibility will be assessed to ensure that they meet the requirements to participate in the study: at least one staff hematologist with experience of managing patients with ALL; a staff member available to coordinate the research; the centre has already prescribed Blincyto to one patient or is likely to prescribe Blincyto to at least [redacted] patients in the subsequent 12 months. The number of eligible hematologists 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.

In case the number of patients that each unit is able to recruit proves to be lower than expected, the inclusion of additional hospitals will be considered.

Patient/caregiver selection:

Haemato-oncologists/nurses in participating centres will include patients and their associated caregivers who fulfil all the selection criteria listed below in a consecutive manner according to the date of initiation of treatment with Blincyto until reaching the target number of patients/caregivers to be recruited per centre. Caregivers can be a spouse, family member, friend or professional helper who has helped with Blincyto treatment. The consecutive selection of patients and caregivers at each site is designed to minimise selection bias and to allow for the study results to be generalisable to the entire population of Blincyto treated patients. To assess generalizability of the data, sites will be asked to keep a log of anonymized demographic profiles (age and sex) of patients administered Blincyto, and their caregivers.

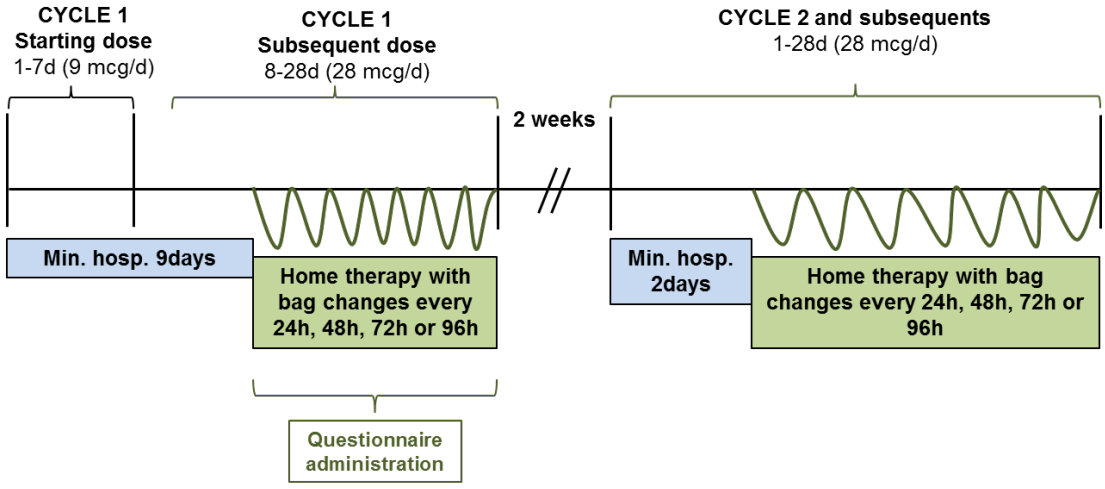
Figure 1. Illustration of Sampling Strategy



Patients/caregivers who agree to participate in the study with written informed consent will be asked to complete a paper questionnaire after first discharge from hospital when they return to clinic in cycle 1 for a bag change or monitoring (Figure 2). Both the patient and the caregiver will be invited to participate in the survey. If the patient is not well enough to complete the questionnaire on returning to clinic after hospital discharge on Blincyto, the patient will be asked again at the next visit in the first cycle. If a caregiver is not available at a visit, they will be asked at the next available visit to participate. Only one caregiver per patient will be recruited.

Appropriate measures will be adopted to ensure physicians do not influence patient/caregiver's choices (eg. patients and caregivers will place their completed questionnaires in a sealed envelope).

Figure 2. Illustration of Treatment Characteristics and Questionnaire Administration



9.2.3 Subject Eligibility

9.2.3.1 Inclusion Criteria

- Patient/caregiver is 18 years of age or older.
- Patient and caregiver of a patient with Ph- R/R B-precursor ALL in the first cycle of treatment with Blincyto after first discharge from hospital, on the day of administration of the questionnaire.
- Patient/caregiver can read and understand the native language of the country in which the study is being conducted.

9.2.3.2 Exclusion Criteria

- Patient and caregiver of a patient who has only received Blincyto as an in-patient.
- Patient and caregiver of a patient who is in a clinical trial of Blincyto.
- Patient/caregiver is currently employed by Amgen/delegate.

