

**Title: Long-term Follow-up of Adult Philadelphia Chromosome-negative Acute Lymphoblastic Leukemia Relapsed Refractory Patients Enrolled in Study 00103311**

Amgen Protocol Number Blinatumomab 20180138

Study Sponsor: Amgen Inc  
One Amgen Center Drive  
Thousand Oaks, California 91320  
United States  
Phone: +1-805-447-1000  
Fax: +1-805-480-4978

Department: Center for Observational Research  
Therapeutic Area: Oncology  
Key Sponsor Contact: PPD [REDACTED]  
Amgen, Inc  
Phone: PPD [REDACTED]  
Email: [REDACTED]

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This document contains confidential information of Amgen Inc.

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The information in this document cannot be used for any purpose other than the evaluation or conduct of the research without the prior written consent of Amgen Inc.

**If you have questions regarding how this document may be used or shared, call the Amgen Medical Information number: Amgen's general number in the US (1-805-447-1000).**

**Investigator's Agreement**

I have read the attached protocol entitled "Long-term follow-up of adult Philadelphia chromosome-negative acute lymphoblastic leukemia relapsed refractory patients enrolled in Study 00103311", dated 29 August 2019, and agree to abide by all provisions set forth therein.

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

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**Signature**

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**Name of Investigator**

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**Date (DD Month YYYY)**

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1. **AMENDMENTS AND UPDATES**

Amendment No.	Date	Section of Protocol	Amendment	Reason
1	29 August 2019			<a href="#">See summary of changes</a>

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2. LIST OF ABBREVIATIONS

Abbreviations	Definition of the Terms
ALL	Acute lymphoblastic leukemia
BITE®	Bispecific T-cell engagers
CTCAE	Common Terminology Criteria for Adverse Events
EDC	electronic data capture
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICH	International Council on Harmonisation
ICJME	International Committee of Medical Journal Editors
IEC	Independent ethics committee
IRB	Institutional review board
OS	overall survival
Ph-	Philadelphia chromosome-negative
PRAC	Pharmacovigilance Risk Assessment Committee

### 3. BACKGROUND AND RATIONALE

Acute lymphoblastic leukemia (ALL) is a hematologic malignancy characterized by the proliferation of immature and abnormal lymphoid cells in the bone marrow and peripheral blood. B-precursor ALL is an aggressive malignant disease. Blinatumomab (Blincyto®) belongs to a class of bispecific antibody constructs called bispecific T-cell engagers (BITE®). This T-cell-mediated target-specific killing is the therapeutic mechanism of action of blinatumomab (Löffler et al, 2000; Wolf et al, 2005). Blinatumomab specifically targets cells that express CD19, a marker solely expressed by B cells, including B-precursor ALL cells. Due to its unique ability to redirect T-cells via CD3 towards a CD19<sup>+</sup> tumor cell lysis, blinatumomab can elicit repeated target cell elimination by cytotoxic T-cells and a polyclonal response of previously primed CD4<sup>+</sup> and C8<sup>+</sup> T-cells.

Blinatumomab received accelerated approval from the Food and Drug Administration (FDA) for the treatments of adults and children with relapsed/refractory Philadelphia chromosome-negative (Ph-) B-cell ALL in 2014: this was converted to full approval in 2017. The European Medicines Agency (EMA) granted conditional approval to blinatumomab for the treatment of adults with relapsed/refractory Ph- B-cell ALL in November 2015, with conditional approval converted to full approval in June 2018 based on the results of a Phase III randomized trial that demonstrated longer median overall survival (OS: 7.7 months versus 4.0 months) in patients treated with blinatumomab compared to standard of care chemotherapy (Kantarjian et al, 2017). This Phase III study was terminated early due to efficacy of meeting the primary endpoint of OS. As a part of the approval of the relapsed/refractory indication in the European Union (EU), the Pharmacovigilance Risk Assessment Committee (PRAC) requested Amgen conduct an additional final OS assessment of patients that were alive at last follow-up in the Phase III trial.

The purpose of this study (20180138) is to conduct a one-time **survival status** assessment on patients that were alive **at the last follow-up and still participating** in the Phase III Study 00103311 **when the study ended earlier than planned**. At the last follow-up, there were 108 patients alive **and still participating**. The data collection/source for collecting **survival** status to be utilized will be the sites/patients from existing blinatumomab study number 00103311. The single output from this study effort will be to generate an updated **OS** Kaplan-Meier probability estimates and Kaplan-Meier plot. These results will be subject of a brief updated study report to be sent to the EMA PRAC.

#### 4. OBJECTIVES

The objective of this study is to update the OS Kaplan-Meier probability estimates and the plot last reported in the randomized Phase 3 blinatumomab 00103311 study.

#### 5. STUDY POPULATION/SAMPLE SIZE/STATISTICAL ANALYSES PLANS

##### 5.1 Study Population and Methods

The population in this study will be the patients who were enrolled originally in the 00103311 trial (A Phase 3, Randomized, Open Label Study Investigating the Efficacy of the BiTE Antibody Blinatumomab Versus Standard of Care Chemotherapy in Adult Subjects With Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia (ALL) (TOWER Study)). This study (20180138) will be a **one-time** follow-up on patients that were **alive and still participating in the Phase III Study 00103311** at the end of the 00103311 study results being reported. **This study will assess OS and, for those patients in the standard of care arm, additionally collect information on blinatumomab use after the trial period in the 00103311 study.**

A follow-up will occur on the remaining alive patients at last follow-up. The sites from which the subjects were enrolled **will ascertain survival status and for those patients in the standard of care arm, any blinatumomab use following the end of the 00103311 study using medical charts, national registries, patient contact, next of kin contact, or other available means per local regulation. In those instances, when informed consent is required, at least 3 attempts to contact the subject will be made by the sites.** The **survival** status of each patient will be assessed as either alive or deceased with a corresponding date of **the status** check or death, as applicable. For subjects where **survival** status cannot be ascertained beyond the date of last follow-up from the 00103311 study, **ie, at least 3 contact attempts are made and no updated survival status can be collected, the subject will be marked as lost to follow-up at the last follow-up date in the 00103311 study. Patients in the standard of care arm will be reviewed or inquired for blinatumomab use. Analysis for OS will be done using randomized treatment assignment (ie, intent-to-treat principle). An additional sensitivity analysis will be done to adjust for the drop-in effect of standard of care patients switching to blinatumomab.**

##### 5.2 Sample Size

The number of patients **alive and still participating** at the last follow-up in the 00103311 study was 108 subjects. An earnest effort to ascertain **survival** status on all subjects will be made. It is unknown how many subjects will have additional follow-up.

