DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 100135

WRITTEN REQUEST

Amgen, Inc.
Attention: Tai H. Yu., MS
Senior Manager, Regulatory Affairs
One Amgen Center Drive
Mail Stop 17-2-A
Thousand Oaks, CA 91320-1799

Dear Mr. Yu:

Reference is made to your July 30, 2014 Proposed Pediatric Study Request (PPSR) for blinatumomab (AMG 103).

BACKGROUND:

Acute lymphocytic leukemia (ALL) is an aggressive malignancy that affects both children and adults. There are approximately 6000 new cases diagnosed annually, and about 60% of them are children. The most common type of ALL is the B-cell precursor type. The prognosis in children is generally better than in adults, and this is presumed to be due to greater disease control in children resulting from the higher intensity of chemotherapy that can be tolerated by the younger patients. However, although 95% of pediatric B-cell precursor ALL patients achieve a first remission, 15% to 20% die from treatment-resistant (refractory) or recurrent disease. With each subsequent relapse, the reinduction rate is lower, and the survival is diminished. In pediatric patients with second or later relapse, the expected complete response rate with currently available drugs is approximately 40%, and the overall survival rate is less than 10%. Allogeneic hematopoietic stem cell transplantation (HSCT) is a curative treatment option for patients who relapse after chemotherapy. The prognosis for patients who relapse after allogeneic HSCT is particularly poor.

The studies described in your PPSR investigate the potential use of blinatumomab in the treatment of pediatric patients with relapsed B-cell precursor ALL. Blinatumomab is a bispecific antibody derivative targeting cell-specific markers on the surface of B cells (cluster of differentiation [CD] 19) and T cells (CD3). Blinatumomab kills CD19-positive B cells through a process resembling standard cytotoxic T-cell functions. Based on its mechanism of action, blinatumomab is expected to have activity against B-cell precursor ALL across all age groups. The dose-schedule planned for the initial marketing application is a flat dose intended for adults.

Dosing of blinatumomab for the pediatric population and the safety and efficacy of the pediatric dose cannot be extrapolated from adult data and will be determined by the studies outlined in this Written Request. FDA is not requesting studies in neonates, because relapsed or refractory ALL by definition

would not occur by 28 days of age, and the benefit risk assessment does not favor use of blinatumomab as first-line therapy at this time.

To obtain needed pediatric information on blinatumomab, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, that you submit information from the studies described below.

- *Nonclinical study(ies)*:

Based on review of the available non-clinical toxicology, no additional animal studies are required at this time to support the clinical studies described in this Written Request.

- *Clinical studies:*

Study 1: A single-arm study of single-agent blinatumomab in pediatric patients with B-cell precursor ALL in second or later bone marrow relapse, in any marrow relapse after allogeneic HSCT, or refractory to other treatments.

Study 2: A multicenter, randomized, open-label study of multiagent chemotherapy with or without blinatumomab in intensification and consolidation for treatment of children with Ph-negative B-cell ALL in first relapse.

- *Objective of each study:*

Study 1: To assess the efficacy of blinatumomab

Study 2: To assess whether incorporation of blinatumomab into the treatment of patients with childhood Ph-negative B-cell ALL at first relapse will improve disease-free survival (DFS).

- *Patients to be Studied:*

  - *Age group in which study(ies) will be performed*:

    Study 1: 1 month to < 18 years.

    Study 2: 1 to less than 31 years of age (inclusive) at the time of relapse.

  - *Number of patients to be studied:*

    Study 1: A minimum of 21 patients will be enrolled in the first stage of the trial and up to 40 evaluable patients in total may be enrolled.

Study 2: Approximately 598 patients will be enrolled. A minimum of 376 patients will be randomized.

Representation of Ethnic and Racial Minorities: The studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

- *Study endpoints:*

  Efficacy endpoints

  Study 1: Rate of complete remission (CR) within the first 2 cycles, duration of CR, and rate of minimal residual disease(MRD)response

  Study 2: Primary endpoint - Disease-free survival
  Secondary endpoint - Overall survival, MRD negativity (< 0.01%) rate prior to HSCT for the HR/IR group and at the end of continuation for the LR group.

  Safety endpoints

  Studies 1 and 2: Safety outcomes must include descriptive analyses of adverse events, including the incidences of overall adverse events, of severe adverse events, of serious adverse events, and of fatal adverse events. The type, incidence, and severity of laboratory abnormalities must also be analyzed for each group. An analysis of the development of anti-drug antibodies (ADA) and the effect on safety outcomes must be included. Safety analyses must be performed separately for each study, in aggregate, and by age group. The analysis for Study 2 must include a comparison of grade 3-5 adverse events between the randomized arms for the portion of the treatment plan that includes blinatumomab.

  Pharmacokinetic endpoints

  Pharmacokinetic samples must be collected by optimal sparse sampling in Study 2. Such data must then be appropriately analyzed using methods such as linear mixed-effects modeling, or nonlinear mixed effects modeling. Data from Study 2 must be used to develop pharmacokinetic and pharmacodynamic (PK-PD) models to explore exposure-response relationships for measures of safety and effectiveness.

- *Known Drug Safety concerns and monitoring:*

  The important risks of blinatumomab that have emerged in clinical studies include neurotoxicity, cytokine release syndrome, tumor lysis syndrome, disseminated intravascular coagulation, elevated liver enzymes, infusion related reactions, medication errors (overdose), infections, neutropenia, decreased immunoglobulins, and capillary leak syndrome.

Studies 1 and 2 will include a) premedications or concomitant medications to mitigate these toxicities, b) monitoring for the occurrence of these toxicities, and c) modification of dosing to ameliorate and/or prevent recurrence of these toxicities.

- *Extraordinary results:* In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request. If you believe this is the case, you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.

