Summary Table of Study Protocol

Title	Long Term Post Marketing Drug Use Result Survey for Blinatumomab in Japan
Protocol version identifier	1.0
Date of last version of the protocol	NA
EU Post Authorization Study (PAS) Register No	EUPAS29685
Active Substance	Blinatumomab
Medicinal Product	BLINCYTO
Product Reference	
Procedure Number	
Joint PASS	No
Research Question and Objectives	To investigate the incidence of CTCAE grade ≥ 3 events of each safety specification of the Japan Risk Management Plan (neurologic events, infections, cytokine release syndrome, tumor lysis syndrome, myelosuppression and pancreatitis) in patients receiving long term administration of blinatumomab
Country(ies) of Study	Japan
Author	PPD Manager, Post Marketing Surveillance, Global Patient Safety, Labeling & Pediatrics – Japan Amgen Astellas BioPharma K.K.

Marketing Authorization Holder

Marketing authorization holder(s)	PPD, President Amgen Astellas BioPharma K.K.
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Study Design Schema

	At the time of registration	Cycle 6			Cycle 7 - 9		Safety follow-up
		Blinatumomab		Interval	Blinatumomab	Interval	
		Day 1 (Before treatment)	End of treatment/Day 29	Day 30 - 84	Day 1 - End of treatment/Day 29	Day 30 - 84	30 ± 3 days after the final treatment [1]
Registration	X						
Patient identification information	X						
Patient background		X[2]					
Pregnancy/Lactation		X					X
Therapeutic history before blinatumomab		X[2]					
Treatment of blinatumomab		X			X		
Concomitant medication/therapy		X					X
Adverse Event		X					X

[1] If administration of blinatumomab will be stopped or terminated between the beginning of cycle 6 and the end of cycle 9, the safety follow-up period shall be 30 ± 3 days after the final administration or up to the day before the implementation of hematopoietic stem cell transplantation or other antitumor therapy.

[2] In case the patient is not continuing from All Case Post Marketing Drug Use Result Survey (20170655 study)

1. Table of Contents

List of Appendices

2. List of Abbreviations

Abbreviations	Definition of the Terms
AE	Adverse event
ALL	Acute lymphoblastic leukemia
BiTE	Bispecific T-cell engagers
CI	Confidence interval
CRF	Case report form
CRO	Contract research organization
CRS	Cytokine release syndrome
CTCAE	Common terminology criteria for adverse events
CTL	Cytotoxic T-lymphocyte
DFS	Disease-free survival
EC	Ethical committee
EDC	Electronic data capture
GPSP	Good Post-marketing Study Practice
HCPs	Health care professionals
ICJME	International committee of medical journal editors
J-NDA	Japan new drug application
J-PSUR	Japan periodic safety update report
J-RMP	Japan risk management plan
PMDA	Pharmaceuticals and medical devices agency
PMS	Post-marketing surveillance
Q	Quartile
SAP	Statistical analysis plan
SD	Standard deviation
TLS	Tumor lysis syndrome

3. Responsible Parties

Sponsor: Amgen Astellas BioPharma K.K., Japan

Collaboration partner: Astellas Pharmaceutical Inc., Japan

Contract Research Organization (CRO): EPS Corporation, Japan

Investigators: Investigators at medical institutions with active contracts for the survey, Japan

4. Abstract

- Study Title

  Long Term Post Marketing Drug Use Result Survey for Blinatumomab in Japan

- Study Background and Rationale

  In the Japan new drug application (J-NDA) for blinatumomab, safety and efficacy data on 35 Japanese subjects were presented. The proposed post-marketing surveillance (PMS) will provide descriptive data from the real-world long term use of blinatumomab in patients in Japan to supplement the data in the J-NDA. Japan Risk Management Plan (J-RMP) includes this survey as a part of post-marketing pharmacovigilance activities.

- Research Question and Objective(s)
  - Primary Objective(s)
    The primary objective of study is to investigate the incidence of CTCAE grade ≥ 3 events of each safety specification of the J-RMP (neurologic events, infections, cytokine release syndrome (CRS), tumor lysis syndrome (TLS), myelosuppression and pancreatitis) in patients receiving long term administration of blinatumomab.
  - Secondary Objective(s)
    None
  - Hypothesis(es)/Estimation
    There is no hypothesis to be tested. Instead, the proposed survey will provide descriptive data on real-world long term use of blinatumomab and adverse event occurrence in patients in Japan.