9.2.4 Baseline Period

This is a cross-sectional survey that does not involve any follow-up of patients and caregivers. Eligibility criteria will be assessed and patient/caregiver questionnaire completed at one point in time within the data collection period.

9.3 Variables

The questionnaire will contain multiple-choice questions with no free text fields.

The patient/caregiver questionnaire will be structured as follows:

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

Section B (Screening) will collect socio-demographic characteristics (age, gender, educational status) about patients/caregivers. The questionnaire will be designed to take a maximum of 10-15 minutes to complete.

The questionnaire will assess the following key concepts related to the patient/caregiver card and brochure:

- Receipt of the patient/caregiver brochure and card.
- Knowledge about key information in the patient/caregiver brochure.
- Behaviours outlined in the patient/caregiver brochure and card.
- Usage of the patient/caregiver brochure and card ie. whether the patient card is filled in with the required information, whether the patient card is shown to healthcare providers while on treatment with Blincyto, whether patients/caregivers read and refer to the educatonal materials and reasons for not reading them.
- Understanding of the patient/caregiver brochure and card.

9.3.1 Exposure Assessment

Patients included in the study will be in the first cycle of treatment with Blincyto.

Caregivers of patients meeting the selection criteria will also be invited to participate.

9.3.2 Outcome Assessment

The primary endpoints for the patient/caregiver survey are:

- Receipt: A categorical variable will describe if patients and caregivers received the brochure and/or card.
- Knowledge: A mean score will be created to summarise individual patient and caregiver scores. An individual patient/caregiver score is calculated as the proportion of all knowledge questions with correct responses.

The secondary endpoints for the patient/caregiver survey are:

- Behaviour: A mean score will be created to summarise individual patient and caregiver scores. An individual patient/caregiver score is calculated as the proportion of all behaviour questions with correct responses.
- Undestanding: Among patient and caregivers who have read the patient/caregiver brochure and card, an ordinal scale will describe the self-reported level of understanding.
- Usage: A mean score will be created to summarise individual patient and caregiver scores. An individual patient/caregiver score is calculated as the sum of the 'value' of responses to all usage questions (ordinal scale) divided by the maximum possible score. Among patients and caregivers who have not read the materials, a categorical variable will describe the reasons for not reading them.

9.3.3 Covariate Assessment

The following sociodemographic characteristics will be collected and used to describe the sample:

- Country
- Age group (<65 years; >65 years)
- Gender (male/female)
- Respondent type (patient/caregiver)
- Educational level (categories vary by country)
- Number of days on Blincyto

9.3.4 Validity and Reliability

Qualitative techniques will be used to ensure that the patient/caregiver questionnaire is readable, understandable and easy-to-use.

The questionnaire will be developed in English and conceptually reviewed by 5 haemato-oncology non-ALL patients (and not treated with Blincyto) and/or caregivers in the UK. The questionnaire will be subsequently translated and linguistically validated with 3 patients/caregivers in each of the participating countries. ALL patients will not be used to validate the questionnaire so that the recruitment for the survey is not affected.

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 the 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 a questionnaire developed for patients and their caregivers. In view of the severity of the disease, responses will be collected through a paper questionnaire in the clinic.

The questionnaire will be developed following standard survey principles. It will mainly include multiple choice questions with no free text fields.

In addition to the paper questionnaire, an identification log will be completed by the study site. The feasibility and recruitment process will be registered in an excel database.

9.5 Study Size

Based on precision calculations provided in Table 2, the survey aims to recruit approximately [redacted] patients and their associated caregivers 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 questions ranging from 0 to 10 (Table 3), a sample size of [redacted] patients and [redacted] caregivers 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.

These confidence intervals are wider than generally used, however, considering the orphan indication for Blincyto, severity of disease and variable patient well-being during treatment that may limit the number of patients available to participate in the study, this sample size is considered feasible and also appropriate to address the study objectives. It is to be noted that the final survey sample size will depend on patients/caregivers' willingness to participate in the survey within the study period (not more than 12 months after data collection).

