BLA 761046

WRITTEN REQUEST – AMENDMENT 1

Merck Sharpe and Dohme,
a Subsidiary of Merck & Co., Inc.
Attention: Megan Wise, PhD
Assocoate Principal Scientist
Global Regulatory Affairs and Clinical Safery
351 North Sumneytown Pike UG2D-2505
North Wales, PA 19454-2505

Dear Dr. Wise:[1]

Please refer to your correspondence dated December 12, 2021, requesting changes to FDA's April 13, 2020, Written Request for pediatric studies for Zinplava (bezlotoxumab).

We have reviewed your proposed changes and are amending the Written Request. All other terms stated in our Written Request issued on April 13, 2020, remain the same. (Text added is underlined. Text deleted is strikethrough.)

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,

[1]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.

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[2].

The epidemiology of CDI in pediatric patients indicates: (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[3,4].

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. 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.

(b) (4)

–The (b) (4) -Written Request amendment includes a decrease in the total sample size from 192 to 140 patients.

(b) (4)

–Review of the (b) (4) blinded safety data was consistent with expectations for a pediatric study population with multiple medical

[2] Lessa FC, Mu Y, Bamberg WM, Beldavs ZG, Dumyati GK.Dunn JR, et al. Burden of *C/ostridium difficile* infection in the United States. N Engl J Med. 2015 Feb 26;372(9):825-34.
[3] Kim J, Shaklee JF, Smathers S, Prasad P, Asti L, Zoltanski J, et al. Risk factors and outcomes associated with severe *C/ostridium difficile* infection in children. Pediatr Infect Dis J 2012;31(2):134-8.
[4] Styczynski J. Infectious complications in children and adults with hematological malignancies. Acta Haematol Pol. 2019 Sep;50(3):167-73.

comorbidities.- (b) (4) Additionally, rReview of common treatment emergent adverse events in the ongoing study have revealed a safety profile consistent with that observed in the registrational trials conducted in adults.-Therefore, (b) (4)

FDA agrees that the revised enrollment target of 140 subjects will (b) (4) allow for an (b) (4) adequate assessment of safety (b) (4) based on the blinded data accrued to date.- (b) (4) -

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.

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, 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. (b) (4) -

- *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.

[redacted] (b) (4)

- *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~~ should commence after the first 12 participants complete all study visits in Age Cohort 1.

- *Number of patients to be studied:*

At least ~~192~~ 140 eligible subjects ~~should~~ must 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 from 12 years to <18 years). A minimum of 24 subjects must be enrolled in each age cohort for PK assessment. At least 12 participants must be between the age of 1 to <6 years, and at least 12 participants must be between the age of 6 to <12 years.

- *Study endpoints:*

  - Pharmacokinetic [redacted] (b) (4) endpoints:

    The PK endpoint for subjects receiving bezlotoxumab must include an evaluation of AUCo-inf for each age cohort. The AUCo-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 (Cmax), terminal half-life, volume of distribution (Vdss), and clearance (Cl) must be evaluated for bezlotoxumab in each age cohort.

- [redacted] Efficacy endpoint(s):

  The primary efficacy endpoint must include the proportion of patients with a sustained clinical response over a period of 12 weeks. Sustained clinical response ~~is defined~~ must be defined in the protocol as initial clinical response of the baseline CDI episode (as assessed by the investigator) AND no CDI recurrence through Week 12. Initial clinical response must be defined in the protocol ~~is defined as~~ 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: [redacted]

  A) Proportion of subjects who experience a CDI recurrence within 12 weeks following bezlotoxumab administration. CDI recurrence ~~is defined as~~ must be defined in the protocol 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 must be defined in the protocol.

~~B) are those who meet 1 or more of the following criteria at or before randomization:~~

~~a. Immunocompromized~~
~~b. Prior history of COi defined as one or more episodes of CDI at any point prior to the baseline episode~~
~~c. Baseline COi episode that met the criteria for severe CDI[4]~~
~~d. C. *difficile* ribotype 027 was isolated from a stool sample collected during the baseline CDI episode~~

~~Received treatment with 1 or more systemic antibacterial drugs known toincrease the risk of COi (during treatment of the baseline COi episode), including but not limited to clindamycin, fluoroquinolones, cephalosporins,aztreonam, penicillins, macrolides, and carbapenems~~

- *Safety Endpoints* (b) (4)

~~Safety outcomes must include~~ The protocols must include a plan for monitoring the following safety outcomes:

a) Deaths
b) Serious adverse events (SAEs)
c) AEs leading to premature discontinuation of study treatment
d) Treatment-emergent AEs
e) Changes in laboratory parameters

~~All AEs~~ The protocol must include a plan for monitoring of all AEs ~~must be monitored~~ until symptom resolution or until the condition stabilizes.

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

- Known Drug Safety concerns and monitoring: The protocol must include a plan for monitoring a~~A~~dverse 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 the protocol ~~should~~ must include plans for monitoring of subjects ~~ed~~ for 24 hours following the start of the infusion. In addition, the protocol must include a plan for monitoring ~~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 adultserum 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 must ~~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 may ~~can will~~ be calculated without stratification.

  All safety parameters ~~must~~ should 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.

The following information pertains to all clinical studies in the Written Request:

- *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.

- *Biological product information:*

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

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

In accordance with section 505A(e)(2), if:

(1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval);
(2) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act; and
(3) you have not marketed the formulation within one year after the Agency publishes such notice, the Agency will publish a second notice indicating you have not marketed the new pediatric formulation.

If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be prepared by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. Under these circumstances, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for preparing an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using such a formulation, the following information must be provided for inclusion in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step preparation instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies must be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.

- *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 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(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.[5] You are encouraged to contact the reviewing Division for further guidance.