- Study Design/Type

  Prospective observational study in post marketing setting without a comparator arm.

- Study Population or Data Resource

  Patients for whom blinatumomab is prescribed at the cycle 6 to 9 at medical institutions

- Summary of Patient Eligibility Criteria

  No exclusion criteria are applied.

- Follow-up

  From the beginning of cycle 6 to the end of cycle 9

- Variables
  - *Outcome Variable(s)*
    CTCAE grade ≥ 3 adverse events (including grade, seriousness and causal relations to drug)
  - *Exposure Variable(s)*
    Daily dosage and duration of blinatumomab administration
  - *Other Covariate(s)*
    Patient demographics and medical history, concomitant medication and therapy

- Study Sample Size

The planned number of patients in this survey was set to 40 patients.

- Data Analysis

  Patient disposition, demographics and characteristics before cycle 1 will be summarized. The number of patients and the incidence rates of CTCAE grade ≥ 3 events are tabulated for each safety specifications and other adverse drug reactions during the survey.

5. Amendments and Updates

None

6. Milestones

Milestone	Planned date
Start of data collection	10 June 2019
End of enrollment	30 September 2022
End of observation	30 September 2023
End of data collection	30 September 2024
Final report of study results	31 March 2025

7. Rationale and Background

7.1 Diseases and Therapeutic Area

Acute lymphoblastic leukemia (ALL) is a heterogeneous hematologic disease characterized by the proliferation of immature lymphoid cells in the bone marrow and peripheral blood. Normal blood cell development in the marrow is therefore arrested and replaced with immature and abnormal lymphoblasts. The proliferation of these immature/abnormal lymphoid cells in the bone marrow subsequently crowd out the production of normal bone marrow elements ultimately resulting in decreased red blood cell, white blood cell and platelet counts (NCCN Clinical Practice Guidelines, 2014). ALL is a rare malignant disease with an overall incidence of 1.1/100,000 per year. ALL has a bimodal distribution with an early peak at 4 to 5 years of age (incidence of 4.5/100,000 per year) followed by a second gradual increase at 50 years (incidence of 2/100,000 per year). It represents 80% of acute childhood leukemia and 20% of acute leukemia cases in adults (Pui and Evans 1998; Jabbour et al, 2005; Larson, 2005; SEER, 1975-2009 [accessed July 2012]). ALL is also a rare disease in Japan. The overall incidence rate of all leukemia in 2007 was 4.9/100,000 (Cancer Statistics in Japan - 2012). The totals of all leukemia and adult cases in 2007 were 10,211 and 9,648, respectively (Cancer Statistics in Japan - 2012). ALL accounts for approximately 20% of adult leukemia cases (Naoe, 2003). Among ALL, acute childhood leukemia represents 80% and adult cases comprise 20%. In adult ALL, whereas previous studies in Japanese patients showed a

~80% CR rate by induction chemotherapy, 6-year survival rate remained15% to 33% (Tanimoto et al, 1998; Ueda et al, 1998; Takeuchi et al, 2002). There are limited data in pediatric ALL in the relapsed/refractory setting specific to Japan. In frontline pediatric ALL, multi-agent chemotherapy based on BFM (Berlin-Frankfurt-Munster) group treatment regimen is the standard as in Western countries. While 5-year Disease-Free Survival (DFS) rates for standard and high-risk patients are approximately 85% and 70%, respectively, DFS in patients who did not respond to induction chemotherapy is less than 40%.

Blinatumomab belongs to a new class of bispecific antibody constructs called bispecific T-cell engagers (BiTE). BiTE has been designed to direct T cells towards target cells. The proximity induced by the BiTE triggers target cell-specific cytotoxicity, which closely resembles standard cytotoxic T-lymphocyte (CTL) activation. This T-cell–mediated target-specific killing is the therapeutic mechanism of action of blinatumomab (Löffler et al, 2000; Wolf et al, 2005). Blinatumomab was approved for patient with relapsed or refractory B-precursor ALL in Japan in September 2018. Patients will be received blinatumomab, administered continuous intravenous (cIV) infusion for a maximum of 9 treatment cycles. Blinatumomab was authorized as an orphan drug in Japan in October 2017.