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

Sample size	Correct Response	95% Lower Confidence Limit	95% Upper Confidence Limit
[redacted]	60%	[redacted]	[redacted]
	70%		
	80%		
	90%		
	60%		
	70%		
	80%		
	90%		
	60%		
	70%		
	80%		
	90%		

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

Sample size	Correct Response	95% Lower Confidence Limit	95% Upper Confidence Limit
[redacted]	60%	[redacted]	
	70%		
	80%		
	90%		
	60%		
	70%		
	80%		
	90%		

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

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

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

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

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Approximately [redacted] patients and [redacted] caregivers will be recruited from approximately [redacted] units across all participating countries in proportion to the volume of patients with R/R Ph- ALL in each country; usage of Blincyto will be unknown in some countries and only estimated at the initiation of launch.

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. All data collected during the survey will be held confidentially.

As discussed in Section 10.3 the identities of patients 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 patient/caregiver has completed the survey.

9.6.1 Obtaining Data Files

Completed paper forms will be forwarded to [redacted] by the site staff for data entry. [redacted] data entry staff will enter the paper questionnaire into a database for analysis.

A database will be created and tested before data entry, two copies of the same database will be prepared. Double data entry will be performed and databases compared until no discrepancies are found. The final database will be transferred to SAS for analysis.

9.6.2 Linking Data Files

In addition to the paper questionnaire, an identification log will be completed by the study site. As described in Section 10.3, a unique code will be assigned to each patient and caregiver, which will be used to link the paper questionnaire with the identification log which will be kept by the investigator and site staff. The feasibility and recruitment process will be registered in an excel database and managed by the study operations staff involved in the recruitment of centres.

9.6.3 Review and Verification of Data Quality

As this study is collecting data from patients and caregivers through a survey questionnaire, it is not planned to generate queries in the study. Double data entry will be performed to minimize potential errors.

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, a descriptive analysis and the analysis of the objectives. Site characteristics (type of centre ie. academic/non-academic) will be described.

Patient/caregiver representativeness: Patients/caregivers approached at the sites for enrollment, whose demographic profile information has been collected in the patient log (age and gender), will be divided into:

- Eligible patients/caregivers who agree to participate in the study
- Eligible patients/caregivers who refuse to participate in the study

9.7.2.2 Missing or Incomplete Data and Lost to Follow-up

Responses to questions in the patient/caregiver questionnaire may be missing or illegible. They will be dealt with in two ways:

- In the primary analysis, missing/illegible 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/illegible data will be ignored in the analysis.

9.7.2.3 Descriptive Analysis

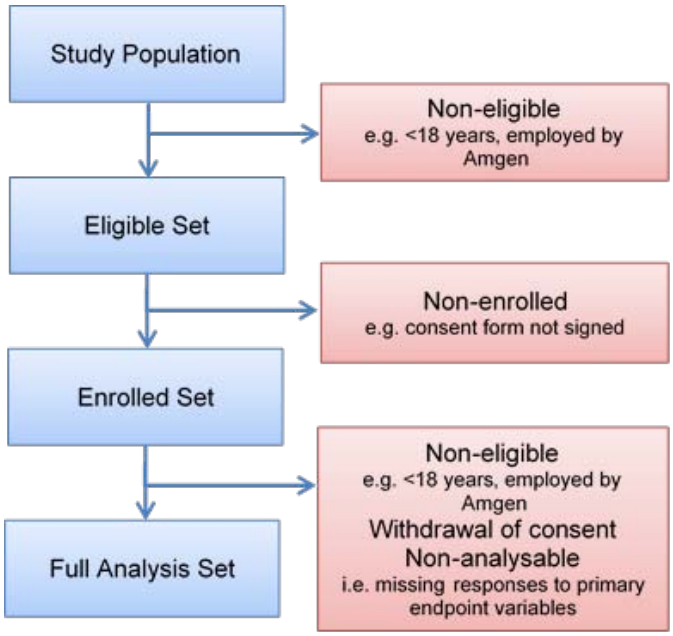
9.7.2.3.1 Description of Study Enrollment

The study populations as identified in the recruitment process will be described. Recruitment rates and a description of the number of patients/caregivers in the study and analysis populations will be provided.

Analysis sets: As shown in Figure 3, datasets for analysis will be further described in the SAP and will include:

- Study population: All adult patients with R/R Ph- B-precursor ALL initiating Blincyto (or their caregivers).
- Eligible Set: All patients/caregivers who fulfill the eligibility criteria.
- Enrolled Set: All eligible patients/caregivers who agree to participate in the study.
- Full Analysis Set: All patients/caregivers who complete the questionnaire of their corresponding survey and have valid responses to allow for the assessment of the primary objective.
- Safety Set: This is the same as the Enrolled Set.

