Summary Table of Study Protocol

Title	All Case 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	EUPAS26530
Active Substance	Blinatumomab
Medicinal Product	BLINCYTO
Product Reference	
Procedure Number	
Joint PASS	No
Research Question and Objectives	To explore the risk factors of neurologic events, and evaluate the treatments taken against cytokine release syndrome (CRS) and the incidence of each safety specification of the Japan Risk Management Plan (neurologic events, CRS, infections and pancreatitis) in patients receiving blinatumomab.
Country(ies) of Study	Japan
Author	[redacted] Manager, Post Marketing Surveillance, Global Patient Safety, Labeling & Pediatrics – Japan Amgen Astellas BioPharma K.K.

Marketing Authorization Holder

Marketing authorization holder(s)	[redacted] Amgen Astellas BioPharma K.K.
MAH Contact	[redacted] Senior Manager, Post Marketing Surveillance, Global Patient Safety, Labeling & Pediatrics – Japan Amgen Astellas BioPharma K.K. Sapia Tower 1-7-12 Marunouchi, Chiyoda-ku, Tokyo 100-0005, Japan Tel: +81.3.5293.9845 Fax: +81.3.6735.4369 E-mail: [redacted]@amgen.com

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Study Design Schema

	At the time of registration	Cycle 1			Cycle 2 - 5		Safety follow-up
		Blinatumomab		Interval	Blinatumomab	Interval	
		Day 1 (Before treatment)	End of treatment/Day 29	Day 30 - 42	Day 1 - End of treatment/Day 29	Day 30 - 42	30 ± 3 days after the final treatment [1]
Registration	X						
Patient identification information	X						
Patient background		X					
Pregnancy/Lactation		X					X
Therapeutic history before blinatumomab		X					
Treatment of blinatumomab		X			X		
Concomitant medication/therapy		X					X
Adverse Event		X					X

[1] If administration of blinatumomab will be stopped or terminated during the 5 cycles of administration period, 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.

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
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

3. Responsible Parties

Sponsor: Amgen Astellas BioPharma K.K., Japan

Collaboration partner: Astellas Pharmaceutical Inc., Japan

Contract Research Organization (CRO): [redacted]

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

4. Abstract

- Study Title

  All Case 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. [redacted]

- Research Question and Objectives
  - Primary Objectives
    The primary objectives of study are to 1) explore the risk factors of neurologic events, 2) evaluate the treatments taken against cytokine release syndrome (CRS) and 3) evaluate the incidence of each safety specification of the J-RMP (neurologic events, CRS, infections and pancreatitis) in the Japanese post-marketing real-world medical practice in patients receiving blinatumomab.
  - Secondary Objectives
    None
  - Hypothesis(es)/Estimation
    There is no hypothesis to be tested. Instead, the proposed survey will provide descriptive data on real-world 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

  All patients for whom blinatumomab is prescribed at medical institutions

- Summary of Patient Eligibility Criteria

  No exclusion criteria are applied.

- Follow-up

  From the beginning of blinatumomab administration to the end of cycle 5

- Variables
  - *Outcome Variable(s)*
    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 390 patients as the number of patients to investigate the risk factors of neurologic events.

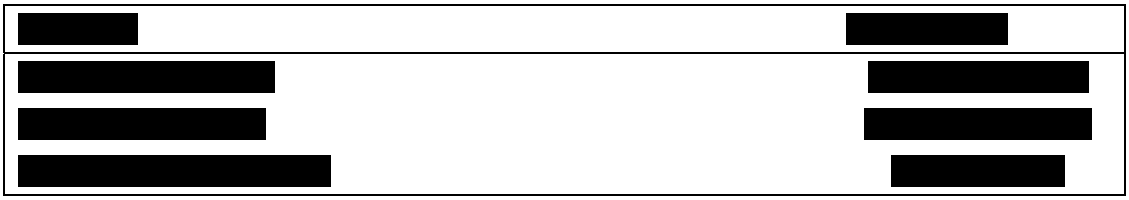
- Data Analysis

  Patient disposition, demographics and baseline characteristics will be summarized. The odds ratio and 95% confidence interval (CI) of high-risk population for low risk population in neurological events are calculated. Also, the treatment for CRS are tabulated. The number of patients and the incidence rates are tabulated for each safety specifications and all adverse drug reactions during the survey.