7.2 Rationale

The safety and efficacy of blinatumomab for patients with relapsed or refractory B-precursor ALL has been demonstrated in the phase 1b/2 clinical trial of Japanese patients and global clinical trials. However, no observational study to examine the real-world long term use data of patients with relapsed or refractory B-precursor ALL has been conducted in Japan. Therefore, this study is set in J-RMP as a part of post-marketing pharmacovigilance activities to examine the safety for the real-world long term use of blinatumomab in patients with relapsed or refractory B-precursor ALL.

7.3 Statistical Inference (Estimation or Hypothesis[es])

There is no formal hypothesis to be tested. Instead, the proposed survey will provide descriptive data on real-world long term use of blinatumomab and adverse event occurrence in patients in Japan.

8. Research Question and Objectives

To obtain the safety information of the product in the real-world long term use of blinatumomab in Japan.

8.1 Primary

The primary objective of study is to investigate the incidence of CTCAE grade ≥ 3 events of each safety specification of the J-RMP in patients receiving long term administration of blinatumomab.

<Safety specification items to focus, as described in J-RMP>

- Important Identified Risks

Neurologic events, Infections, CRS, TLS, Myelosuppression, Pancreatitis

9. Research Methods

9.1 Study Design

This study is a non-interventional (observational) study of patients in Japan who will be treated with blinatumomab at the cycle 6 or later in the post-marketing setting without comparator arm.

9.2 Setting and Study Population

Patients for whom blinatumomab is prescribed in the cycle 6 or later at participating medical institutions will be registered without eligibility criteria, so that data can be collected on how blinatumomab will be used in Japan. This study targets the patients who started the blinatumomab cycle 6 therapy before concluding the contract with medical institutions, as well.

9.2.1 Study Period

Study Period: From 6 months after blinatumomab launch date to when observation of all patients registered is completed (May 2019 to September 2023)

Enrollment Period: From 6 months after blinatumomab launch date to when the registration of the target number of subjects is completed (May 2019 to September 2022)

9.2.2 Selection and Number of Sites

About 250 nation-wide medical institutions equipped with department of Hematology, Medical Oncology, Pediatric Oncology, others and medical experts of committing participation and co-operation of the study.

9.2.3 Subject/Patient/Healthcare Professional Eligibility

9.2.3.1 Inclusion Criteria

Patients for whom blinatumomab is prescribed in the cycle 6 or later at medical institutions.

9.2.3.2 Exclusion Criteria

No exclusion criteria are applied.

9.2.4 Matching

No matching is used.

9.2.5 Baseline Period

Patient background at the start of cycle 1 blinatumomab administration will be collected as baseline data.

9.2.6 Study Follow-up

Each patient will be followed from the beginning of cycle 6 to the end of cycle 9.

If administration of blinatumomab will be stopped or terminated between the beginning of cycle 6 and the end of cycle 9, the safety follow-up period shall be 30 ± 3 days after the final administration or up to the day before the implementation of hematopoietic stem cell transplantation or other antitumor therapy.

9.3 Variables

Information described in Sections 9.3.1-9.3.3 is collected in case report form (CRF) per a patient. CTCAE grade ≥ 3 or higher adverse event and other safety information are collected throughout the follow-up period.

9.3.1 Exposure Assessment

Daily dosage, period and reason for change/termination of blinatumomab are collected in CRF.

9.3.2 Outcome Assessment

CTCAE grade ≥ 3 or higher adverse events (including grade, seriousness and causal relations to drug) during the observational period or safety follow-up period are collected by using CRF and applicable safety reporting form. If adverse events or serious adverse events are due to the primary disease, all signs and symptoms obtained are reported. Mortality due to disease progression when information on symptoms and symptoms cannot be obtained is reported as the primary tumor (e.g. relapsed or refractory B-cell ALL).

9.3.3 Covariate Assessment

Following data are collected in patient registration form and CRF.

Patient information for registration: patient ID, sex, birth year/month, continuation status from 20170655 study, date of informed, start date of cycle 6 blinatumomab administration

Patient demographics and medical history (in case the patient is not continuing from 20170655 study): pregnancy/lactation, medical history (including central nervous system lesion or symptom, hepatic dysfunction and renal dysfunction), therapeutic history before blinatumomab administration to B-cell ALL, history of hematopoietic stem cell transplantation, Philadelphia chromosome examination

Pregnancy and lactation during observation period: birth (planned) years/month

Concomitant medication (excluding complication treatment medicine and CTCAE grade ≤ 2 adverse event treatment medicine): medicine name, duration, dosage

Concomitant therapy to primary disease: therapy name, duration

9.3.4 Validity and Reliability

It is a prospective, observational cohort study, so variables, which can be measured at medical sites in the real-world medical practice, are selected for this survey in reference to prior blinatumomab clinical trials and advice from local medical experts.

