BLA 761046

WRITTEN REQUEST

Merck Sharp and Dohme Corp.
a subsidiary of Merck & Co., Inc.
Attention: Megan Wise, PhD
Associate Principal Scientist
Global Regulatory Affairs and Clinical Safety
351 North Sumneytown Pike, UG2D-68
North Wales, PA 19454-2505

Dear Dr. Wise:

Reference is made to your December 18, 2019 Proposed Pediatric Study Request for ZINPLAVA (bezlotoxumab) Injection, 25 mg/mL.

This study investigates the potential use of bezlotoxumab to reduce the recurrence of *Clostridioides difficile* infection (CDI) in pediatric patients 1 to 18 years of age who are receiving antibacterial drug treatment for CDI and are at a high risk for CDI recurrence. Bezlotoxumab is a fully human monoclonal antibody (mAb) that binds *C. difficile* toxin B. Bezlotoxumab was approved by the FDA on October 21, 2016, to reduce recurrence of CDI in patients 18 years of age or older who are receiving antibacterial drug treatment for CDI and are at high risk for CDI recurrence.

BACKGROUND:

C. difficile is an anaerobic, spore-forming gram-positive bacillus that produces toxins. The current theory of pathogenesis is that toxigenic strains of *C. difficile*, either endogenous to the colon or exogenously acquired, rapidly multiply after disruption of the normal bacterial colonic flora and result in clinical disease. Antibacterial drug exposure, which results in alteration of the normal microbiota of the gut, is one of the key driving forces for colonization or infection with *C. difficile*.

Disease presentation in pediatric patients is similar to adults. Clinical features and laboratory test abnormalities include fever, diarrhea, abdominal tenderness, abdominal distension, leukocytosis, volume depletion, electrolyte imbalance, and occasionally, pseudomembranous colitis. The incidence of CDI in the US during 2011 for the pediatric population (1-17 years) was 24.7 per 100,000 persons[1].

[1] Lessa FC, Mu Y, Bamberg WM, Beldavs ZG, Dumyati GK,Dunn JR, et al. Burden of *Clostridium difficile* infection in the United States. N Engl J Med. 2015 Feb 26;372(9):825-34.

The epidemiology of CDI in pediatric patients indicate: (1) a trend towards an increasing incidence of CDI, (2) a trend towards the increasing presence of NAP1/BI/027 isolates, and (3) increasing reports in the literature of severe CDI cases.

The risk factors for CDI in pediatric patients are similar to adults (e.g., antibacterial drug use, use of multiple antibacterial drugs, and long duration of hospital stay). However, in pediatric patients, CDI is also associated with other additional host factors, namely malignancy, stem cell and solid organ transplantation, inflammatory bowel disease, and immune suppression. The CDI risk appears to be highest in pediatric patients with malignancies. Data, albeit limited, suggest that the proportion of pediatric patients who have a recurrence of CDI ranges from 7.5% to 38%, which is similar to that seen in adults[2,3].

Neonates and infants less than 1 year of age will be excluded from the Written Request due to high rates of asymptomatic *C. difficile* colonization and co-infection with other diarrheal pathogens, which makes the diagnosis of CDI and evaluation of treatment outcomes in this population impossible or highly impracticable.

To obtain needed pediatric information on bezlotoxumab, 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 nonclinical toxicology data, including nonclinical juvenile toxicity studies, no additional animal studies are required at this time to support the clinical studies described in this Written Request.

- *Clinical studies:*

A randomized, double-blind, placebo-controlled clinical trial to evaluate the safety, tolerability, pharmacokinetics, and efficacy of a single infusion of bezlotoxumab compared to placebo in pediatric patients from 1 to less than 18 years of age receiving antibacterial drug treatment for CDI.

The efficacy of bezlotoxumab in pediatric patients 1 to less than 18 years of age will be supported by extrapolation from adequate and well-controlled adult studies. The course of the disease and the effects of therapy are similar between adults and pediatric patients.

[2] Kim J, Shaklee JF, Smathers S, Prasad P, Asti L, Zoltanski J, et al. Risk factors and outcomes associated with severe *Clostridium difficile* infection in children. Pediatr Infect Dis J 2012;31(2):134-8.
[3] Styczynski J. Infectious complications in children and adults with hematological malignancies. Acta Haematol Pol. 2019 Sep;50(3):167-73.

- *Study Objectives:*

To describe the safety, pharmacokinetics (PK) and efficacy of bezlotoxumab to reduce the recurrence of CDI in pediatric patients aged 1 to less than 18 years. The PK data obtained in this study will be used to support dosing recommendations in the pediatric population that are within the range previously demonstrated to be safe and efficacious in adults.

- *Patients to be Studied:*

Pediatric patients aged 1 to less than 18 years old receiving antibacterial drug treatment for CDI.

- *Age groups to be studied:*

Two age cohorts will be enrolled as follows:

Cohort 1: 12 to < 18 years old
Cohort 2: 1 to < 12 years old

Enrollment into the trial will begin with Age Cohort 1, and Age Cohort 2 will commence after the first 12 participants complete all study visits in Age Cohort 1.

- *Number of patients to be studied:*

At least 192 eligible subjects should be enrolled and randomized to either bezlotoxumab or placebo in a 3:1 ratio, stratified by age of enrollment (from 1 year to <12 years, and ≥ 12 years to < 18 years). A minimum of 24 subjects should be enrolled in each age cohort for PK assessment. At least 12 participants should be between the age of 1 to <6 years, and at least 12 participants should be between the age of 6 to <12 years.