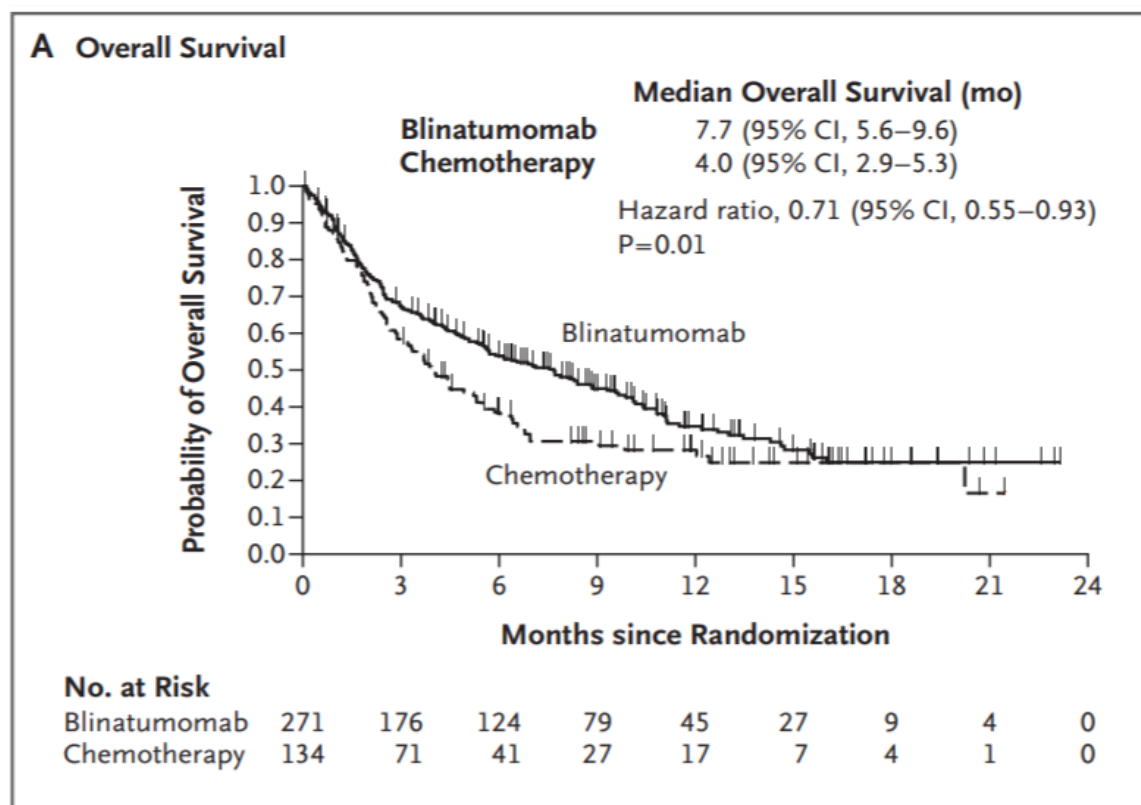
### 5.3 Outcome Assessment

The endpoint in this study is OS. Overall survival is defined as the time from randomization to the blinatumomab arm or investigator choice chemotherapy arm (the 2 treatment arms in the 00103311 trial) until death or censoring at the last date known to be alive. Updated OS Kaplan-Meier probability estimates and an updated Kaplan-Meier plot using all randomized subjects from 00103311 trial will capture the additional follow-up survival data for those subjects that were alive and still participating at the end of the 00103311 study.

### 5.4 Statistical Analysis

For the analysis, OS Kaplan-Meier probabilities and plot last reported in the 00103311 study will be updated to provide an **updated** table of survival probabilities at defined time points (3 months, 6 months, 12 months, 18 months, 24 months, 36 months, 60 months) with relevant 95% confidence intervals and an **updated** plot which also adds an elongated x-axis of up to 60 months. For reference, the OS plot presented in the published study ([Kantarjian et al, 2017](#)) is presented below:

**Figure 1. Probability of Overall Survival in the Two Groups (blinatumomab or chemotherapy). Overall Survival was Calculated as the Time From Randomization to Death From any Cause. The Median Duration of Follow-up for Overall Survival was 11.7 Months in the Blinatumomab Group and 11.8 Months in the Chemotherapy Group**



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A sensitivity analysis will be conducted assessing whether patients in the standard of care arm who had blinatumomab use during the 00103311 trial and after the study's termination had an effect on the survival outcomes of this group.

## **6. PROTECTION OF HUMAN SUBJECTS**

This study will comply with all applicable laws regarding subject privacy. No direct **patient** contact or collection of additional data **from patients** will occur beyond **survival** status assessment **and blinatumomab use for patients in the standard of care arm after the conclusion of the 00103311 trial** by the sites. Study results will be in tabular form and aggregate analyses that omits subject identification. Any publications and reports will not include subject identifiers.

### **6.1 Informed Consent**

Where an informed consent is required per local regulations, an initial sample informed consent form is provided for the investigator to prepare the informed consent document to be used at his or her site. Updates to the sample informed consent form are to be communicated formally in writing from the Amgen Study Manager to the investigator. The written informed consent form is to be prepared in the language(s) of the potential patient population.

Before a subject's participation in the study, the investigator will explain to the subject, or his/her legally authorized representative, the aims, methods, anticipated benefits, and potential hazards of the study, and answer all questions regarding the study.

The acquisition of informed consent is to be documented in the subject's medical records, and the informed consent form is to be signed and personally dated by the subject or a legally acceptable representative and by the person who conducted the informed consent discussion. The original signed informed consent form is to be retained in accordance with institutional policy, and a copy of the informed consent form(s) must be provided to the subject or the subject's legally authorized representative.

If local regulations do not require an informed consent to be signed but mandate that the subject is notified about the study, the investigator should document the notification process in the subject's medical record.

## **6.2 Institutional Review Board/Independent Ethics Committee (IRB/IEC)**

A copy of the protocol, proposed ICF, where applicable, other written patient information, must be submitted to the IEC or other relevant ethical review board for written approval. A copy of the written approval of the protocol and ICF, where applicable, must be received by Amgen before study can be executed.

The investigator must submit and, where necessary, obtain approval from the IEC or other relevant ethical review board for all subsequent protocol amendments and changes to the informed consent document, as applicable. The investigator is to notify the IEC or other relevant ethical review board of deviations from the protocol or serious adverse event(s) occurring at the site and other adverse event reports received from Amgen, in accordance with local procedures and statutes.

The investigator is responsible for obtaining other relevant ethical review board approval/renewal throughout the duration of the study. Copies of the investigator's reports, where applicable by local regulations and the IEC or other relevant ethical review board continuance of approval must be sent to Amgen.

## **6.3 Subject Confidentiality**

The investigator must ensure that the subject's confidentiality is maintained for documents submitted to Amgen. Subject will be assigned a unique identifier by the sponsor. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred. For serious adverse events reported to Amgen, subjects are to be identified by their unique subject identification number, initials (for faxed reports, in accordance with local laws and regulations), and age (in accordance with local laws and regulations).

Documents that are not submitted to Amgen (eg, signed informed consent forms) are to be kept in confidence by the investigator, except as described below. In compliance with governmental regulations/International Council on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB/IEC direct access to review the subject's original medical records for verification of data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform

and obtain the consent of the subject to permit such individuals to have access to his/her study-related records, including personal information.

#### **6.4 Subjects Decision to Withdraw**

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

Withdrawal of consent for a study means that the subject does not wish to or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in the analysis of the study and, where permitted, publicly available data can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate steps for withdrawal of their consent from the study.

### **7. COLLECTION, RECORDING, AND REPORTING OF SAFETY INFORMATION AND PRODUCT COMPLAINTS**

#### **7.1 Definition of Safety Events**

##### **7.1.1 Adverse Events**

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

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

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

It is the investigator's responsibility to evaluate whether an adverse event is related to an Amgen product prior to reporting the adverse event to Amgen.

##### **7.1.2 Serious Adverse Events**

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

- is fatal
- is life threatening (places the subject at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity

- is a congenital anomaly/birth defect
- is an “other 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 subject or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events could include allergic bronchospasm, convulsions, and blood dyscrasias, drug-induced liver injury, events that necessitate an emergency room visit, outpatient surgery, or other events that require other urgent intervention.

#### 7.1.3 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).

#### 7.1.4 Product Complaints

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

Drug(s) or device(s) includes investigational product.

Product complaints of blinatumomab will be reported.

## 7.2 Safety Collection, Recording and Submission to Amgen Requirements

This study is collecting retrospective and in some cases, prospective information.

**Retrospective Observation Period (time period from final study contact on the 00103311 study to subject/next of kin contact for 20180138 study data collection):** this study is analyzing secondary data from medical charts or national registries. The safety outcomes of death as listed in [Section 5.3](#) will be documented and analyzed in this study. These will be reported in aggregate in the final study report as an update to the OS probabilities reported in the 00103311 study. See [Section 5.3](#) for safety outcomes and definitions. Submission of safety outcomes as individual safety reports to Amgen is not required. Safety events suspected to be related to any medicinal product should be reported to the local authority in line with the local country requirements.

**Prospective Observation Period (time period from when a subject [or next of kin] is contacted to the date of final study contact):** When an ICF is required to collect data, the study may collect prospective information during interactions with subjects or next of kin. All safety events (adverse events, product complaints, and other safety findings) considered to have occurred following subject exposure to blinatumomab will be collected from the signing of the informed consent to the final study contact. The Investigator is responsible for ensuring that all safety events they become aware of during study period, are recorded in the subject's appropriate study documentation. Those safety events which are considered serious must also be submitted as individual safety reports to Amgen Safety via the applicable Amgen Safety Reporting Form (paper or electronic form) within 1 business day of Investigator awareness. Non-serious adverse events must be reported in an expeditious manner, not to exceed 15 calendar days of Investigator awareness.

Safety events that are suspected to be related to any medicinal product where there is no exposure to blinatumomab should be reported to the local authority in line with the local country requirements.

If the electronic data capture (EDC) system is unavailable to the site staff, the adverse event which is considered serious must still be reported to Amgen within 1 business day of the Investigator's awareness, using the paper Adverse Event Contingency Report Form. Non-serious adverse events must be reported in an

expeditious manner, not to exceed 15 calendar days of Investigator awareness. For EDC studies where the first notification of an Adverse Event is reported to Amgen via the Adverse Event Contingency Report Form, the data must be entered into the EDC system when the system is again available.

See [Appendix A](#) for sample Safety Report Form(s), [Appendix B](#) for Additional Safety Reporting Information regarding the adverse event grading scale used in this study, and [Appendix C](#) 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.