Exposures, outcomes, and all other variables observed and measured by each medical site will be collected through paper CRF and entered into a database constructed by the external service provider, EPS Corporation, Tokyo, Japan. Standardized error check program will be constructed in the data management system. If a logical discrepancy in CRF and clear error is identified, a query form will be prepared and delivered to the institutional site physicians for clarification and correction. Site physicians and staff are requested to check the data against medical records, and accuracy and completeness of data consistent with information in medical records is confirmed and attested by signature of investigators.

9.4 Data Sources

The original source of the data used in the survey is patient medical records. Data are collected through CRF, which are populated by the investigators.

Laboratory test values will be measured by each medical site with their own method.

9.5 Study Size

The targeted number of patients was set to 40 subjects to enable a consistent comparison and discussion on the safety during the maintenance phase in Japanese

patients and blinatumomab clinical trial (00103311 study) by collecting the information from the similar number of subjects as 36 subjects who underwent maintenance therapy of blinatumomab in 00103311 study. The incidence of CTCAE grade ≥ 3 neurologic events, infections and myelosuppression between cycles 6 and 9 in 00103311 study was 8.3% (3/36), 22.2% (8/36) and 16.7% (6/36) respectively. The collection of 40 subjects who transition to cycle 6 enables that the events with a true incidence of 8% or above are collected from at least 1 subject with 95% confidence, and thus a consistent evaluation for CTCAE grade ≥ 3 neurologic events, infections and myelosuppression is considered possible.

9.6 Data Management

Data are collected by paper CRF.

Data management is conducted by EPS Corporation under its own standard operating procedure with oversight by the Amgen Astellas BioPharma K.K.

9.6.1 Obtaining Data Files

Not applicable

9.6.2 Linking Data Files

Not applicable

9.6.3 Review and Verification of Data Quality

Quality and completeness will be annually confirmed by self-inspection per the local good post-marketing study practice (GPSP).

9.7 Data Analysis

Patient disposition, demographics and baseline characteristics will be summarized. The number of patients and the incidence rates of CTCAE grade ≥ 3 events are tabulated for each safety specifications and other adverse drug reactions during the survey. Statistical test (chi-square, etc.) will be applied, depending on the type of variable (nominal, ordinal, etc.). Imputation for missing data will be considered if it is possible and empirically worth to do imputation of missing data. Statistical analysis will be conducted by EPS Corporations in accordance with the Statistical Analysis Plan (SAP), provided by Amgen Astellas BioPharma K.K.

9.7.1 Planned Analyses

For the timely sharing of the collected data with PMDA and Health care professionals (HCPs), analysis of interim data will be performed at the timing of Japan periodic safety update report (J-PSUR). After the last patient enrolled to meet the expected sample size

completes the observational period, a data analysis will be performed and a final report summarizing the results of the survey will be completed shortly thereafter. For final analyses, the local external medical experts will review the survey analysis results.

9.7.1.1 Primary Analysis

The primary analysis will be conducted after all the survey data are collected and cleaned.

Patient disposition, demographics and baseline characteristics will be summarized. Statistical test (chi-square, etc.) will be applied, depending on the type of variable (nominal, ordinal, etc.). See Sections 9.7.2.4 and 9.7.3 for analyses planned to address specified endpoints.

9.7.2 Planned Method of Analysis

9.7.2.1 General Considerations

In general, a descriptive analysis is conducted. Categorical variables are summarized with frequencies and percentage. Continuous variables are summarized with mean, standard deviation (SD), median, 1st Quartile (Q), and 3rd Q. When statistical testing and inference are applied, two-sided p-value of <0.05 is considered significant and the 95% CI is estimated. Adjustment for multiple comparisons is not considered.