5. Amendments and Updates

None

6. Milestones



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 use data of patients with relapsed or refractory B-precursor ALL has been conducted in Japan. [redacted]

7.3 Statistical Inference (Estimation or Hypothesis)

There is no formal hypothesis to be tested. Instead, the proposed survey will provide descriptive data on real-world 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 use of blinatumomab in Japan.

8.1 Primary

The primary objective of study are to 1) explore the risk factors of neurologic events, 2) evaluate the treatments taken against CRS and 3) evaluate the incidence of each safety specification of J-RMP in the Japanese post-marketing real-world medical practice in patients receiving blinatumomab..

[redacted]

[redacted]

[redacted]

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 in the post-marketing setting without comparator arm. Pharmaceuticals and medical devices agency (PMDA) instructed to implement an all-case PMS for blinatumomab as an approval condition because of orphan drug (limited Japanese cases in clinical trials). The surveillance was a drug use result survey to evaluate safety for treatment period (up to 5 cycles).

<All-case survey>

It is a survey that is conducted to collect information on all patients who have been treated with the product since its launch until a data from certain number of cases have been accumulated, and it is required for products that needs the background information of patients treated with the product as well as safety and effectiveness issues related to the product for reaffirming approval details and collecting information which is essential for proper use at the earliest possible stage, thoroughly. PMDA may instruct to implement an all-case survey as an approval condition when there is a very limited cases or even no cases existing in clinical trials in Japan and when there are any concerns about the pharmaceutical product regarding the occurrence of serious adverse drug reactions.

<Drug use result survey>

It is a survey to detect and confirm safety and effectiveness information in the real-world medical practice.

9.2 Setting and Study Population

All patients for whom blinatumomab is prescribed 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 therapy before concluding the contract with medical institutions, as well.

9.2.1 Study Period

Study Period: From blinatumomab launch date to when observation of all patients registered is completed (November 2018 to September 2022)

Enrollment Period: From blinatumomab launch date to when the approval condition for all-case survey is lifted (November 2018 to June 2024)

Once the achievement of the target enrollment number of patients is prospected, after it is confirmed based the information such as enrollment status that the target information can be collected, it will consult with PMDA and decide whether to switch to case registration that does not require collection of case report form (CRF). However, patient registration is continued until the approval condition for all-case survey is lifted, and the system that collects the CRF and obtains appropriate information can be maintained as necessary.

9.2.2 Selection and Number of Sites

About [redacted] medical institutions (all institutions using blinatumomab) [redacted] 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

All patients for whom blinatumomab is prescribed 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 administration will be collected as baseline data.

9.2.6 Study Follow-up

Each patient will be followed from the beginning of administration to the end of cycle 5.

If administration of blinatumomab will be stopped or terminated during the 5 cycles of administration period, 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 2 CRFs (vol.1 and vol.2) per a patient. Vol. 1 is used to collect data at baseline and from the beginning of administration to the end of cycle 2; vol. 2 is used to collect data from the beginning of cycle 3 to the end of cycle5. 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 (vol. 1 and 2).

9.3.2 Outcome Assessment

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, date of informed, start date of blinatumomab administration, reason for blinatumomab usage, experience of blinatumomab usage

Patient demographics and medical history: 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): 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 Electronic data capture (EDC) system and paper CRFs. Standardized error check program is installed in EDC system and generates alerts automatically. 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

Of the events which have been set as safety specification, neurologic events are shown to have the association with blinatumomab and are serious events due to which some patients have died. Thus, the targeted number of patients was set focusing on neurologic events. It have been reported that 2 to 19% of patients with ALL are “patients with a current or history of central nervous system lesions”, who are considered to be one of the high-risk populations. Moreover, in the pooled of blinatumomab clinical trials (20130265 study, 00103311 study, 20120216 study and MT103-205 study), the incidence of neurologic events was 58.6% (258/440). Based on the above information, the ratio of high-risk population and low-risk population in patients who received blinatumomab treatment after marketing was assumed to be 1:9, the incidence of neurologic events in the low-risk population was assumed to be 55%. Under this assumption, given that the odds ratio of high-risk population to low-risk population is 3.0, 390 patients will be required to ensure the power of 80% using a test with two-sided significance level of 5%.