- *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/Safety Endpoints/Monitoring:*

Pharmacokinetic Endpoints:
The PK endpoint for subjects receiving bezlotoxumab must include an evaluation of $AUC_{0\text{-}inf}$ for each age cohort. The $AUC_{0\text{-}inf}$ of bezlotoxumab will be determined from a single IV dose based upon blood samples collected at selected time points following infusion as agreed upon in the protocol.

In addition, maximum concentration (C_{max}), terminal half-life, volume of distribution (V_{dss}), and clearance (Cl) must be evaluated for bezlotoxumab in each age cohort.

Efficacy Endpoints:
The primary efficacy endpoint must include the proportion of participants with a sustained clinical response over a period of 12 weeks. Sustained clinical response is defined as initial clinical response of the baseline CDI episode (as assessed by the investigator) AND no CDI recurrence through Week 12. Initial clinical response is defined as improvement in the number and character of bowel movements AND does not require further CDI therapy within 2 days after completion of up to 21 days of antibacterial drug treatment for CDI.

Important secondary endpoints must include:

A) Proportion of subjects who experience a CDI recurrence within 12 weeks following bezlotoxumab administration. CDI recurrence is defined as the development of diarrhea associated with a positive test for the presence of *C. difficile* toxin in stool and for which the participant, in the investigator's opinion, requires and receives antibacterial drug treatment for CDI.

B) The proportion of participants who have a CDI recurrence and proportion of participants who achieve sustained clinical response within 12 weeks of study medication infusion in the subset of participants at high risk for CDI recurrence. Participants at high risk for CDI recurrence are those who meet 1 or more of the following criteria at or before randomization:

    a. Immunocompromised
    b. Prior history of CDI defined as one or more episodes of CDI at any point prior to the baseline episode
    c. Baseline CDI episode that met criteria for severe CDI[4]
    d. *C. difficile* ribotype 027 was isolated from a stool sample collected during the baseline CDI episode
    e. Received treatment with 1 or more systemic antibacterial drugs known to increase the risk of CDI (during treatment of the baseline CDI episode), including but not limited to clindamycin, fluoroquinolones, cephalosporins, aztreonam, penicillins, macrolides, and carbapenems

Safety Endpoints:

Safety outcomes must include:

a) Deaths
b) Serious adverse events (SAEs)
c) AEs leading to premature discontinuation of study treatment

[4] Criteria based upon Van Dorp (Clin Infect Dis. 2017 Jan15;64(2):192-198.) and Na (PLoS One. 2015 Apr 23;10(4):e0123405)

d) Treatment-emergent AEs
e) Changes in laboratory parameters

All AEs must be monitored until symptom resolution or until the condition stabilizes.

A Data Monitoring Committee (DMC) must be included because CDI presents an elevated risk of death or other serious outcomes.

- *Known Drug Safety concerns and monitoring:* Adverse events, including laboratory parameters and survival should be assessed for all subjects who receive any amount of study drug. Specific AEs, such as infusion-related reactions have been reported with the use of bezlotoxumab and should be monitored for 24 hours following the start of the infusion. In addition, subjects should be monitored for treatment-emergent antibodies to bezlotoxumab in serum through 12 weeks following administration of bezlotoxumab.

- *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:*

  - *dosage form: sterile solution*
  - *route of administration: intravenous*
  - *regimen: single 10mg/kg dose (the dose may be adjusted to match adult serum drug exposures after PK data are analyzed from the first 9 bezlotoxumab-treated subjects in the 12 to < 18-year-old cohort)*

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

The study is not powered for the assessment of efficacy. The sample size is chosen to provide a sufficient number of participants with bezlotoxumab exposure to assess the safety profile in the pediatric population.

The proportion of subjects with sustained clinical response (primary efficacy endpoint) over 12 weeks must be summarized within each treatment arm by age group along with 95% confidence intervals (CIs). Additionally, the difference in proportions between the treatment groups stratified by age category at randomization will be calculated along with the corresponding 95% CI.

The secondary efficacy endpoints will be summarized in the same manner as the primary efficacy endpoint. However, for the endpoints assessed in the subset of participants at high risk of CDI recurrence, the difference in proportions between the treatment groups and corresponding 95% confidence interval will be calculated without stratification.

All safety parameters must be summarized descriptively for the whole safety population. Summaries should be grouped by treatment; further stratification by age group might be done where deemed appropriate.

- *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 FD&C Act, regardless of whether the study demonstrates that bezlotoxumab 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 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.

- *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.[5] 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 FDA.gov[6] and referenced in the guidance for industry *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*.

- *Timeframe for submitting reports of the study(ies):* Reports of the above studies must be submitted to the Agency on or before November 30, 2022. Please keep in mind that pediatric exclusivity attaches only to existing exclusivity, 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.

  If FDA has not determined whether bezlotoxumab 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 study will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the study.

[5] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[6] https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM312964.pdf

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(ies) 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(ies) 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(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.

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.[7]
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.

[7] https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm316937.htm

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 on the Clinical Trials website.[8]

If you have any questions, call J. Christopher Davi, MS, Senior Regulatory Project Manager, at (301) 796-0702.

Sincerely,

{See appended electronic signature page}

John Farley, MD, MPH
Acting Director
Office of Infectious Diseases
Center for Drug Evaluation and Research

[8] www.ClinicalTrials.gov

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JOHN J FARLEY
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