#### 7.2.1 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 48 hours.

Information will be recorded on the Pregnancy Notification Worksheet (see [Appendix C](#)). The worksheet must be submitted to Amgen Safety within 1 business day of learning of a subject's pregnancy. (Note: Investigator is not required to provide any information on the Pregnancy Notification Worksheet that violates the country or regions local privacy laws).

After receipt of the Pregnancy Notification Worksheet, Amgen Safety will provide Investigator with an authorisation form and questionnaire to collect additional information. After obtaining the female subject's signed authorization for release of pregnancy and infant health 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 48 hours of the blinatumomab. This information will be forwarded to Amgen 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 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 as a pregnancy exposure case.

If the outcome of the pregnancy meets a criterion for immediate classification as a serious adverse event (eg, 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 or Were Pregnant at the Time of Enrollment**

In the event a male subject fathers a child following exposure to blinatumomab and for an additional 48 hours after discontinuing blinatumomab the information will be recorded on the Pregnancy Notification Worksheet. The worksheet (see [Appendix C](#)) must be submitted to Amgen Safety within 1 business day of the Investigator awareness of the pregnancy. (Note: Investigator is not required to provide any information on the Pregnancy Notification Worksheet that violates the country or regions local privacy laws).

After receipt of the Pregnancy Notification Worksheet, Amgen Safety will provide Investigator with an authorisation form and questionnaire to collect additional information. The Investigator will attempt to obtain a signed authorization for release of pregnancy and infant health information directly from the pregnant female partner to obtain additional pregnancy information.

After obtaining the female partner's signed authorization for release of pregnancy and infant health 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 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 Global Patient Safety regardless of fetal status (presence or absence of anomalies) or indication for procedure.

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### Collection of Lactation Information

Investigator will collect lactation information on any female subject who breastfeeds while taking blinatumomab through 48 hours.

Information will be recorded on the Lactation Notification Worksheet (see [Appendix C](#)) and submitted to Amgen Safety within 1 business day of the Investigator's awareness.

With the female subjects signed authorization for release of mother and infant health information, the Investigator will collect mother and infant health information and complete the lactation questionnaire on any female subject who breastfeeds while taking blinatumomab through 48 hours after discontinuing blinatumomab.

#### 7.2.2 Safety Reporting Requirement to Regulatory Bodies

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

## 8. ADMINISTRATIVE AND LEGAL OBLIGATIONS

### 8.1 Protocol Amendments and Study Termination

Amgen may amend the protocol at any time. If Amgen amends the protocol, written agreement from the Investigator must be obtained where applicable per local governing law and/or regulations. The IRB/IEC or other relevant ethical review board must be informed of all amendments and give approval. The Investigator must send a copy of the approval letter from the IRB/IEC or other relevant ethical review board to Amgen.

Amgen reserves the right to terminate the study at any time. Both Amgen and the Investigator reserve the right to terminate the Investigator's participation in the study according to the contractual agreement. The Investigator is to notify the IRB/IEC or other relevant ethical review board in writing of the study's completion or early termination and send a copy of the notification to Amgen.

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## 9. PUBLICATION INTENT

Results of this study is intended to be submitted to regulatory agency EMA PRAC to fulfill a commitment as part of approval for blinatumomab in EU countries.

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

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

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

## 10. REFERENCES

Kantarjian H, Stein A, Gökbuget N, et al. Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia. *NEJM*. 2017;376(9):836-847.

Löffler A, Kufer P, Lutterbüse R, et al. A recombinant bispecific single-chain antibody, CD19 x CD3, induces rapid and high lymphoma-directed cytotoxicity by unstimulated T lymphocytes. *Blood*. 2000;95:2098-2103.

NCCN Practice Guidelines in Oncology, Acute Lymphoblastic Leukemia. NCCN.org Version 1.0 2014.

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.

11. APPENDICES

## Appendix A. Sample Safety Reporting Form(s)

### Completion Instructions - Electronic Adverse Event Contingency Report Form (For use for Observational Research Studies using Electronic Data Capture [EDC])

NOTE: This form is to be used under restricted conditions outlined on page 1 below. If you must fax an event report to Amgen, you must also enter that event into the EDC system (eg, Rave) when it becomes available.

#### General Instructions

The protocol will provide instruction on what types of events to report for the study. This form is to be used ONLY to report events that must be captured in the Amgen safety database. \*Indicates a mandatory field.

What to report on this form:

- All adverse events associated with the Amgen drug irrespective of causal relationship of the event to the study drug or seriousness, unless instructed differently by the protocol
- The following safety findings are to be reported on this form as events regardless of association with an adverse event
  - Medication errors, overdose, whether accidental or intentional, misuse, or abuse, involving the Amgen product
  - 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)
  - Product complaint ONLY IF ASSOCIATED WITH AN ADVERSE EVENT

The following should not be reported on this form and should be reported via the normal process set up for the study

- Pregnancy and lactation reports
- Product complaints without association with an AE

#### 1. Site Information

**Site Number\*** – Enter your assigned site number for this study

**Investigator\*, Country\*, Reporter\*, Phone No., and Fax No.** – Enter information requested

#### 2. Subject Information

**Subject ID Number\*** – Enter the entire number assigned to the subject

**Age at event onset, Sex, and Race** – Enter the subject's demographic information

**End of Study date** – If the subject has already completed the study or terminated the study early, enter the End of Study date

*If you are submitting follow-up information to a previous report, provide the adverse event term for the previous report as well as the start date for the initial event.*

#### 3. Adverse Event

**Provide the date the Investigator became aware of this Information**

**Adverse Event Diagnosis or Syndrome\*** –

- If the diagnosis is known, it should be entered. Do not list all signs/symptoms if they are included in the diagnosis.
- If a diagnosis is not known, the relevant signs/symptoms should be entered.
- If the event is fatal, the cause of death should be entered and autopsy results should be submitted, when available.

**Date Started\*** – Enter date the adverse event first started rather than the date of diagnosis or hospitalization. For serious events, the start date is the date the event started, not the date on which the event met serious criteria. **This is a mandatory field.**

**Date Ended** – Enter date the adverse event ended. For serious events, this is not the date when the event no longer met serious criteria. If the event has not ended at the time of the initial report, a follow-up report should be completed when the end date is known. If the event is fatal, enter the date of death as the end date.

**Is event serious?\*** – Indicate Yes or No. **This is a mandatory field.**

**Serious Criteria Code\*** – **This is a mandatory field for serious events.** Enter all reasons why the reported event has met serious criteria:

Immediately life-threatening: Use only if the subject was at immediate risk of death from the event as it occurred.

Emergency treatment is often required to sustain life in this situation. Protocol specified hospitalizations are exempt.

**At the top of Page 2, provide your Site Number and the Subject ID Number in the designated section.**

#### 4. IP Administration including Lot # and Serial # when known / available.

- If the investigator decides an event should be reported in an expedited manner, but it does not meet other serious

**Completion Instructions - Electronic Adverse Event Contingency Report Form  
(for use for Studies using Electronic Data Capture (EDC))**

Note, this form is to be used under restricted conditions outlined on page 1 of the form. If you must fax an event report to Amgen, you must also enter that event into the EDC system (eg, Rave) when it becomes available.

criteria, "Other Medically Important Serious Event" may be the appropriate serious criterion.

**Relationship to Amgen drug under study\*** – The Investigator must determine and enter the relationship of the event to the Amgen drug under study at the time the event is initially reported. **This is a mandatory field.**

**Relationship to Amgen device\*** – The Investigator must determine and enter the relationship of the event to the Amgen device (e.g. prefilled syringe, auto-injector) at the time the event is initially reported. **If the study involves an Amgen device, this is a mandatory field. This question does not apply to non-Amgen devices used in the study (e.g. heating pads, infusion pumps)**

**Outcome of Event** – Enter the code for the outcome of the event at the time the form is completed if outcome is known.

Resolved – End date is known

➢ Not resolved / Unknown – End date is unknown

➢ Fatal – Event led to death

**5. Hospitalization**

If the subject was hospitalized, enter admission and discharge dates. Hospitalization is any in-patient hospital admission for medical reasons, including an overnight stay in a healthcare facility, regardless of duration. A pre-existing condition that did not worsen while on study which involved a hospitalization for an elective treatment, is not considered an adverse event. Protocol specified hospitalizations are exempt.

**At the top of Page 2, provide your Site Number and the Subject ID Number in the designated section.**

**6. Amgen drug Under Study Administration including Lot # and Serial # when known / available.**

**Initial Start Date** – Enter date the product was first administered, regardless of dose.

**Date of Dose Prior to or at the time of the Event** – Enter date the product was last administered prior to, or at the time of, the onset of the event.

**Dose, Route, and Frequency at or prior to the event** – Enter the appropriate information for the dose, route and frequency at, or prior to, the onset of the event.