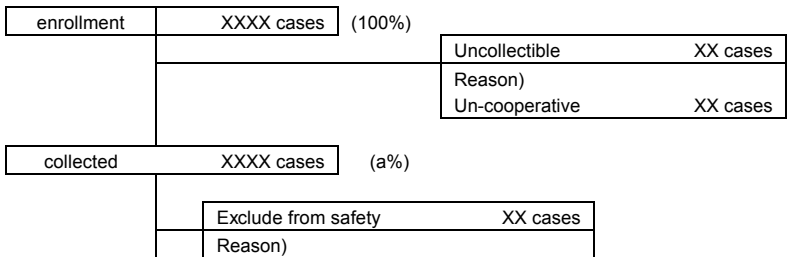
9.7.2.2 Missing or Incomplete Data and Lost to Follow-up

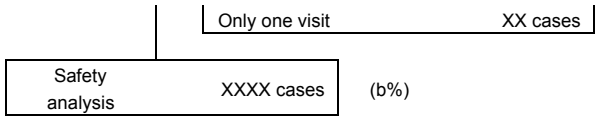
Participating investigators (physicians) and co-medicals are requested to make an effort to provide as complete information as possible through CRF. It is assumed that blinatumomab prescriptions would typically be started and patients observed at hospitals with experts of oncology. The rate of lost to follow-up is estimated to be close to 0% as possible. Imputation for missing data will be considered if it is possible and empirically worth to do imputation of missing data.

9.7.2.3 Descriptive Analysis

9.7.2.3.1 Description of Study Enrollment

All enrolled patients will be summarized in the tree of patient disposition, as described below:





Percentage of a% and b% (corresponding to enrollment) will be calculated.

9.7.2.3.2 Description of Subject/Patient Characteristics

Patient characteristics will be summarized for the following variables.

Patients demographic: sex, birth year/month, reason for usage, experience of usage, pregnancy/lactation, medical history (including central nervous system lesion or symptom, hepatic dysfunction and renal dysfunction), therapeutic history before blinatumomab administration to B-cell ALL, history of hematopoietic stem cell transplantation, Philadelphia chromosome examination, pregnancy and lactation during observation period, concomitant medication, concomitant therapy to primary disease

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

Analysis for specified endpoints will be conducted as follows:

- Primary endpoint for safety:

The number of patients and the incidence rates of CTCAE grade ≥ 3 events are tabulated for each safety specifications and other adverse drug reactions during the survey (see Section 11.1 the definition of adverse event, serious adverse event, and other safety findings to be collected).

9.7.2.5 Sensitivity Analysis

9.7.2.5.1 Subgroup Analysis

If necessary, summarize the number of patients and the incidence rates of each safety specifications and all adverse drug reactions for each patient background, such as adults and pediatric.

9.7.2.5.2 Stratified Analysis

Stratified analysis will be conducted by covariates as below:

- Patient demographics (e.g., age group, preexisting disease etc.)
- Medication status (e.g., dosage and duration of blinatumomab therapy, concomitant medication for ALL)

9.7.2.5.3 Sensitivity Analysis for Residual Confounding and Bias

No sensitivity analysis is pre-planned.

9.7.2.5.4 Other Sensitivity Analysis

No sensitivity analysis is pre-planned.

9.7.3 Analysis of Safety Endpoint(s)/Outcome(s)

See Section 9.7.2.4.

9.8 Quality Control

Quality control is conducted by checking whether data management operations were conducted based on the standard operation procedures of data management, and all results of quality control, including deviations and their measurements, are documented/reported and corrected deviations appropriately if they were found.

9.9 Limitations of the Research Methods

This is a prospective, observational cohort study, so it has a limitation of internal validity and strength of external validity in comparison with an interventional clinical study. Limitations common to this type of study, along with how to reduce errors, are summarized below.

Limitations	How to reduce errors
Missing and incomplete data are unavoidable, because there are some cases that data could not collected at all evaluation time points, and some patients could be lost to follow-up.	Efforts will be made to collect as complete data as possible and instructions to investigators. After examining the extent of missingness and incompleteness of study data, an appropriate statistical data imputation method will be considered if it is possible and empirically worth to do imputation of missing data.
Selection bias, information bias and confounding cannot be excluded.	Selection of participating medical institutions nationwide and enrollment of all patients who will receive blinatumomab prescriptions in the cycle 6 or later at the eligible institutions as much as possible during enrollment period without exclusion criteria. Analysis results will be interpreted with caution, acknowledging the limitations, whether or not appropriate statistical methods could be applied to address the bias.

10. Protection of Human Subjects

The study protocol is reviewed and approved by the local regulatory agency, PMDA as well as external ethical committee (EC). The study and data collection are conducted in accordance with the Pharmaceutical and Medical Device Act, GPSP and Helsinki Declaration. Local Medical Act provides the physician and co-medical 'Confidentiality Obligation' of patients that is set forth in the study agreement between the representatives of study site and Amgen Astellas BioPharma K.K.

