DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring MD 20993

WRITTEN REQUEST

BLA 125118
IND (b) (4)

Bristol-Myers Squibb Company
P.O. Box 4000
Princeton, New Jersey 08543-4000

Attention: Ashley Pereira
Director, Global Regulatory Sciences

Dear Dr. Pereira:

Reference is made to your January 3, 2013, Proposed Pediatric Study Request for abatacept.

BACKGROUND:

This study investigates the potential use of abatacept for the treatment of polyarticular juvenile idiopathic arthritis (PJIA).

PJIA is a descriptive term for persistent juvenile idiopathic arthritis (JIA) of more than 6 weeks with multiple joint involvement and onset in patients less than 16 years of age, where other diagnoses (such as infections, malignancy, trauma, reactive arthritis, and specific connective tissue diseases such as systemic lupus erythematosus) have been excluded. The overall prevalence of JIA is estimated to be 294,000 children between the ages of 0 and 17 in the United States.[1] A limited number of treatments are approved for PJIA, including corticosteroids, methotrexate (MTX), the TNF inhibitors etanercept and adalimumab, and the T-cell co-stimulatory modulator abatacept. Because PJIA patients may not respond to a given treatment or class of treatments, treatments with different mechanisms of action would be an important public health benefit.

The efficacy of abatacept has been evaluated in a randomized, double-blind, placebo-controlled, withdrawal trial of intravenous (IV) abatacept in patients with PJIA 6 to 17 years of age, which was a required study under the Pediatric Research Equity Act (PREA). In that trial, all patients received abatacept for 4 months, and responders were randomized to either receive abatacept or placebo infusions until they experienced a flare or 6 months had elapsed, whichever was shorter. Because patients received active treatment as soon as a disease flare (defined by JIA ACR30 criteria) occurred, the use of a placebo control group was limited and no patient experienced uncontrolled or severe disease activity due to placebo treatment. Neonates and other children under 2 years of age were not included in this study because PJIA rarely occurs in this age group. PJIA patients ages 2 to less than 6 years old are not included because there are potential safety concerns arising from juvenile animal studies with abatacept, which showed that juvenile animals were much more sensitive to the

[1] M Espinosa and BS Gottlieb, "Juvenile Idiopathic Arthritis," Pediatrics in Review, 2012; 33:303-313

immunosuppressive effects of abatacept, and theoretical concerns that disturbing CTLA-4 balance in the developing immune system could result in an increased risk of autoimmunity. Because there are currently no data to define what ages would be at risk in human children, and there are other available therapies for PJIA patients 2 to 5 years old, the age range of children with PJIA for the study in this written request will be limited to the age range already shown to be safe in previous studies, i.e., ages 6 to 17 years.

To obtain needed pediatric information on abatacept, 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 pharmacokinetic (PK) and safety study of subcutaneous (SC) abatacept in PJIA patients 6 to 17 years of age.

- ☐ Efficacy of SC abatacept will be supported by demonstrating the proposed SC abatacept regimen is able to achieve the steady state trough concentration (C_{min}) associated with efficacy in the IV abatacept PJIA study used to support the approval of abatacept for PJIA.

Study 2: Interim results from the long-term safety registry of intravenous (IV) abatacept in PJIA patients 6 to 17 years of age.

- *Objective of each study:*

Study 1: The primary objective of the study is to estimate abatacept steady state trough concentration (C_{min}) in children and adolescents with PJIA 6 to 17 years of age. Secondary objectives will include assessment of efficacy and safety of abatacept administered subcutaneously in PJIA patients and assessment of C_{min} as agreed upon with the Agency by each weight-tiered dosing category. Weight-tiered dosing is intended to accommodate fixed, subcutaneous doses while maintaining systemic exposure within the target therapeutic range defined by the previously performed IV PJIA study.

Study 2: The primary objective of the study is to assess for the occurrence of malignancies, other autoimmune diseases, and serious infections in PJIA patients treated with abatacept.

- *Patients to be Studied:*

  - *Age group in which study will be performed*:

Study 1: PJIA patients 6 to 17 years of age.
Study 2: PJIA patients 6 to 17 years of age.

- *Number of patients to be studied:*

Study 1: Enroll 160 patients with PJIA 6 to 17 years of age for safety and PK. This should include a sufficient number of patients 6 to 10 years old, and 12 to 17 years old to assess PK by weight-tiered dosing categories.

Study 2: Enroll at least 500 patients with PJIA 6 to 17 years of age for assessment of long-term safety.