- *Drug information:*

  Study 1
  - Dosage form: blinatumomab (lyophilized; (b) (4) µg/mL)
  - Route of administration: continuous intravenous infusion (IV)
  - Regimen: An initial dose of 5 µg/m^2/day blinatumomab in the first week of treatment in cycle 1 followed by 15 µg/m^2/day starting from the second week of treatment in cycle 1 and subsequent treatment cycles will be tested.

  Study 2
  - Dosage form: blinatumomab (lyophilized; (b) (4) µg/mL)
  - Route of administration: continuous intravenous infusion (IV)
  - Regimen: 15 µg/m^2/day

  Use an age-appropriate formulation in the study(ies) described above.

- *Statistical information, including power of study(ies) and statistical assessments:*

  Study 1: This study will use a two-stage design to assess the efficacy of blinatumomab. A minimum of 21 patients will be enrolled in the first stage of the trial and up to 40 evaluable patients in total may be enrolled, in order to test a complete response rate of 10% versus 27.5% at a two-sided 5% type I error and an 80% power. Due to the exploratory nature of this study, no adjustment of the type I error due to multiple comparisons will be required. P-values of secondary endpoints will be interpreted descriptively.

  Study 2: This study will randomize a minimum of 376 patients; a minimum of 170 high or intermediate risk (HR/IR) patients, and a minimum of 206 low risk (LR) patients. Risk stratification will be based on site of relapse, time to relapse, and minimal residual disease status following a uniform first block of chemotherapy (Block 1). Randomization will be performed separately for the HR/IR group and for the LR group, at the end of Block 1, in a 1:1 ratio to either receive chemotherapy backbone alone or receive blinatumomab as part of the treatment regimen.

The primary efficacy analysis will be an intent-to-treat comparison of disease-free survival (DFS) between the two treatment arms separately for the HR/IR group and for the LR group. The two treatment arms for the HR/IR group will be compared using un-stratified log-rank test at a 1-sided 0.025 level of significance. The two treatment arms for the LR group will be compared using unstratified log-rank test at a 1-sided 0.05 level of significance.

A sample size of 170 HR/IR patients (1:1 ratio randomization for treatment regimen assignment) will provide approximately 80% power for the HR/IR group to detect an improvement of 18% in 2-year DFS rate with blinatumomab over the expected 2-year DFS rate of 45% with chemotherapy backbone alone at the 1-sided 0.025 significance level. A sample size of 206 LR patients (1:1 ratio randomization for treatment regimen assignment) will provide approximately 80% power for the LR group to detect an improvement of 11% in 3-year DFS rate with blinatumomab over the expected 3-year DFS rate of 73% with chemotherapy backbone alone at the 1-sided 0.05 significance level.

Overall survival will be compared between the two treatment arms, for the HR/IR group and the LR group separately, at the final DFS analysis and again at 1 year later if the final DFS analysis meets its level of statistical significance.

- *Labeling that may result from the study(ies)*: You must submit proposed pediatric labeling to incorporate the findings of the study(ies). Under section 505A(j) of the FD&C Act, regardless of whether the study(ies) demonstrate that blinatumomab is safe, pure, and potent, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies). Under section 505A(k)(2) of the FD&C Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the study(ies).

- *Format and types of reports to be submitted*: You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(ies) should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement.

  Under section 505A(d)(2)(B) of the FD&C Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. All post-market reports that would be reportable under section 21 CFR 600.80 should include adverse events occurring in an adult or a pediatric patient. In general, the

format of the post-market adverse event report should follow the model for a periodic safety update report described in the Guidance for Industry E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs and the Guidance addendum. You are encouraged to contact the reviewing Division for further guidance.

Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on the FDA website at http://www.fda.gov/CDER/REGULATORY/ersr/Studydata.pdf and referenced in the FDA Guidance for Industry, *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072349.pdf.

- *Timeframe for submitting reports of the study(ies):* Reports of the above studies must be submitted to the Agency on or beforeDecember 31, 2019. Please keep in mind that pediatric exclusivity can attach only to existing exclusivity, if any, that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, if there is unexpired exclusivity that is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such exclusivity is otherwise due to expire.

  If FDA has not determined whether blinatumomab is eligible for reference product exclusivity under section 351(k)(7) of the PHS Act, you may submit a request for reference product exclusivity with supporting data and information to the Agency. Note that neither the issuance of this formal pediatric Written Request, nor any request for exclusivity made by you confers or otherwise implies that you are eligible for reference product exclusivity under section 351(k)(7) of the PHS Act.

- *Response to Written Request:* Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the study(ies). If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

Submit protocols for the above study(ies) to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC WRITTEN REQUEST STUDY**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the study(ies) must be submitted as a biologics license application (BLA) or as a supplement to your approved BLA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your

submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission to the Office of New Drugs, Immediate Office, Therapeutic Biologics and Biosimilars Team, 10903 New Hampshire Ave, Building 22, Mail Stop 6411, Silver Spring, MD 20993. If you wish to fax it, the fax number is 301-796-9855.

In accordance with section 505A(k)(1) of the FD&C Act, *Dissemination of Pediatric Information*, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following circumstances:

1. the type of response to the Written Request (i.e. complete or partial response);
2. the status of the application (i.e. withdrawn after the supplement has been filed or pending);
3. the action taken (i.e. approval, complete response); or
4. the exclusivity determination (i.e. granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

Please note that, if your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the PHS Act, you are required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on submission of such information can be found at www.ClinicalTrials.gov.

If you have any questions, call Kris Kolibab, Regulatory Project Manager, at (240) 402-0277.

Sincerely,

{See appended electronic signature page}

Gregory Reaman, MD
Associate Director
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GREGORY H REAMAN
11/12/2014