**Action Taken with Product** – Enter the status of the product administration.

**7. Concomitant Medications**

Indicate if there are any medications.

**Medication Name, Start Date, Stop Date, Dose, Route, and Frequency** – Enter information for any other medications the subject is taking. Include any study drugs not included in section 5 (Product Administration) such as chemotherapy, which may be considered co-suspect.

**Co-suspect** – Indicate if the medication is co-suspect in the event

**Continuing** – Indicate if the subject is still taking the medication

**Event Treatment** – Indicate if the medication was used to treat the event

**8. Relevant Medical History**

Enter medical history that is relevant to the reported event, not the event description. This may include pre-existing conditions that contributed to the event allergies and any relevant prior therapy, such as radiation. Include dates if available.

**9. Relevant Laboratory Tests**

Indicate if there are any relevant laboratory values.

For each test type, enter the test name, units, date the test was run and the results.

**10. Other Relevant Tests**

Indicate if there are any tests, including any diagnostics or procedures.

For each test type, enter the date, name, results and units (if applicable).

**At the top of Page 3, provide your Site Number and the Subject ID Number in the designated section.**

**11. Case Description**

**Describe Event** – Enter summary of the event. Provide narrative details of the events listed in section 3. Include any therapy administered, such as radiotherapy; (excluding medications, which will be captured in section 6). If necessary, provide additional pages to Amgen.

**Complete the signature section at the bottom of page 3 and fax the form to Amgen.** If the reporter is not the investigator, designee must be identified on the Delegation of Authority form.

A Study # 20180138 AMG 103	<b>Electronic Adverse Event Contingency Report Form</b> <u>For Restricted Use</u>
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<b>Reason for reporting this event via fax</b> <b>The Clinical Trial Database (eg. Rave):</b> <input type="checkbox"/> Is not available due to internet outage at my site <input type="checkbox"/> Is not yet available for this study <input type="checkbox"/> Has been closed for this study
--

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

<b>1. SITE INFORMATION</b>			
Site Number	Investigator	Country	
Reporter	Phone Number ( )	Fax Number ( )	

<b>2. SUBJECT INFORMATION</b>				
Subject ID Number	Age at event onset	Sex <input type="checkbox"/> F <input type="checkbox"/> M	Race	If applicable, provide End of Study date

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 \_\_\_\_

<b>3. ADVERSE EVENT</b>															
Provide the date the Investigator became aware of this information: Day _____ Month _____ Year _____															
Adverse Event <b>diagnosis</b> or syndrome If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report <i>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.</i>	Date Started	Date Ended	Check only if event occurred before first dose of drug under study	Is event serious?	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	Check only if event is related to study procedure eg, biopsy							
	Day Month Year	Day Month Year	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No	<table border="1" style="width:100%; border-collapse: collapse;"> <tr> <td style="text-align: center;">&lt;drug/device &gt;</td> <td style="text-align: center;">&lt;drug/device &gt;</td> <td style="text-align: center;">&lt;drug/device &gt;</td> <td style="text-align: center;">&lt;drug/device &gt;</td> </tr> <tr> <td style="text-align: center;">No/ Yes</td> <td style="text-align: center;">No/ Yes</td> <td style="text-align: center;">No/ Yes</td> <td style="text-align: center;">No/ Yes</td> </tr> </table>	<drug/device >	<drug/device >	<drug/device >	<drug/device >	No/ Yes	No/ Yes	No/ Yes	No/ Yes	Resolved Not resolved Fatal Unknown
<drug/device >	<drug/device >	<drug/device >	<drug/device >												
No/ Yes	No/ Yes	No/ Yes	No/ Yes												

Serious Criteria: 01 Fatal      03 Required/prolonged hospitalization      05 Congenital anomaly / birth defect  
 02 Immediately life-threatening      04 Persistent or significant disability /incapacity      06 Other medically important serious event

<b>4. Was subject hospitalized or was a hospitalization prolonged due this event?</b> <input type="checkbox"/> No <input type="checkbox"/> Yes If yes, please complete all of Section 4	
Date Admitted Day    Month    Year	Date Discharged Day    Month    Year

	Site Number	Subject ID Number
--	-------------	-------------------





## Appendix B. Additional Safety Reporting Information

### Adverse Event Severity Scoring System

For oncology studies, the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 is to be used. The CTCAE is available at the following location:

[http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/ctc.htm](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)

## Appendix C. Pregnancy and Lactation Notification Worksheets

Amgen Proprietary - Confidential

### AMGEN<sup>®</sup> Pregnancy Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): [svc-ags-in-us@amgen.com](mailto:svc-ags-in-us@amgen.com)

#### 1. Case Administrative Information

Protocol/Study Number: 20180138

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 age (at onset): \_\_\_\_\_ (in years)

#### 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 last menstrual period (LMP) mm\_\_\_\_/dd\_\_\_\_/yyyy\_\_\_\_  Unknown  N/A

Estimated date of delivery mm\_\_\_\_/dd\_\_\_\_/yyyy\_\_\_\_

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: \_\_\_\_\_

FORM-115199

Version 1.0

Effective Date: 24-Sept-2018

Amgen Proprietary - Confidential

**AMGEN** Lactation Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): [svc-ags-in-us@amgen.com](mailto:svc-ags-in-us@amgen.com)

1. Case Administrative Information				
Protocol/Study Number: <u>20180138</u>				
Study Design: <input type="checkbox"/> Interventional <input checked="" type="checkbox"/> Observational (If Observational: <input checked="" type="checkbox"/> Prospective <input type="checkbox"/> Retrospective)				
2. Contact Information				
Investigator Name _____		Site # _____		
Phone (____) _____	Fax (____) _____	Email _____		
Institution _____				
Address _____				
3. Subject Information				
Subject ID # _____		Subject age (at onset): <u>   </u> (in years)		
4. Amgen Product Exposure				
Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm ____/dd ____/yyy ____
Was the Amgen product (or study drug) discontinued? <input type="checkbox"/> Yes <input type="checkbox"/> No				
If yes, provide product (or study drug) stop date: mm ____/dd ____/yyy ____				
Did the subject withdraw from the study? <input type="checkbox"/> Yes <input type="checkbox"/> No				
5. Breast Feeding Information				
Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? <input type="checkbox"/> Yes <input type="checkbox"/> No				
If No, provide stop date: mm ____/dd ____/yyy ____				
Infant date of birth: mm ____/dd ____/yyy ____				
Infant gender: <input type="checkbox"/> Female <input type="checkbox"/> Male				
Is the infant healthy? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown <input type="checkbox"/> 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: _____		

FORM-115201

Version 1.0

Effective Date: 24-Sept-2018

## Amendment 1.0

### Protocol Title: Long-term Follow-up of Adult Philadelphia Chromosome-negative Acute Lymphoblastic Leukemia Relapsed Refractory Patients Enrolled in Study 00103311

Amgen Protocol Number Blinatumomab 20180138

Amendment Date: 29 August 2019

#### Rationale:

This protocol is being amended to:

- Add Signature page (Investigator's Agreement), amendments and updates ([Section 1](#), AMENDMENTS AND UPDATES), and list of abbreviations ([Section 2](#), LIST OF ABBREVIATIONS) sections to the protocol
- Clarify language regarding data collection in [Section 5.1](#) (Study Population and Methods)
- Add section for safety outcome assessment ([Section 5.3](#), Outcome Assessment)
- Add language regarding sensitivity analysis to [Section 5.4](#) (Statistical Analysis)
- Add safety reporting language and applicable safety forms since study has changed to include primary and secondary data collection
- Add "Protection of Human Subjects" and "Administrative and Legal Obligations" sections to the protocol
- Make editorial and administrative changes for grammatical reasons as well as for internal consistency within the protocol.

**Description of Changes:**

[Section: Global](#)

**Change:** The Amgen global version date was changed from 25 January 2019 to **29 August 2019**

[Section: Global](#)

**Change:** Editorial, typographical, and formatting changes were made throughout the document.

[Section: Title Page](#)

**Replace:**

Key Sponsor Contact: **PPD**  
Amgen, Inc  
Phone: **PPD**  
Email: **PPD**

Date: 25 January 2019  
Version: 1

**With:**

Key Sponsor Contact: **PPD**  
Amgen, Inc  
Phone: **PPD**  
Email: **PPD**

Date: **29 August 2019**  
Version: **Amendment 1.0**

[Section: Title Page](#)

**Add:**

If you have questions regarding how this document may be used or shared, call the Amgen Medical Information number: Amgen's general number in the US (1-805-447-1000).

Section: [Investigator's Agreement](#) (new section)

Add:

**Investigator's Agreement**

I have read the attached protocol entitled "Long-term follow-up of adult Philadelphia chromosome-negative acute lymphoblastic leukemia relapsed refractory patients enrolled in Study 00103311", dated 29 August 2019, and agree to abide by all provisions set forth therein.