Before registering the patient to this study, physician informed the patient about the aim, method, and potential risk of the study and utilization of the patient's data in keeping individual patient's information unidentified.

11. Collection, Recording, and Reporting of Safety Information and Product Complaints

The external vendor, EPS Corporation, in charge of day-to-day survey operation will check incoming safety information (adverse events, use in pregnant/lactating women) on data management system and CRF daily, and report the information to the Safety Department at Amgen Astellas BioPharma K.K. in accordance with standard operating procedures of Amgen Astellas BioPharma K.K.

11.1 Definition of Safety Events

11.1.1 Adverse Events

An adverse event is any untoward medical occurrence in a 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 investigator's responsibility to evaluate whether an adverse event is related to an Amgen Astellas BioPharma K.K. product prior to reporting the adverse event to Amgen Astellas BioPharma K.K.

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 patient at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an "other medically important serious event" 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 medically important serious events" refer to important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events could include allergic bronchospasm, convulsions, and blood dyscrasias, drug-induced liver injury, events that necessitate an emergency room visit, outpatient surgery, or other events that require other urgent intervention.

11.1.3 Other Safety Findings

Other Safety Findings (regardless of association with an adverse event) 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 Astellas BioPharma K.K. or by distributors and partners for whom Amgen Astellas BioPharma K.K. manufactures the material. This includes any drug(s), device(s) or combination products provisioned and/or repackaged/modified by Amgen Astellas BioPharma K.K. Drug(s) or device(s) includes investigational product.

Product complaints are collected separately from this survey in accordance with standard operating procedures of product complaints of Amgen Astellas BioPharma K.K.

11.2 Safety Collection, Recording and Submission to Amgen Requirements

This study is collecting information from investigators prospectively at a point in survey. All safety events (adverse events, product complaints, and other safety findings) considered to have occurred following patient exposure to blinatumomab will be

collected during observational study period from start of cycle 6 administration to final study contact with the exception of the protocol-exempted events listed below. The investigator is responsible for recording safety events that they become aware of during study period in the patient's appropriate study documentation. Collected safety events must be submitted as individual safety reports to Amgen Astellas BioPharma K.K. via the Safety Reporting Form (paper form) provided by the Safety Department of Amgen Astellas BioPharma K.K. promptly.

Protocol Exempted Events

CTCAE grade ≤ 2 events are not required to be individually reported or collected in the study. If any of the exempted events have a fatal outcome, they should be considered a serious adverse event and must be collected and reported individually to Amgen Astellas BioPharma K.K. promptly. All safety information that is not specified in this section is to be collected and submitted to Amgen Astellas BioPharma K.K. promptly. Protocol-exempted events and safety events that are suspected to be related to any medicinal product other than Blinatumomab should be reported to the local authority in line with the local country requirements.

See Appendix C for sample Safety Report Form(s) and Appendix E for sample Pregnancy and Lactation Notification Worksheets. The Investigator 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 information recorded in the study documentation where safety data may also be recorded.

11.2.1 Collection of Pregnancy and Lactation Information

Female Subjects Who Become Pregnant

Investigator will collect pregnancy information on any female subject who becomes pregnant following exposure to Blinatumomab through observational study period. Information will be recorded on the Pregnancy Notification Worksheet (see Appendix E) or CRF. The worksheet or CRF must be submitted to Amgen Astellas BioPharma K.K. Safety promptly. (Note: Investigator is not required to provide any information on the Pregnancy Notification Worksheet or CRF that violates the country or regions local privacy laws).

After receipt of the Pregnancy Notification Worksheet or CRF, Amgen Astellas BioPharma K.K. Safety will provide investigator with a questionnaire to collect additional information. The investigator will collect pregnancy and infant health information and

complete the pregnancy questionnaire for any female subject who becomes pregnant following exposure to Blinatumomab through observational study period. This information will be forwarded to Amgen Astellas BioPharma K.K. Safety. Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).

Any termination of pregnancy will be reported to Amgen Astellas BioPharma K.K. Safety, regardless of fetal status (presence or absence of anomalies) or indication for procedure.

While pregnancy itself is not considered to be an adverse event or serious adverse event, any pregnancy complication or report of a congenital anomaly or developmental delay, fetal death, or suspected adverse reactions in the neonate will be reported as an adverse event or serious adverse event. Note that an elective termination with no information on a fetal congenital malformation or maternal complication is generally not considered an adverse event, but still must be reported to Amgen Astellas BioPharma K.K. as a pregnancy exposure case.