Figure 3. Study Population and Datasets Flow-chart



9.7.2.3.2 Description of Subject/Patient Characteristics

The following sociodemographic and treatment characteristics will be summarised: age group, gender, country, respondent type, educational level and number of days on Blincyto.

9.7.2.4 Analysis of the Primary and Secondary Endpoint(s)

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

- **Receipt** will be assessed through the percentage of patients and caregivers who received the brochure and/or card.
- A mean **knowledge** score will be created to summarise individual patient and caregiver scores. An individual patient/caregiver score is calculated as the proportion of all knowledge questions with correct responses.

The secondary analyses are:

- A mean **behaviour** score will be created to summarise individual patient and caregiver scores. An individual patient/caregiver score is calculated as the proportion of all behaviour questions with correct responses.
- Among patient and caregivers who have read the patient/caregiver brochure and/or card, an ordinal scale will describe the self-reported level of **understanding**.

- A mean **usage** score will be created to summarise individual patient and caregiver scores. An individual patient/caregiver score is calculated as the sum of the 'value' of responses to all usage questions (ordinal scale) divided by the maximum possible score. Among patients and caregivers who have 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, educational level, and whether the materials were read or not.

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 this survey 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.

Paper questionnaires received at [redacted] will be tracked and identified at arrival and stored in a secure and controlled area following [redacted] procedures.

9.9 Limitations of the Research Methods

The number of patients willing/able to participate in the survey may be lower than expected because of the severity of the condition and complications during the first cycle of Blincyto: neutropenic fever, infections, and neurological side effects. Responses by caregivers may be anticipated to be different (better?) than patients, as they are often more attentive of the details of the management of their family member or friend, especially in these patients, many of whom will experience side effects and be quite ill during their therapy with Blincyto. This will be assessed by analyzing patients and caregivers separately.

The questionnaire has been designed to facilitate completion by the patient/caregiver on paper. For this reason, some of the questions that address secondary endpoints refer to 'educational materials' in general (eg. understanding, usage) and do not allow drawing conclusions for each type of material ie. card and brochure. However, most of the questions apply only to the brochure and some of the questions apply only to the card.

The survey will exclude patients (caregivers of patients) who have only received Blincyto in hospital. This restriction will result in a more meaningful assessment as only patients/caregivers who have the chance to have used the materials will be included; materials are mainly used in the outpatient setting where MEs are more likely to occur. In addition, the completion of the survey by the patient/caregiver will be restricted to the period after first discharged from hospital and ambulatory treatment at home. This time interval is expected to allow sufficient time for the provision and usage of the materials, and the occurrence of MEs (if any), without hindering recruitment.

The survey may be affected by selection bias within centres and non-participation. Consecutive recruitment based on treatment initiation during the study period will be used to avoid selection bias. A log of patients initiating Blincyto during the study period will be kept to check this recruitment process.

Only patients/caregivers able to understand and complete the informed consent and questionnaire will be included in the survey. Efforts will be made to write the questions in such a way that they can be readily understood by patients/caregivers with different educational levels so that ineligibility and inaccurate or missing responses for this reason are kept to a minimum. Non-response of items should be minimized due to the rigorous process of questionnaire development, validation and testing.

Patients/caregivers' responses may be biased if they are allowed to refer to the aRMM educational brochure and patient card. As a result, this would be minimized by explaining that responses should be based on assessing what they currently know and that they should not refer to the materials. At the time of completing the questionnaire, in the hospital clinic setting keeping materials out of reach should be readily feasible.

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.

Recall bias is an inherent limitation of questions asking about the past. However, in this situation where the first cycle of therapy is administered over a short period of time (28 days), this should be minimal.

The conduct of the survey may cause centres to provide more information to patients and caregivers. This 'Hawthorne' effect will be minimized by training sites to provide limited information about the survey in communications with the patients/caregivers.

The size of the study populations will allow an acceptable level of precision (considering the rarity of the disease) for each strata (patients and caregivers) for the study primary endpoints. Subgroup analyses will be exploratory and limited due to the small number of patients.