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

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Name of Investigator

\_\_\_\_\_  
Date (DD Month YYYY)

Section: [1. AMENDMENTS AND UPDATES](#) (new section)

Add:

**1. AMENDMENTS AND UPDATES**

Amendment No.	Date	Section of Protocol	Amendment	Reason
1	29 August 2019		See summary of changes	

Section: 2. LIST OF ABBREVIATIONS (new section)

Add:

## 2. LIST OF ABBREVIATIONS

Abbreviations	Definition of the Terms
ALL	Acute lymphoblastic leukemia
BITE®	Bispecific T-cell engagers
CTCAE	Common Terminology Criteria for Adverse Events
EDC	electronic data capture
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICH	International Council on Harmonisation
ICJME	International Committee of Medical Journal Editors
IEC	Independent ethics committee
IRB	Institutional review board
OS	overall survival
Ph-	Philadelphia chromosome-negative
PRAC	Pharmacovigilance Risk Assessment Committee

Section: 3. BACKGROUND AND RATIONALE, Paragraphs 2 and 3

Replace:

Blinatumomab received accelerated approval from the Food and Drug Agency (FDA) for the treatments of adults and children with relapsed/refractory Philadelphia chromosome negative (Ph-) B-cell ALL in 2014; this was converted to full approval in 2017. The European Medicines Agency (EMA) granted conditional approval to blinatumomab for the treatment of adults with relapsed/refractory Ph- B-cell ALL in November 2015, with conditional approval converted to full approval in June 2018 based on the results of a Phase III randomized trial that demonstrated longer median overall survival (OS: 7.7 months versus 4.0 months) in patients treated with blinatumomab compared to standard of care chemotherapy (Kantarjain et al 2017). This Phase III study was terminated early due to efficacy of meeting the primary endpoint of OS. As a part of the approval of the relapsed/refractory indication in the EU, the PRAC requested Amgen conduct an additional final overall survival assessment of patients that were alive at last follow-up in the Phase III trial.

The purpose of this study (20180138) is to conduct a one-time vital assessment on patients that were alive at last follow-up in the Phase III study 00103311. At the last follow-up, there were approximately 108 patients alive. The data collection/source for collecting vital status to be utilized will be the sites/patients from existing blinatumomab study number 00103311. The single output from this study effort will be to generate an updated overall survival Kaplan-Meier probability estimates and Kaplan-Meier plot. These results will be subject of a brief updated study report to be sent to the EMA PRAC.

**With:**

Blinatumomab received accelerated approval from the Food and Drug Administration (FDA) for the treatments of adults and children with relapsed/refractory Philadelphia chromosome negative (Ph-) B-cell ALL in 2014: this was converted to full approval in 2017. The European Medicines Agency (EMA) granted conditional approval to blinatumomab for the treatment of adults with relapsed/refractory Ph- B-cell ALL in November 2015, with conditional approval converted to full approval in June 2018 based on the results of a Phase III randomized trial that demonstrated longer median overall survival (OS: 7.7 months versus 4.0 months) in patients treated with blinatumomab compared to standard of care chemotherapy (Kantarjian et al, 2017). This Phase III study was terminated early due to efficacy of meeting the primary endpoint of OS. As a part of the approval of the relapsed/refractory indication in the European Union (EU), the Pharmacovigilance Risk Assessment Committee (PRAC) requested Amgen conduct an additional final OS assessment of patients that were alive at last follow-up in the Phase III trial.

The purpose of this study (20180138) is to conduct a one-time **survival status** assessment on patients that were alive **at the last follow-up and still participating** in the Phase III Study 00103311 **when the study ended earlier than planned**. At the last follow-up, there were 108 patients alive **and still participating**. The data collection/source for collecting **survival** status to be utilized will be the sites/patients from existing blinatumomab study number 00103311. The single output from this study effort will be to generate an updated **OS** Kaplan-Meier probability estimates and Kaplan-Meier plot. These results will be subject of a brief updated study report to be sent to the EMA PRAC.

Section: 4. OBJECTIVES

**Delete:**

The objective of this study is to update the ~~overall survival (OS)~~ Kaplan-Meier probability estimates and the plot last reported in the randomized Phase 3 blinatumomab 00103311 study.

Section: 5.1 Study Population and Methods, Title and paragraphs 1 and 2

**Replace:**

**5.1 Study Population And Methods**

The population in this study will be the patients who were enrolled originally in the 00103311 trial (A Phase 3, Randomized, Open Label Study Investigating the Efficacy of the BiTE Antibody Blinatumomab Versus Standard of Care Chemotherapy in Adult Subjects With Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia (ALL) (TOWER Study)). This study will be a single additional vital status follow-up on patients that were alive at the end of the 00103311 study results being reported.

A final follow-up will occur on the remaining alive patients at last follow-up. At least three attempts to contact subjects will be made by the sites from which the subjects were enrolled, and a vital status will be ascertained from medical chart, patient contact, next of kin contact, or national death registry. The vital status of each patient will be assessed as either alive or deceased with corresponding date of vital check or death, as applicable. For subjects where vital status cannot be ascertained beyond the date of last follow-up from the 00103311 study, subject will be marked as lost to follow-up at last follow-up date if no response at least 1 month from last contact.

**With:**

**5.1 Study Population and Methods**

The population in this study will be the patients who were enrolled originally in the 00103311 trial (A Phase 3, Randomized, Open Label Study Investigating the Efficacy of the BiTE Antibody Blinatumomab Versus Standard of Care Chemotherapy in Adult Subjects With Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia (ALL) (TOWER Study)). This study will be a **one-time** follow-up on patients that were alive **and still participating in the Phase III study 00103311** at the end of the 00103311 study results being reported. **This study will assess OS and, for those**

patients in the standard of care arm, additionally collect information on blinatumomab use after the trial period in the 00103311 study.

A follow-up will occur on the remaining alive patients at last follow-up. The sites from which the subjects were enrolled **will ascertain survival status and for those patients in the standard of care arm, any blinatumomab use following the end of the 00103311 study using medical charts, national registries, patient contact, next of kin contact, or other available means per local regulation. In those instances, when informed consent is required, at least 3 attempts to contact the subject will be made by the sites.** The survival status of each patient will be assessed as either alive or deceased with a corresponding date of the status check or death, as applicable. For subjects where survival status cannot be ascertained beyond the date of last follow-up from the 00103311 study, **ie, at least 3 contact attempts are made and no updated survival status can be collected, the subject will be marked as lost to follow-up at the last follow-up date in the 00103311 study. Patients in the standard of care arm will be reviewed or inquired for blinatumomab use. Analysis for OS will be done using randomized treatment assignment (ie, intent-to-treat principle). An additional sensitivity analysis will be done to adjust for the drop-in effect of standard of care patients switching to blinatumomab.**

[Section: 5.2 Sample Size](#)

**Replace:**

The number of patients alive at the last follow-up in the 00103311 study was 108 subjects. An earnest effort to ascertain vital status on all subjects will be made. It is unknown how many subjects will have additional follow-up.

**With:**

The number of patients alive **and still participating** at the last follow-up in the 00103311 study was 108 subjects. An earnest effort to ascertain **survival** status on all subjects will be made. It is unknown how many subjects will have additional follow-up.

[Section: 5.3 Outcome Assessment](#) (new section)

**Add:**

**5.3 Outcome Assessment**

The endpoint in this study is OS. Overall survival is defined as the time from randomization to the blinatumomab arm or investigator choice chemotherapy arm

(the 2 treatment arms in the 00103311 trial) until death or censoring at the last date known to be alive. Updated OS Kaplan-Meier probability estimates and an updated Kaplan-Meier plot using all randomized subjects from 00103311 trial will capture the additional follow-up survival data for those subjects that were alive and still participating at the end of the 00103311 study.

Section: 5.4 Statistical Analysis, Paragraph 1

**Delete:**

~~The endpoint in this study is overall survival. Overall survival is defined as time from randomization of blinatumomab or investigator choice chemotherapy (the two treatment arms in the 00103311 trial) until the event of death or censoring at end of follow-up.~~

Section: 5.4 Statistical Analysis, Paragraph 2

**Replace:**

For the analysis, overall survival Kaplan-Meier probabilities and plot last reported in the 00103311 study will be updated to provide a final table of survival probabilities at defined time points (3 months, 6 months, 12 months, 18 months, 24 months, 36 months, 60 months) with relevant 95% confidence intervals and a final plot which also adds an elongated x-axis of up to 60 months. For reference, the overall survival plot presented in the published study (Kantarjian et al 2017) is presented below.