If the outcome of the pregnancy meets a criterion for immediate classification as a serious adverse event (e.g., female subject experiences a spontaneous abortion, stillbirth, or neonatal death or there is a fetal or neonatal congenital anomaly) the investigator will report the event as a serious adverse event.

Male Subjects with Partners who Become Pregnant

In the event a male subject fathers a child following exposure to Blinatumomab, the information will be recorded on the Pregnancy Notification Worksheet or CRF. The worksheet (see Appendix E) or CRF must be submitted to Amgen Astellas BioPharma K.K. Safety promptly. (Note: Investigator is not required to provide any information on the Pregnancy Notification Worksheet or CRF that violates the country or regions local privacy laws).

After receipt of the Pregnancy Notification Worksheet or CRF, Amgen Astellas BioPharma K.K. Safety will provide investigator with a questionnaire to collect additional information. The investigator will collect pregnancy outcome and infant health information on the pregnant partner and her baby and complete the pregnancy questionnaires. This information will be forwarded to Amgen Astellas BioPharma K.K. Safety. Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).

Any termination of the pregnancy will be reported to Amgen Astellas BioPharma K.K. Safety regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Collection of Lactation Information
Investigator will collect lactation information on any female subject who breastfeeds while taking Blinatumomab through observational study period.
Information will be recorded on the Lactation Notification Worksheet (see Appendix E) or CRF and submitted to Amgen Astellas BioPharma K.K. Safety promptly.
The investigator will collect mother and infant health information and complete the lactation questionnaire on any female subject who breastfeeds while taking Blinatumomab through observational study period.

12. Administrative and Legal Obligations

12.1 Protocol Amendments and Study Termination

Amgen Astellas BioPharma K.K. may amend the protocol at any time. If Amgen Astellas BioPharma K.K. amends the protocol, the Investigator must follow amendments.

Amgen Astellas BioPharma K.K. reserves the right to terminate the study at any time.

13. Plans for Disseminating and Communicating Study Results

Communication material will be developed for HCPs for updating safety information and for the enlightenment of usage of blinatumomab in a right way at the point of J-PSUR.

13.1 Publication Policy

The results of final analyses will be submitted for publication as conference abstracts and/or medical journal articles.

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 Astellas BioPharma K.K. for corporate review.

14. Compensation

Participating institutions will receive payments for completing CRF and associated study-related activities. The amount of compensation will follow the standards set by Amgen Astellas BioPharma K.K. based on a fair market value assessment and local industry guideline. Compensation to the enrolled patients and their families in relation to health damage caused by adverse drug reactions in spite of proper use of drugs will be paid from the Japanese public relief system for sufferers from adverse drug reactions of any post marketed products, which is managed by the PMDA.

15. References

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Ueda T, Miyawaki S, Asou N, et al. Response-oriented individualized induction therapy with six drugs followed by four courses of intensive consolidation, 1 year maintenance and intensification therapy: the ALL90 study of the Japan Adult Leukemia Study Group. Int J Hematol. 1998; 68: 279-289.

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Wolf E, Hofmeister R, Kufer P, Schlereth B, Baeuerle PA. BiTEs: bispecific antibody constructs with unique anti-tumor activity. Drug Discov Today. 2005;10:1237-1244.

16. Appendices

Appendix A. List of Stand-alone Documents

Not Applicable

Appendix B. ENCePP Checklist for Study Protocols

Study title:
Long Term Post Marketing Drug Use Result Survey for Blinatumomab in Japan

EU PAS Register® number:
Study reference number (if applicable):

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 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS Register®	☐	☒	☐	
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	8
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)	☒	☐	☐	7.2
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☒	☐	☐	7.3
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

[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.

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.4
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.7
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	9.7
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	☒	☐	☐	9.2.1
4.2.2 Age and sex	☒	☐	☐	9.2
4.2.3 Country of origin	☒	☐	☐	9.2
4.2.4 Disease/indication	☒	☐	☐	9.2
4.2.5 Duration of follow-up	☒	☐	☐	9.2.6
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2

Comments:

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)	☒	☐	☐	9.3.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	9.3.4

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.3 Is exposure categorised according to time windows?	☐	☐	☒	
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	9.3.1
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

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?	☒	☐	☐	9.3.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.2
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	9.3.4
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	9.7.2.5
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.9
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.9

Comments:

Section 8: Effect measure 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 and other characteristics?	☒	☐	☐	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)	☒	☐	☐	9.3.1
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3.2
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3.3
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), Medical Dictionary for Regulatory Activities (MedDRA))	☐	☒	☐	
9.3.3 Covariates and other characteristics?	☐	☒	☐	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

All adverse events are encoded by MedDRA under regulatory (PMDA) requirement.