10. Protection of Human Subjects

10.1 Informed Consent

In accordance with local regulations and the ethical principles that have their origin in the principles of the Declaration of Helsinki, patients should provide written consent before enrollment into the study. Investigators must ensure that patients and/or their caregivers, are clearly and fully informed about the purpose of the study, potential risks, the patient/caregiver's rights and responsibilities when participating in this study. If local regulations do not require an ICF to be signed by the patient/caregiver, the site staff should document key elements of the informed consent process in the patient's medical record.

Informed consent for the survey questionnaire will be sought. By signing the ICF, the patient/caregiver consents to participate in the questionnaire.

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

This type of study requires review and approval by a central ethics committee (EC) in the participating countries and ICF from the patients for their participation in the survey. Thus, the study will be conducted under the auspices of an independent EC (and any local EC as applicable) in each country, as defined in local regulations, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

10.3 Patient/Caregiver Confidentiality

The confidentiality of records that could identify patients within the database will be protected, and all privacy and confidentiality rules will be followed in accordance with the applicable regulatory requirement(s).

For the purposes of protecting a patient/caregiver's identity, a unique code will be assigned to each patient/caregiver, such as a series of numbers and/or letters (for example, CA180330-0001-00001). The data that is recorded with the patient/caregiver's assigned code is 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 patient/caregiver's assigned code and the patient/caregiver's identity. However, in case

of an audit or inspection, subject to local laws and regulations, government officials, IRB/EC representatives and sponsor representatives may access this information at the study site. Data that could directly identify the patient will not be collected in the "study database".

The investigator's personal data, which may be included in the study database, shall be treated in compliance with all local applicable laws and regulations.

When archiving or processing personal data pertaining to the investigator, all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by the sponsor, whichever is longer. The investigator must contact Amgen prior to destroying any records associated with the study. Location of database and supporting documentation will be outlined in the final study report.

11. Collection of Safety Information and Product Complaints

As the questionnaire is completely multiple choice, very few reports of adverse events 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 physician'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.

Product complaints of Blincyto will be reported.

11.2 Safety Reporting Requirements

[redacted] is responsible for ensuring that safety events (adverse events, product complaints and other safety findings) reported by the physician, patient/caregiver or interviewer that occur in patients treated with Blincyto after study enrolment 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 physician 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. The IEC or other relevant ethical review board in the participating countries must be informed of all amendments and give approval. The Investigator **must** send a copy of the approval letter from the IEC or other relevant ethical review board in the participating countries to Amgen.

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. The Investigator is to notify the IEC or other

relevant ethical review board in the participating countries in writing of the study's completion or early termination and send a copy of the notification to Amgen.

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

Patients/caregivers will not receive any incentives for their participation in the survey. Investigators will receive a compensation for the recruitment of participants into the study if permitted under applicable regional laws or regulatory guidelines. This compensation will be based on a Fair Market Value (FMV) assessment (eg., time and effort) in each participating country.

15. References

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16. Appendices

Appendix A. List of Stand-alone Documents

No.	Title
1	*Patient/Caregiver Questionnaire*

Appendix B. ENCePP Checklist for Study Protocols

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

Doc.Ref. EMA/540136/2009

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: A cross-sectional survey of patients and caregivers receiving Blincyto in routine clinical practice in Europe to evaluate the effectiveness of additional risk minimisation measures

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:

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			3. Reporter ID		
name	phone	fax	Name or ID	phone	fax
address			address		
city	state/province		city	state/province	
postal code	country		postal code	country	

4. HCP Contact Details (if other than reporter)			5. Patient			
name			Initials (optional)	Sex ☐ F ☐ M	Age (at time of event)	Was consent obtained to follow-up with HCP? ☐ Yes ☐ No
country						
address						
city	state/province	postal code	Weight ☐ lbs ☐ kg	Height ☐ in ☐ cm	Race	Is patient also reporter? ☐ Yes ☐ No
phone	fax					

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 — Prefilled Syringe? ☐ Yes ☐ No — Lot # ☐ Unknown — Vial size