**With:**

For the analysis, **OS** Kaplan-Meier probabilities and plot last reported in the 00103311 study will be updated to provide an **updated** table of survival probabilities at defined time points (3 months, 6 months, 12 months, 18 months, 24 months, 36 months, 60 months) with relevant 95% confidence intervals and an **updated** plot which also adds an elongated x-axis of up to 60 months. For reference, the **OS** plot presented in the published study (Kantarjian et al, 2017) is presented below.

Section: 5.4 Statistical Analysis, Paragraph 3

**Add:**

**A sensitivity analysis will be conducted assessing whether patients in the standard of care arm who had blinatumomab use during the 00103311 trial and after the study's termination had an effect on the survival outcomes of this group.**

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Section: 6. PROTECTION OF HUMAN SUBJECTS (was Section 5 in previous version)

**Replace:**

5. Subject Confidentiality

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

**With:**

**6. PROTECTION OF HUMAN SUBJECTS**

This study will comply with all applicable laws regarding subject privacy. No direct **patient** contact or collection of additional data **from patients** will occur beyond **survival** status assessment **and blinatumomab use for patients in the standard of care arm after the conclusion of the 00103311 trial** by the sites. Study results will be in tabular form and aggregate analyses that omits subject identification. Any publications and reports will not include subject identifiers.

**6.1 Informed Consent**

**Where an informed consent is required per local regulations, an initial sample informed consent form is provided for the investigator to prepare the informed consent document to be used at his or her site. Updates to the sample informed consent form are to be communicated formally in writing from the Amgen Study Manager to the investigator. The written informed consent form is to be prepared in the language(s) of the potential patient population.**

**Before a subject's participation in the study, the investigator will explain to the subject, or his/her legally authorized representative, the aims, methods, anticipated benefits, and potential hazards of the study, and answer all questions regarding the study.**

**The acquisition of informed consent is to be documented in the subject's medical records, and the informed consent form is to be signed and personally dated by the subject or a legally acceptable representative and by the person who conducted the informed consent discussion. The original signed informed consent form is to be retained in accordance with institutional policy, and a copy**

of the informed consent form(s) must be provided to the subject or the subject's legally authorized representative.

If local regulations do not require an informed consent to be signed but mandate that the subject is notified about the study, the investigator should document the notification process in the subject's medical record.

## **6.2 Institutional Review Board/Independent Ethics Committee (IRB/IEC)**

A copy of the protocol, proposed ICF, where applicable, other written patient information, must be submitted to the IEC or other relevant ethical review board for written approval. A copy of the written approval of the protocol and ICF, where applicable, must be received by Amgen before study can be executed.

The investigator must submit and, where necessary, obtain approval from the IEC or other relevant ethical review board for all subsequent protocol amendments and changes to the informed consent document, as applicable. The investigator is to notify the IEC or other relevant ethical review board of deviations from the protocol or serious adverse event(s) occurring at the site and other adverse event reports received from Amgen, in accordance with local procedures and statutes.

The investigator is responsible for obtaining other relevant ethical review board approval/renewal throughout the duration of the study. Copies of the investigator's reports, where applicable by local regulations and the IEC or other relevant ethical review board continuance of approval must be sent to Amgen.

## **6.3 Subject Confidentiality**

The investigator must ensure that the subject's confidentiality is maintained for documents submitted to Amgen. Subject will be assigned a unique identifier by the sponsor. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred. For serious adverse events reported to Amgen, subjects are to be identified by their unique subject identification number, initials (for faxed reports, in accordance with local laws and regulations), and age (in accordance with local laws and regulations).

Documents that are not submitted to Amgen (eg, signed informed consent forms) are to be kept in confidence by the investigator, except as described below. In compliance with governmental regulations/International Council on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines, it is required that

the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB/IEC direct access to review the subject's original medical records for verification of data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform and obtain the consent of the subject to permit such individuals to have access to his/her study-related records, including personal information.

#### **6.4 Subjects Decision to Withdraw**

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

Withdrawal of consent for a study means that the subject does not wish to or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in the analysis of the study and, where permitted, publicly available data can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate steps for withdrawal of their consent from the study.

Section: 7. COLLECTION, RECORDING, AND REPORTING OF SAFETY INFORMATION AND PRODUCT COMPLAINTS (was Section 4 in previous version)

#### **Delete:**

~~This study is analyzing secondary data from medical charts and the only objective is to assess vital status/survival. No safety data will be collected or reported.~~

Section: 7.1 Definition of Safety Events (new section)

#### **Add:**

### **7.1 Definition of Safety Events**

#### **7.1.1 Adverse Events**

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

An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease

---

temporally associated with the use of a product(s), whether or not considered related to the product(s). The definition of an adverse event includes:

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

It is the investigator's responsibility to evaluate whether an adverse event is related to an Amgen product prior to reporting the adverse event to Amgen.

#### 7.1.2 Serious Adverse Events

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

- is fatal
- is life threatening (places the subject at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an "other 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 subject or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events could include allergic bronchospasm, convulsions, and blood dyscrasias, drug-induced liver injury, events that necessitate an emergency room visit, outpatient surgery, or other events that require other urgent intervention.

#### 7.1.3 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).

#### 7.1.4 Product Complaints

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

Product complaints of blinatumomab will be reported.

[Section: 7.2 Safety Collection, Recording and Submission to Amgen Requirements](#)  
(new section)

**Add:**

#### 7.2 Safety Collection, Recording and Submission to Amgen Requirements

This study is collecting retrospective and in some cases, prospective information.

**Retrospective Observation Period (time period from final study contact on the 00103311 study to subject/next of kin contact for 20180138 study data collection):** this study is analyzing secondary data from medical charts or national registries. The safety outcomes of death as listed in Section 5.3 will be documented and analyzed in this study. These will be reported in aggregate in the final study report as an update to the OS probabilities reported in the 00103311 study. See Section 5.3 for safety outcomes and definitions. Submission of safety outcomes as individual safety reports to Amgen is not required. Safety events suspected to be related to any medicinal product should be reported to the local authority in line with the local country requirements.

**Prospective Observation Period (time period from when a subject [or next of kin] is contacted to the date of final study contact):** When an ICF is required to collect data, the study may collect prospective information during interactions with subjects or next of kin. All safety events (adverse events, product complaints,

and other safety findings) considered to have occurred following subject exposure to blinatumomab will be collected from the signing of the informed consent to the final study contact. The Investigator is responsible for ensuring that all safety events they become aware of during study period, are recorded in the subject's appropriate study documentation. Those safety events which are considered serious must also be submitted as individual safety reports to Amgen Safety via the applicable Amgen Safety Reporting Form (paper or electronic form) within 1 business day of Investigator awareness. Non-serious adverse events must be reported in an expeditious manner, not to exceed 15 calendar days of Investigator awareness.

Safety events that are suspected to be related to any medicinal product where there is no exposure to blinatumomab should be reported to the local authority in line with the local country requirements.

If the electronic data capture (EDC) system is unavailable to the site staff, the adverse event which is considered serious must still be reported to Amgen within 1 business day of the Investigator's awareness, using the paper Adverse Event Contingency Report Form. Non-serious adverse events must be reported in an expeditious manner, not to exceed 15 calendar days of Investigator awareness. For EDC studies where the first notification of an Adverse Event is reported to Amgen via the Adverse Event Contingency Report Form, the data must be entered into the EDC system when the system is again available.

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

#### **7.2.1 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 48 hours.

Information will be recorded on the Pregnancy Notification Worksheet (see Appendix C). The worksheet must be submitted to Amgen Safety within 1 business day of learning of a subject's pregnancy. (Note: Investigator is not required to provide any information on the Pregnancy Notification Worksheet that violates the country or regions local privacy laws).

After receipt of the Pregnancy Notification Worksheet, Amgen Safety will provide Investigator with an authorisation form and questionnaire to collect additional information. After obtaining the female subject's signed authorization for release of pregnancy and infant health 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 48 hours of the blinatumomab. This information will be forwarded to Amgen 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 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 as a pregnancy exposure case.

If the outcome of the pregnancy meets a criterion for immediate classification as a serious adverse event (eg, 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 or Were Pregnant at the Time of Enrollment**

In the event a male subject fathers a child following exposure to blinatumomab and for an additional 48 hours after discontinuing blinatumomab the information will be recorded on the Pregnancy Notification Worksheet. The worksheet (see Appendix C) must be submitted to Amgen Safety within 1 business day of the

Investigator awareness of the pregnancy. (Note: Investigator is not required to provide any information on the Pregnancy Notification Worksheet that violates the country or regions local privacy laws).