Based on the above, the planned number of patients in this survey was set to 390 patients as the number of patients to investigate the risk factors of neurologic events.

Also, in the pooled of blinatumomab clinical trials (20130265 study, 00103311 study, 20120216 study and MT103-205 study), the incidence of CRS and CRS-related events was 18.9% (83/440), and the incidence of infection events was 60.0% (264/440). Assuming that the true incidence of CRS and CRS-related events is 18.9% and the true incidence of infection is 60.0%, when 390 patients are collected, it is possible to collect 61 patients and 218 patients respectively with 95% confidence.

Furthermore, in the pooled of blinatumomab clinical trials (20130265 study, 00103311 study, 20120216 study and MT103-205 study), the incidence of pancreatitis events was 0.5% (2/440). Assuming that the true incidence of pancreatitis events is 0.5%, when 390 patients are collected, it is possible to collect 1 patient with 85% confidence.

Base on the above, it is considered that the incidence of CRS and infections can be investigated, and the treatments taken against CRS can be evaluated. On the other hand, for pancreatitis, information on the cases that have observed is surely collected and the incidence is evaluated.

9.6 Data Management

Data collection is conducted by using a validated EDC and eCRF system, developed by an external service provider, Fujitsu FIP, Tokyo, Japan, and paper CRF.

Data management is conducted by another external service provider, EPS Corporation, Tokyo, Japan 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 odds ratio and 95% CI of high-risk population for low risk population in neurological events are calculated. Also, the treatment for CRS are tabulated. The number of patients and the incidence rates are tabulated for each safety specifications and all 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, Tokyo, Japan 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. The odds ratio and 95% CI of high-risk population for low risk population in neurological events are also calculated.

9.7.2.2 Missing or Incomplete Data and Lost to Follow-up

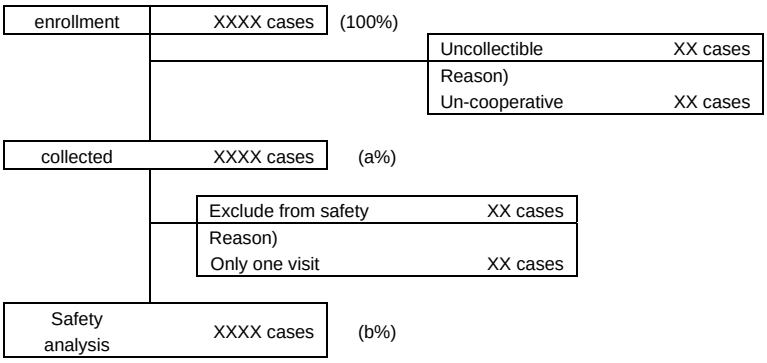
Participating investigators (physicians) and co-medicals are requested to make an effort to provide as complete information as possible through CRF. It is assumed that blinatumomab prescriptions would typically be started and patients observed at hospitals with experts of oncology. The rate of lost to 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 odds ratio and 95% CI of high-risk population for low risk population in neurological events are calculated. Also, the treatment for CRS are tabulated. The number of patients and the incidence rates are tabulated for each safety specifications and all 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 through the use of EDC 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.

Information bias and confounding cannot be excluded.	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 in charge of day-to-day survey operation will check incoming safety information (adverse events, use in pregnant/lactating women) on EDC 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 observation study period (from start of administration to final study contact). The investigator is responsible for ensuring that all safety events they become aware of during study period, are recorded in the patient's appropriate study documentation. Safety events must be submitted as individual case safety reports to Amgen Astellas BioPharma K.K. via the Safety Reporting Forms provided by the Safety Department of Amgen Astellas BioPharma K.K. promptly.

If the EDC system is unavailable to the site staff to report the adverse event, the information is to be reported to Amgen Astellas BioPharma K.K. via an Adverse Event Contingency Report Form. When the first notification of an Adverse Event is reported to Amgen Astellas BioPharma K.K. via the Adverse Event Contingency Report Form, the data must be entered into the EDC system when the system is again available.

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.