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	9.7.2.3
10.4 Are stratified analyses included?	☒	☐	☐	9.7.2.5
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9.7.2.5
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7.2.2 9.9
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.7.2.5

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?	☒	☐	☐	9.6.3 9.8
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

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).	☒	☐	☐	9.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10
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?	☒	☐	☐	12

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)?	☒	☐	☐	9.7.1
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	13

Comments:

Name of the main author of the protocol: _____

Date: 25/October/2018

Signature: _____

Appendix C. Sample Safety Reporting Form(s)

Project ID:	AMGEN	**Observational Research Safety Reporting Form**	**Date of Reporter Awareness:**
			Date Reported to Amgen:
	Fax reports to: Amgen Local Office	*<<populate LAO fax here or delete language>>*	

1. Initial: ☐ **Follow-up:** ☐

2. Site Number: **Subject Number:**

3. Indicate event type: *(Please tick all that apply)* ☐ **AE/Other Safety Finding** ☐ **Product Complaint (PC)** ☐ **Adverse Device Effect (ADE)**

4. Contact Details (Vendor/Investigator)

Name	*Phone*	*Fax*
Address		
City	*State/Province*	
Postal Code	*Country*	

5. Reporter ID

Name or ID	*Phone*	*Fax*
Address		
City	*State/Province*	
Postal Code	*Country*	

6. HCP Contact Details (if other than reporter)

Name		
Country		
Address		
City	*State/Province*	*Postal Code*
Phone	*Fax*	

7. 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

8. Medical History (include primary diagnosis)

9. Suspect Product Information (include dosing details)

Product/Device: _____

Indication: _____

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

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

Allergy: _____

Prefilled Syringe? ☐ Yes ☐ No

Other Device _____

Lot # _____ ☐ Unknown

Serial # _____ ☐ Unavailable / Unknown

Vial Size

10. AE, Other Safety Finding, or PC/ADE 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; Prolonged Hospitalization? ☐ Yes ☐ No; Admitting dx _____; Date Admitted (day month year); Date Discharged (day month year)	**Serious Criteria** 01 Fatal; 02 Immediately life-threatening; 03 Required/Prolonged hospitalization; 04 Persistent or significant disability /incapacity; 05 Congenital anomaly/birth defect; 06 Other significant medical hazard; 07 Non serious	**Action Taken** 1=none; 2=dose reduced; 3=dose increased; 4=drug withdrawn; 5=drug rechallenge (state outcome)	**Outcome** 01 Recovered/ Resolved; 02 Recovering/ Resolving; 03 Not recovered/not resolved; 04 Recovered/ resolved with sequelae; 05 Fatal; 06 Unknown	**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
								Y N Y N
								Y N Y N
								Y N Y N

Reporter Signature: _____ **Page 3 of ____**

The data provided by you will be transferred as a report to Global Patient Safety at Amgen Inc (USA) and will be exclusively used for safety and quality purposes

FORM-067756 Ver. #: 4.0 Effective date: 06-Nov-2017

11. Concomitant Medications (eg, chemotherapy)

Medication Names	Start Date Day Month Year	Stop Date Day Month Year	Co-suspect No	Co-suspect Yes	Continuing No	Continuing Yes	Dose	Route	Frequency	Treatment Meds

12. Relevant Laboratory Values (include dates, allergies, and any relevant prior therapy)

Date Day Month Year											
	Test										
	Unit										

13. Other Relevant Test (diagnostics and procedures)

Date Day Month Year	Additional Tests	Results	Units

14. Description: Provide chronological summary and details of AE symptoms, PC or ADE that are listed in section 10 (signs, diagnosis, treatment, concomitant medications including those used to treat event).

Reporter Signature: _____ Page 4 of ____

The data provided by you will be transferred as a report to Global Patient Safety at Amgen Inc (USA) and will be exclusively used for safety and quality purposes

FORM-067756 Ver. #: 4.0 Effective date: 06-Nov-2017

Appendix D. Additional Safety Reporting Information

Refer to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for adverse event grading and information. The CTCAE scale is available at the following location: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

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

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