After receipt of the Pregnancy Notification Worksheet, Amgen Safety will provide Investigator with an authorisation form and questionnaire to collect additional information. The Investigator will attempt to obtain a signed authorization for release of pregnancy and infant health information directly from the pregnant female partner to obtain additional pregnancy information.

After obtaining the female partner's signed authorization for release of pregnancy infant health 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 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 Global Patient Safety regardless of fetal status (presence or absence of anomalies) or indication for Rateprocedure.

#### **Collection of Lactation Information**

Investigator will collect lactation information on any female subject who breastfeeds while taking blinatumomab through 48 hours.

Information will be recorded on the Lactation Notification Worksheet (see Appendix C) and submitted to Amgen Safety within 1 business day of the Investigator's awareness.

With the female subjects signed authorization for release of mother and infant health information, the Investigator will collect mother and infant health information and complete the lactation questionnaire on any female subject who breastfeeds while taking blinatumomab through 48 hours after discontinuing blinatumomab.

#### **7.2.2 Safety Reporting Requirement to Regulatory Bodies**

Amgen will report safety data as required in accordance with local requirements to regulatory authorities, Investigators/institutions, IRBs/IECs, or other relevant ethical review board(s) in accordance with Pharmacovigilance guidelines and in

compliance with local regulations. The Investigator is to notify the appropriate IRB/IEC or other relevant ethical review board of serious adverse events in accordance with local procedures and statutes.

Section: 8. ADMINISTRATIVE AND LEGAL OBLIGATIONS (new section)

**Add:**

## **8. ADMINISTRATIVE AND LEGAL OBLIGATIONS**

### **8.1 Protocol Amendments and Study Termination**

Amgen may amend the protocol at any time. If Amgen amends the protocol, written agreement from the Investigator must be obtained where applicable per local governing law and/or regulations. The IRB/IEC or other relevant ethical review board must be informed of all amendments and give approval. The Investigator must send a copy of the approval letter from the IRB/IEC or other relevant ethical review board to Amgen.

Amgen reserves the right to terminate the study at any time. Both Amgen and the Investigator reserve the right to terminate the Investigator's participation in the study according to the contractual agreement. The Investigator is to notify the IRB/IEC or other relevant ethical review board in writing of the study's completion or early termination and send a copy of the notification to Amgen.

Section: 9. PUBLICATION INTENT (It was section 6 in previous version)

**Replace:**

Results of this study is intended to be submitted to regulatory agency EMA PRAC to fulfill a commitment as part of approval for blinatumomab in EU countries.

There are no additional plans to publish these data.

**With:**

Results of this study is intended to be submitted to regulatory agency EMA PRAC to fulfill a commitment as part of approval for blinatumomab in EU countries.

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

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

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

[Section: 10. REFERENCES](#)

Replace:

**10. References**

Löffler A, Kufer P, Lutterbüse R, et al. A recombinant bispecific single-chain antibody, CD19 x CD3, induces rapid and high lymphoma-directed cytotoxicity by unstimulated T lymphocytes. *Blood*. 2000;95:2098-2103

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.

NCCN Practice Guidelines in Oncology, Acute Lymphoblastic Leukemia. NCCN.org Version 1.0 2014

Kantarjian H, Stein A, Gökbüget N, et al. Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia. *NEJM*. 2017;376(9): 836-847

With:

## 10. REFERENCES

Kantarjian H, Stein A, Gökbuget N, et al. Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia. *NEJM*. 2017;376(9):836-847.

Löffler A, Kufer P, Lutterbüse R, et al. A recombinant bispecific single-chain antibody, CD19 x CD3, induces rapid and high lymphoma-directed cytotoxicity by unstimulated T lymphocytes. *Blood*. 2000;95:2098-2103.

NCCN Practice Guidelines in Oncology, Acute Lymphoblastic Leukemia. NCCN.org Version 1.0 2014.

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.

Section: 11. APPENDICES (new section)

Add:

**Appendix A. Sample Safety Reporting Form(s)**

**Completion Instructions - Electronic Adverse Event Contingency Report Form**  
**(For use for Observational Research Studies using Electronic Data Capture [EDC])**

NOTE: This form is to be used under restricted conditions outlined on page 1 below. If you must fax an event report to Amgen, you must also enter that event into the EDC system (eg, Rave) when it becomes available.

**General Instructions**

The protocol will provide instruction on what types of events to report for the study. This form is to be used ONLY to report events that must be captured in the Amgen safety database. \*Indicates a mandatory field.

What to report on this form:

- All adverse events associated with the Amgen drug irrespective of causal relationship of the event to the study drug or seriousness, unless instructed differently by the protocol
- The following safety findings are to be reported on this form as events regardless of association with an adverse event
  - Medication errors, overdose, whether accidental or intentional, misuse, or abuse, involving the Amgen product
  - 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)
  - Product complaint ONLY IF ASSOCIATED WITH AN ADVERSE EVENT

The following should not be reported on this form and should be reported via the normal process set up for the study

- Pregnancy and lactation reports
- Product complaints without association with an AE

**1. Site Information**

**Site Number\*** – Enter your assigned site number for this study

**Investigator\*, Country\*, Reporter\*, Phone No., and Fax No.** – Enter information requested

**2. Subject Information**

**Subject ID Number\*** – Enter the entire number assigned to the subject

**Age at event onset, Sex, and Race** – Enter the subject's demographic information

**End of Study date** – If the subject has already completed the study or terminated the study early, enter the End of Study date

*If you are submitting follow-up information to a previous report, provide the adverse event term for the previous report as well as the start date for the initial event.*

**3. Adverse Event**

**Provide the date the Investigator became aware of this Information**

**Adverse Event Diagnosis or Syndrome\*** –

- If the diagnosis is known, it should be entered. Do not list all signs/symptoms if they are included in the diagnosis.
- If a diagnosis is not known, the relevant signs/symptoms should be entered.
- If the event is fatal, the cause of death should be entered and autopsy results should be submitted, when available.

**Date Started\*** – Enter date the adverse event first started rather than the date of diagnosis or hospitalization. For serious events, the start date is the date the event started, not the date on which the event met serious criteria. **This is a mandatory field.**

**Date Ended** – Enter date the adverse event ended. For serious events, this is not the date when the event no longer met serious criteria. If the event has not ended at the time of the initial report, a follow-up report should be completed when the end date is known. If the event is fatal, enter the date of death as the end date.

**Is event serious?\*** – Indicate Yes or No. **This is a mandatory field.**

**Serious Criteria Code\*** – **This is a mandatory field for serious events.** Enter all reasons why the reported event has met serious criteria:

Immediately life-threatening: Use only if the subject was at immediate risk of death from the event as it occurred. Emergency treatment is often required to sustain life in this situation. Protocol specified hospitalizations are exempt.

**At the top of Page 2, provide your Site Number and the Subject ID Number in the designated section.**

**4. IP Administration including Lot # and Serial # when known / available.**

- If the investigator decides an event should be reported in an expedited manner, but it does not meet other serious

**Completion Instructions - Electronic Adverse Event Contingency Report Form  
(for use for Studies using Electronic Data Capture (EDC))**

Note, this form is to be used under restricted conditions outlined on page 1 of the form. If you must fax an event report to Amgen, you must also enter that event into the EDC system (eg, Rave) when it becomes available.

criteria, "Other Medically Important Serious Event" may be the appropriate serious criterion.

**Relationship to Amgen drug under study\*** – The Investigator must determine and enter the relationship of the event to the Amgen drug under study at the time the event is initially reported. **This is a mandatory field.**

**Relationship to Amgen device\*** – The Investigator must determine and enter the relationship of the event to the Amgen device (e.g. prefilled syringe, auto-injector) at the time the event is initially reported. **If the study involves an Amgen device, this is a mandatory field. This question does not apply to non-Amgen devices used in the study (e.g. heating pads, infusion pumps)**

**Outcome of Event** – Enter the code for the outcome of the event at the time the form is completed if outcome is known.

Resolved – End date is known

➢ Not resolved / Unknown – End date is unknown

➢ Fatal – Event led to death

**5. Hospitalization**

If the subject was hospitalized, enter admission and discharge dates. Hospitalization is any in-patient hospital admission for medical reasons, including an overnight stay in a healthcare facility, regardless of duration. A pre-existing condition that did not worsen while on study which involved a hospitalization for an elective treatment, is not considered an adverse event. Protocol specified hospitalizations are exempt.

**At the top of Page 2, provide your Site Number and the Subject ID Number in the designated section.**

**6. Amgen drug Under Study Administration including Lot # and Serial # when known / available.**

**Initial Start Date** – Enter date the product was first administered, regardless of dose.

**Date of Dose Prior to or at the time of the Event** – Enter date the product was last administered prior to, or at the time of, the onset of the event.