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:*

Study 1:

- ☐ *Pharmacokinetic Endpoints:*

The PK endpoints must include abatacept steady-state trough concentration (C_{min}) at Day 113. Abatacept C_{min} should also be evaluated at Day 57, Day 85, and Day 113 by weight tiered dosing categories (<25 kg, 25 to <50 kg, and $\geq$50 kg).

Efficacy parameters will be regarded as exploratory and may include the American College of Rheumatology (ACR) response criteria for JIA, which includes core set variables of number of active joints, number of joints with limitation of motion, physician global assessment of disease activity, patient/parent global assessment of patient overall well-being, functional ability as measured by the Children's Health Assessment Questionnaire (CHAQ) and C-reactive protein.

- ☐ *Safety Endpoints:*

Safety outcomes must include the proportion of patients with adverse events, deaths, serious adverse events, adverse events leading to discontinuation, and assessment of immunogenicity and immune responsiveness as agreed upon with the Agency.

Study 2:

- ☐ *Safety Endpoints:*

Safety outcomes must include the proportion of patients with deaths, serious adverse events, adverse events leading to discontinuation, and assessment of immunogenicity. The occurrence of malignancies, other autoimmune diseases, and serious infections should be evaluated specifically. Occurrence of these serious events should be formally compared to the expected rate of these events in historical controls.

- *Known Drug Safety concerns and monitoring:*

  You will monitor for serious infections and hypersensitivity reactions, including anaphylaxis. Live vaccines should not be given with abatacept.

- *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*
    - Abatacept solution for SC injection
  - *route of administration*
    - SC
  - *regimen*
    - Patients will receive a weekly dose of SC abatacept based on their weight. Patients weighing <25 kg will receive 50 mg. Patients weighing 25 to <50 kg will receive 87.5 mg. Patients weighing ≥50 kg will receive 125 mg.

  Study 2:
  - *dosage form*
    - Abatacept lyophilized powder for reconstitution and IV infusion
  - *route of administration*
    - IV
  - *regimen*
    - Patients less than 75 kg receive 10 mg/kg, patients weighing 75 kg to 100 kg receive 750 mg, and patients weighing more than 100 kg receive 1000 mg. Infusions are administered at weeks 0, 2, and 4 then every 4 weeks thereafter.

  Use an age-appropriate formulation in the studies described above. If an age-appropriate formulation is not currently available, you must develop and test an age-appropriate formulation and, if it is found safe and effective in the studied pediatric population(s), you must seek marketing approval for that age-appropriate formulation.

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

  Study 1:
  A sample size of approximately 160 subjects aged 6-17 years will allow not only assessment of the PK parameters, but also will allow an appropriate assessment of the safety of SC abatacept in PJIA. The sample size approximates the sample size of the 4-month ,open-label, lead-in phase of the original IV abatacept PJIA study (IM101033). This will allow a comparison of the

mean abatacept steady state trough concentration and its associated range between Study 1 and Study IM101033 and an evaluation of the safety and immunogenicity of SC abatacept in PJIA with similar precision as previously obtained for IV abatacept. A sufficient number of patients must complete the study to assess PK by weight-tiered dosing categories. Analysis of safety endpoints will be descriptive.

Study 2:
The sample size of Study 2 will be at least 500 patients with PJIA treated with abatacept to be followed for a total of 10 years. Interim results on the accrued safety data available on at least 500 patients enrolled in the study will be expected. Descriptive statistics on the incidence of serious infections, autoimmune disorders, and malignancies should be provided and compared to the expected rate of these events based on historical controls.

- *Labeling that may result from the study*: You must submit proposed pediatric labeling to incorporate the findings of the study. Under section 505A(j) of the Act, regardless of whether the study demonstrates that abatacept is safe and effective, 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. Under section 505A(k)(2) of the 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.

- *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 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 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 314.80 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
  http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequire

ments/ElectronicSubmissions/UCM199759.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/Cder/guidance/7087rev.htm.

- *Timeframe for submitting reports of the study:* Reports of the above studies must be submitted to the Agency on or before September 30, 2016. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity 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, to ensure that a particular patent or exclusivity 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 patent or exclusivity is otherwise due to expire.

- *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. 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.

  Furthermore, if you agree to conduct the study, but have not submitted the study reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

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

Reports of the study must be submitted as a new drug application (NDA) or as a supplement to your approved NDA 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 Director, Office of Generic Drugs, HFD-600, Metro Park North IV, 7519 Standish Place, Rockville, MD 20855-2773. If you wish to fax it, the fax number is 240-276-9327.

In accordance with section 505A(k)(1) of the 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 Public Health Service Act (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 Colette Jackson, Senior Regulatory Health Project Manager, at 301-796-1230.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Deputy Director
Office of Drug Evaluation II
Office of New Drugs
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/

MARY H PARKS
09/13/2013