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 has to 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. and Amgen 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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16. Appendices

Appendix A. List of Stand-alone Documents

Not Applicable

Appendix B. ENCePP Checklist for Study Protocols

Study title:
All Case 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)	☒	☐	☐	9.1
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?	☐	☐	☒	
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)

AMGEN Study # XXXXXXXX AMG XXX	**Electronic Adverse Event Contingency Report Form** For Restricted Use

Reason for reporting this event via fax

The Clinical Trial Database (eg. Rave):

☐ Is not available due to internet outage at my site
☐ Is not yet available for this study
☐ Has been closed for this study

<<For completion by COM/Study manager/Author prior to providing to sites: SELECT OR TYPE IN A FAX#>>

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

Subject ID Number	Age at event onset	Sex	Race	If applicable, provide End of Study date
		☐F ☐M		

If this is a follow-up to an event reported in the **EDC system (eg, Rave)**, provide the adverse event term: _____
and start date: Day ____ Month _____ Year _____

3. ADVERSE EVENT

Provide the date the Investigator became aware of this information: Day____ Month____ Year____

Adverse Event diagnosis or syndrome If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report *List one event per line. If event is fatal, enter the cause of death. Entry of "death" is not acceptable, as this is an outcome.*	Date Started Day Month Year	Date Ended Day Month Year	Check only if event occurred before first dose of drug under study	Is event serious?	If serious, enter Serious Criteria code *(see codes below)*	Relationship Is there a reasonable possibility that the Event may have been caused by Amgen drug under study or an Amgen device used to administer the Amgen drug under study?								Outcome of Event -Resolved -Not resolved -Fatal -Unknown	Check only if event is related to study procedure eg, biopsy
						<drug/device> No✓	<drug/device> Yes✓	<drug/device> No✓	<drug/device> Yes✓	<drug/device> No✓	<drug/device> Yes✓	<drug/device> No✓	<drug/device> Yes✓		
				☐Yes ☐No											
				☐Yes ☐No											
				☐Yes ☐No											

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 medically important serious event

4. Was subject hospitalized or was a hospitalization prolonged due this event? ☐No ☐Yes If yes, please complete all of Section 4

Date Admitted Day Month Year	Date Discharged Day Month Year

AMGEN Study # XXXXXXXX AMG XXX	**Electronic Adverse Event Contingency Report Form** For Restricted Use

Site Number	Subject ID Number

5. Was drug under study administered/taken prior to this event? ☐No ☐Yes If yes, please complete all of Section 5

Amgen Drug/Amgen Device:		Date of Initial Dose Day Month Year	Prior to, or at time of Event Date of Dose Day Month Year	Dose	Route	Frequency	Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld	Lot # and Serial #
<<Drug/Device>>	☐ blinded ☐ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
<< Drug/Device>>	☐ blinded ☐ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

6. CONCOMITANT MEDICATIONS (eg, chemotherapy) Any Medications? ☐ No ☐ Yes If yes, please complete:

Medication Name(s)	Start Date Day Month Year	Stop Date Day Month Year	Co-suspect No✓	 Yes✓	Continuing No✓	 Yes✓	Dose	Route	Freq.	Treatment Med No✓	 Yes✓

7. RELEVANT MEDICAL HISTORY ***(include dates, allergies and any relevant prior therapy)***

8. RELEVANT LABORATORY VALUES ***(include baseline values)*** Any Relevant Laboratory values? ☐ No ☐ Yes If yes, please complete:

Test												
Date Day Month Year	Unit											

9. OTHER RELEVANT TESTS ***(diagnostics and procedures)*** Any Other Relevant tests? ☐ No ☐ Yes If yes, please complete:

Date Day Month Year	Additional Tests	Results	Units

AMGEN Study # XXXXXXXX AMG XXX	**Electronic Adverse Event Contingency Report Form** For Restricted Use

Site Number	Subject ID Number

10. CASE DESCRIPTION ***(Provide narrative details of events listed in section 3)*** Provide additional pages if necessary. For each event in section 3, where relationship=Yes, please provide rationale.

Signature of Investigator or Designee -	Title	Date
I confirm by signing this report that the information on this form, including seriousness and causality assessments, is being provided to Amgen by the investigator for this study, or by a Qualified Medical Person authorized by the investigator for this study.		

Appendix D. Additional Safety Reporting Information

Not Applicable

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