Allergy: _____ — Other Device _____ — Serial # ☐ Unavailable / Unknown

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

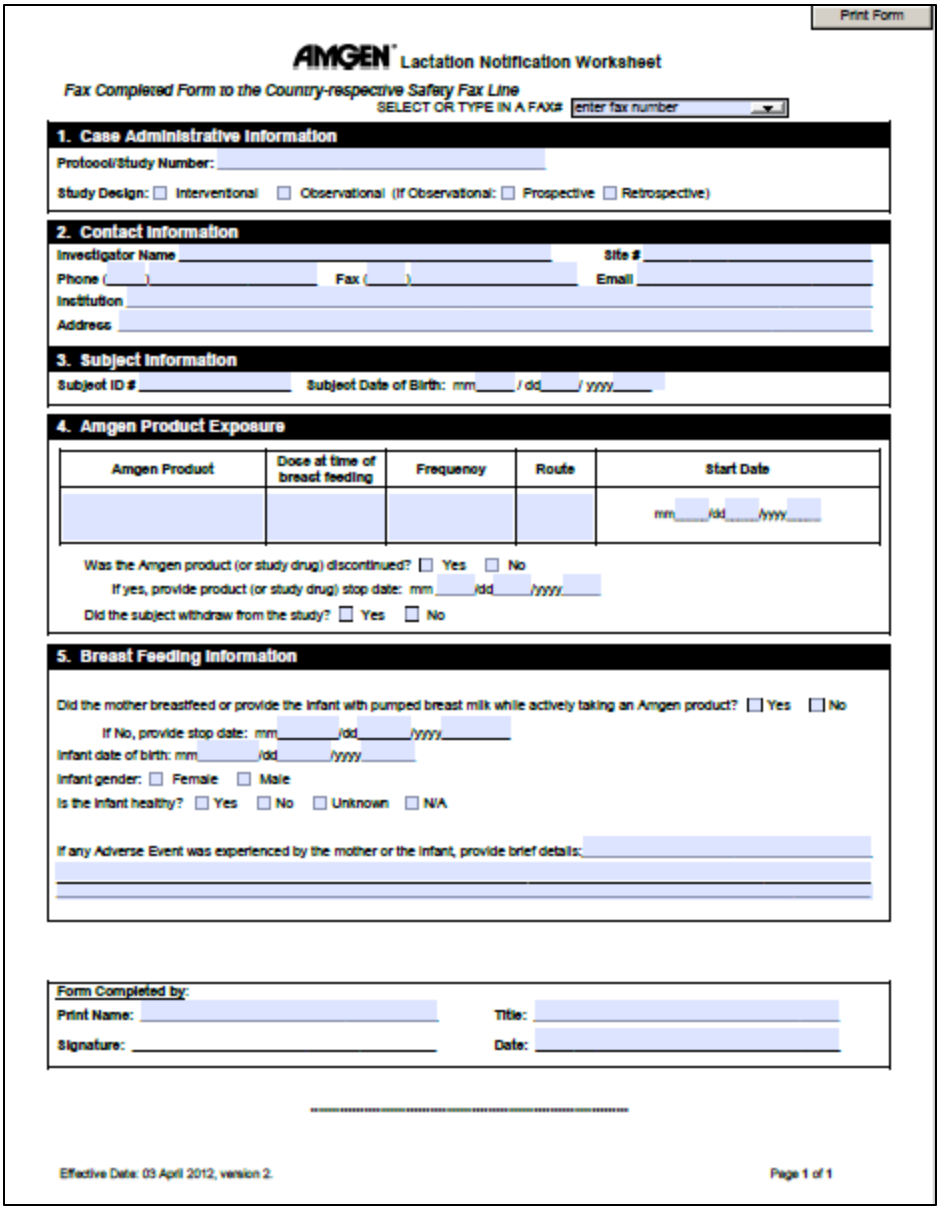
If any Adverse Event was experienced by the infant, provide brief details: _____

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 Materials

Bincyto Patient Card

Version 1.0 BLINCYTO® (blinatumomab) Approved: September –2015

Educational Brochure for Patients and Caregivers

Patient Card

Please show this card to all emergency and healthcare providers

Information about BLINCYTO®▼(blinatumomab)

My name is _____

I am being treated with BLINCYTO a treatment for relapsed/refractory acute lymphoblastic leukemia, which can lower my immune system.

I started treatment on _____

Before providing any treatment, please call my prescribing physician at the number below. If any medical evaluations are undertaken, please provide copies of all medical records, including any treatments and/or test results, to the doctor(s) named below.

	Name	Hospital	City	Phone Number
Haematologist Oncologist				
Haematology Nurse				

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get to <##>. By reporting side effects, you can help provide more information on the safety of this medicine.