**Dose, Route, and Frequency at or prior to the event** – Enter the appropriate information for the dose, route and frequency at, or prior to, the onset of the event.

**Action Taken with Product** – Enter the status of the product administration.

**7. Concomitant Medications**

Indicate if there are any medications.

**Medication Name, Start Date, Stop Date, Dose, Route, and Frequency** – Enter information for any other medications the subject is taking. Include any study drugs not included in section 5 (Product Administration) such as chemotherapy, which may be considered co-suspect.

**Co-suspect** – Indicate if the medication is co-suspect in the event

**Continuing** – Indicate if the subject is still taking the medication

**Event Treatment** – Indicate if the medication was used to treat the event

**8. Relevant Medical History**

Enter medical history that is relevant to the reported event, not the event description. This may include pre-existing conditions that contributed to the event allergies and any relevant prior therapy, such as radiation. Include dates if available.

**9. Relevant Laboratory Tests**

Indicate if there are any relevant laboratory values.

For each test type, enter the test name, units, date the test was run and the results.

**10. Other Relevant Tests**

Indicate if there are any tests, including any diagnostics or procedures.

For each test type, enter the date, name, results and units (if applicable).

**At the top of Page 3, provide your Site Number and the Subject ID Number in the designated section.**

**11. Case Description**

**Describe Event** – Enter summary of the event. Provide narrative details of the events listed in section 3. Include any therapy administered, such as radiotherapy; (excluding medications, which will be captured in section 6). If necessary, provide additional pages to Amgen.

**Complete the signature section at the bottom of page 3 and fax the form to Amgen.** If the reporter is not the investigator, designee must be identified on the Delegation of Authority form.

A Study # 20180138 AMG 103	<b>Electronic Adverse Event Contingency Report Form</b> <u>For Restricted Use</u>
----------------------------------	--

**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 <input type="checkbox"/> F <input type="checkbox"/> M	Race	If applicable, provide End of Study date

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 <b>diagnosis</b> or syndrome If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report <i>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.</i>	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?	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 >	<drug/device >	<drug/device >	<drug/device >		
						No/ Yes	No/ Yes	No/ Yes	No/ Yes		
			<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No							
			<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No							
			<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> 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

	Site Number	Subject ID Number
--	-------------	-------------------

A Study # 20180138 AMG 103	<b>Electronic Adverse Event Contingency Report Form</b> <u>For Restricted Use</u>
----------------------------------	--

<b>5. Was drug under study administered/taken prior to this event?</b> <input type="checkbox"/> No <input type="checkbox"/> Yes If yes, please complete all of Section 5																
Amgen Drug/Amgen Device:		Date of Initial Dose			Date of Dose			Dose	Route	Frequency		Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld	Lot # and Serial #			
		Day	Month	Year	Day	Month	Year									
<<Drug/Device>> <input type="checkbox"/> blinded <input type="checkbox"/> open label												Lot # _____ <input type="checkbox"/> Unknown Serial # _____ <input type="checkbox"/> Unavailable / Unknown				
<<Drug/Device>> <input type="checkbox"/> blinded <input type="checkbox"/> open label												Lot # _____ <input type="checkbox"/> Unknown Serial # _____ <input type="checkbox"/> Unavailable / Unknown				
<b>6. CONCOMITANT MEDICATIONS (eg, chemotherapy)</b> Any Medications? <input type="checkbox"/> No <input type="checkbox"/> Yes If yes, please complete:																
Medication Name(s)		Start Date			Stop Date			Co-suspect		Continuing		Dose	Route	Freq.	Treatment Med	
		Day	Month	Year	Day	Month	Year	No✓	Yes✓	No✓	Yes✓				No✓	Yes✓
<b>7. RELEVANT MEDICAL HISTORY (include dates, allergies and any relevant prior therapy)</b>																
<b>8. RELEVANT LABORATORY VALUES (include baseline values)</b> Any Relevant Laboratory values? <input type="checkbox"/> No <input type="checkbox"/> Yes If yes, please complete:																
Date	Test	Unit	Day	Month	Year											
Date	Unit	Day	Month	Year												
Date	Unit	Day	Month	Year												
Date	Unit	Day	Month	Year												
<b>9. OTHER RELEVANT TESTS (diagnostics and procedures)</b> Any Other Relevant tests? <input type="checkbox"/> No <input type="checkbox"/> Yes If yes, please complete:																
Date		Additional Tests					Results				Units					
Day	Month	Year														
			Site Number					Subject ID Number								



## Appendix B. Additional Safety Reporting Information

### Adverse Event Severity Scoring System

For oncology studies, the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 is to be used. The CTCAE is available at the following location:

[http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/ctc.htm](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)

## Appendix C. Pregnancy and Lactation Notification Worksheets

Amgen Proprietary - Confidential

### AMGEN<sup>®</sup> Pregnancy Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): [svc-ags-in-us@amgen.com](mailto:svc-ags-in-us@amgen.com)

1. Case Administrative Information				
Protocol/Study Number: <u>20180138</u>				
Study Design: <input type="checkbox"/> Interventional <input checked="" type="checkbox"/> Observational (If Observational: <input checked="" type="checkbox"/> Prospective <input type="checkbox"/> Retrospective)				
2. Contact Information				
Investigator Name _____		Site # _____		
Phone (____) _____		Fax (____) _____		Email _____
Institution _____				
Address _____				
3. Subject Information				
Subject ID # _____		Subject Gender: <input type="checkbox"/> Female <input type="checkbox"/> Male		Subject age (at onset): _____ (in years)
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? <input type="checkbox"/> Yes <input type="checkbox"/> No				
If yes, provide product (or study drug) stop date: mm ____/dd ____/yyyy ____				
Did the subject withdraw from the study? <input type="checkbox"/> Yes <input type="checkbox"/> No				
5. Pregnancy Information				
Pregnant female's last menstrual period (LMP)		mm ____/dd ____/yyyy ____	<input type="checkbox"/> Unknown <input type="checkbox"/> N/A	
Estimated date of delivery		mm ____/dd ____/yyyy ____		
If N/A, date of termination (actual or planned)		mm ____/dd ____/yyyy ____		
Has the pregnant female already delivered? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown <input type="checkbox"/> N/A				
If yes, provide date of delivery: mm ____/dd ____/yyyy ____				
Was the infant healthy? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown <input type="checkbox"/> N/A				
If any Adverse Event was experienced by the infant, provide brief details: _____				
_____				
_____				
Form Completed by:				
Print Name: _____		Title: _____		
Signature: _____		Date: _____		

FORM-115199

Version 1.0

Effective Date: 24-Sept-2018

Amgen Proprietary - Confidential

**AMGEN** Lactation Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): [svc-ags-in-us@amgen.com](mailto:svc-ags-in-us@amgen.com)

<b>1. Case Administrative Information</b>														
Protocol/Study Number: <u>20180138</u>														
Study Design: <input type="checkbox"/> Interventional <input checked="" type="checkbox"/> Observational (If Observational: <input checked="" type="checkbox"/> Prospective <input type="checkbox"/> Retrospective)														
<b>2. Contact Information</b>														
Investigator Name _____		Site # _____												
Phone (____) _____	Fax (____) _____	Email _____												
Institution _____														
Address _____														
<b>3. Subject Information</b>														
Subject ID # _____		Subject age (at onset): <u>   </u> (in years)												
<b>4. Amgen Product Exposure</b>														
<table border="1"><thead><tr><th>Amgen Product</th><th>Dose at time of breast feeding</th><th>Frequency</th><th>Route</th><th>Start Date</th></tr></thead><tbody><tr><td> </td><td> </td><td> </td><td> </td><td>mm ____/dd ____/yyy ____</td></tr></tbody></table>					Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date					mm ____/dd ____/yyy ____
Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date										
				mm ____/dd ____/yyy ____										
Was the Amgen product (or study drug) discontinued? <input type="checkbox"/> Yes <input type="checkbox"/> No														
If yes, provide product (or study drug) stop date: mm ____/dd ____/yyy ____														
Did the subject withdraw from the study? <input type="checkbox"/> Yes <input type="checkbox"/> No														
<b>5. Breast Feeding Information</b>														
Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? <input type="checkbox"/> Yes <input type="checkbox"/> No														
If No, provide stop date: mm ____/dd ____/yyy ____														
Infant date of birth: mm ____/dd ____/yyy ____														
Infant gender: <input type="checkbox"/> Female <input type="checkbox"/> Male														
Is the infant healthy? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown <input type="checkbox"/> N/A														
If any Adverse Event was experienced by the mother or the infant, provide brief details: _____														
_____														
_____														
<b>Form Completed by:</b>														
Print Name: _____		Title: _____												
Signature: _____		Date: _____												

FORM-115201

Version 1.0

Effective Date: 24-Sept-2018