Bincyto Educational Brochure for Patients and Caregivers

BLINCYTO® ▼ (blinatumomab)

Important Risk Minimisation Information for Patients and Caregivers

This educational brochure contains important information you should know before receiving BLINCYTO.

This educational material is essential to ensure the safe and effective use of the drug and appropriate management of the important selected risks. Please read it carefully before taking the medicinal product.

If you have any questions about BLINCYTO please speak to your doctors or nurses, or refer to the Patient Leaflet, provided with this brochure.

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get to <##>. By reporting a side effect, you can help provide more information on the safety of this medicine.

This information is not intended to take the place of discussions with your doctor or other healthcare professionals who are treating your relapsed/refractory Philadelphia chromosome negative acute lymphoblastic leukemia. Read the BLINCYTO patient leaflet provided to you by the doctors or nurses, as well as this educational brochure.

Overview of BLINCYTO treatment

What is BLINCYTO?

BLINCYTO is a medicine that works by enabling your immune system to attack and destroy the abnormal white blood cancer cells.

What is BLINCYTO used for?

BLINCYTO is a treatment for relapsed/refractory acute lymphoblastic leukemia. Acute lymphoblastic leukaemia is a cancer of the blood in which a particular kind of white blood cell called "B-lymphocyte" is growing out of control.

How is BLINCYTO given?

BLINCYTO will be given to you through a vein (intravenous) continuously for 4 weeks using an infusion pump (this is 1 treatment cycle). You will then have a 2-week break where you will not be given the infusion. Your infusion catheter will be attached to you at all times during each cycle of your treatment.

BLINCYTO is usually given for 2 treatment cycles. If you respond to BLINCYTO treatment after the first 2 cycles, your doctor may decide to give you up to 3 additional cycles of treatment. The number of treatment cycles which you will be given will depend on how you tolerate and respond to BLINCYTO. Your doctor will discuss with you how long your treatment will last. Your treatment may also be interrupted depending on how you tolerate BLINCYTO.

It is recommended that the first 9 days of treatment will be given to you in a hospital or in a clinic under the supervision of a doctor or nurse experienced in the use of anti-cancer medicines. If you have or had neurological problems, it is recommended that the first 14 days of treatment will be given to you in a hospital or clinic. Your doctor will discuss withyou if you can continue treatment at home after your initial hospital stay. Treatment may include a bag change by a nurse.

Your doctor will determine when your BLINCYTO infusion bag will be changed, which may range from every day to every 4 days. The infusion rate (how quickly the medicine goes into your vein) may be faster or slower depending on how often the bag is changed .

Important things for you and/or your caregiver to know about using BLINCYTO

Infusion pump and its accessories	• You will receive BLINCYTO solution through an infusion that delivers the medicine directly through a tube inserted into a vein. • You will have the pump connected to you 24 hours a day for 28 days. Do not unlock the pump. • Make sure the tubing stays connected to the pump at all times. • **Do not let the tubing become tangled or twisted at any time.** • **Do not lie on the tubing.** • **Do not change the pump settings on purpose**: o If the pump alarm goes off at any time, contact your doctor or nurse immediately. o If the pump stops working unexpectedly or if the infusion bag empties too quickly, get help from your doctor or nurse immediately. • **Do not pull the tubing or unplug the pump at any time.** • **If you notice blood in the tubing, contact your doctor or nurse immediately.** Keep the pump, the tubing, and the covering at the site where it is inserted into your vein dry at all times. • If you have any concerns regarding how your pump is working, please contact your doctor or nurse.
Nervous system problems	• BLINCYTO may make you feel dizzy, confused, or cause shaky hands, fits or trouble with walking, speaking or writing. • Call your doctor or nurse immediately if you experience these symptoms. For more information, see the patient leaflet. • **Do not drive your car, use heavy machinery or engage in hazardous activities while receiving this medicine.**

Amgen is currently conducting a study to collect side effect information in patients receiving BLINCYTO including information on medication errors in some European countries. In addition, a patient survey is being conducted to assess knowledge and receipt of patient educational materials, about neurologic events and medication errors. Medication errors are unintended errors in the prescribing, dispensing, or administration of a medicinal product while in the control of the healthcare professional, patient, or consumer. Your physician will be able to tell you whether these studies are being conducted in your country.

If the studies are available in your country, your participation in these studies is encouraged. Please ask your physician for more information.