  For studies started after December 17, 2017, study data must 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.

[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

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 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.

  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, submit your proposed changes using strikethrough and underline (Text added is underlined. Text deleted is strikethrough.) 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 on the Clinical Trials website.[8]

For ease of reference, a complete copy of the Written Request, as amended, is attached to this letter.

Reports of the studies that meet the terms of the Written Request dated April 13, 2020, as amended by this letter must be submitted to the Agency on or before November 30, 2022, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

If FDA has not determined whether Zinplava 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 Written Request amendment, 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.

Submit reports of the studies as a supplement to an approved BLA with the proposed labeling changes you believe are warranted based on the data derived from these studies.

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

When submitting the reports, 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 Act, 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:

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

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website.[9]

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

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
Director
Office of Infectious Diseases
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE: Pediatric Written Request – Amendment 1

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

BLA 761046

WRITTEN REQUEST – AMENDMENT 1

Merck Sharpe and Dohme,
a Subsidiary of Merck & Co., Inc.
Attention: Megan Wise, PhD
Assocoate Principal Scientist
Global Regulatory Affairs and Clinical Safery
351 North Sumneytown Pike UG2D-2505
North Wales, PA 19454-2505

Dear Dr. Wise:[1]

Please refer to your correspondence dated December 12, 2021, requesting changes to FDA's April 13, 2020, Written Request for pediatric studies for Zinplava (bezlotoxumab).

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,

[1]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.

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[2].

The epidemiology of CDI in pediatric patients indicates: (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[3,4].

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. 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.

The Written Request amendment includes a decrease in the total sample size from 192 to 140 patients. Review of the blinded safety data was consistent with expectations for a pediatric study population with multiple medical comorbidities. Additionally, review of common treatment emergent adverse events in the ongoing study have revealed a safety profile consistent with that observed in the registrational trials conducted in adults.Therefore, FDA agrees that the revised enrollment target of 140 subjects will allow for an adequate assessment of safety based on the blinded data accrued to date.

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.

---

[2] Lessa FC, Mu Y, Bamberg WM, Beldavs ZG, Dumyati GK.Dunn JR, et al. Burden of *C/ostridium difficile* infection in the United States. N Engl J Med. 2015 Feb 26;372(9):825-34.
[3] Kim J, Shaklee JF, Smathers S, Prasad P, Asti L, Zoltanski J, et al. Risk factors and outcomes associated with severe *C/ostridium difficile* infection in children. Pediatr Infect Dis J 2012;31(2):134-8.
[4] Styczynski J. Infectious complications in children and adults with hematological malignancies. Acta Haematol Pol. 2019 Sep;50(3):167-73.

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, 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.

- *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.

- *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 should commence after the first 12 participants complete all study visits in Age Cohort 1.

- *Number of patients to be studied:*

  At least 140 eligible subjects must 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 from 12 years to <18 years). A minimum of 24 subjects must be enrolled in each age cohort for PK assessment. At least 12 participants must be between the age of 1 to <6 years, and at least 12 participants must be between the age of 6 to <12 years.

- *Study endpoints:*

  - Pharmacokinetic endpoints:

    The PK endpoint for subjects receiving bezlotoxumab must include an evaluation of AUCo-inf for each age cohort. The AUCo-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 (Cmax), terminal half-life, volume of distribution (Vdss), and clearance (Cl) must be evaluated for bezlotoxumab in each age cohort.

  - Efficacy endpoint(s):

    The primary efficacy endpoint must include the proportion of patients with a sustained clinical response over a period of 12 weeks. Sustained clinical response must be defined in the protocol as initial clinical response of the baseline CDI episode (as assessed by the investigator) AND no CDI recurrence through Week 12. Initial clinical response must be defined in the protocol 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 must be defined in the protocol 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 must be defined in the protocol.

- *Safety Endpoints*

  The protocols must include a plan for monitoring the following safety outcomes:

a) Deaths
b) Serious adverse events (SAEs)
c) AEs leading to premature discontinuation of study treatment
d) Treatment-emergent AEs
e) Changes in laboratory parameters

The protocol must include a plan for monitoring of all AEs 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: The protocol must include a plan for 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 the protocol must include plans for monitoring of subjects for 24 hours following the start of the infusion. In addition, the protocol must include a plan for monitoring for treatment-emergent antibodies to bezlotoxumab in serum through 12 weeks following administration of bezlotoxumab.

- *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 must 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 may be calculated without stratification.

All safety parameters should 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.

The following information pertains to all clinical studies in the Written Request:

- *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.

- *Biological product information:*

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

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

  In accordance with section 505A(e)(2), if:

  (1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval);
  (2) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act; and
  (3) you have not marketed the formulation within one year after the Agency publishes such notice, the Agency will publish a second notice indicating you have not marketed the new pediatric formulation.

  If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be prepared by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. Under these circumstances, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for preparing an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency.

If you conduct the requested studies using such a formulation, the following information must be provided for inclusion in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step preparation instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies must be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.

- *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 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(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.[5] You are encouraged to contact the reviewing Division for further guidance.

[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.

For studies started after December 17, 2017, study data must 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 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.

  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.

[6] https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM312964.pdf

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, submit your proposed changes using strikethrough and underline (Text added is underlined. Text deleted is strikethrough.) 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 on the Clinical Trials website.[8]

For ease of reference, a complete copy of the Written Request, as amended, is attached to this letter.

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

Reports of the studies that meet the terms of the Written Request dated April 13, 2020, as amended by this letter must be submitted to the Agency on or before November 30, 2022, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

If FDA has not determined whether Zinplava 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 Written Request amendment, 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.

Submit reports of the studies as a supplement to an approved BLA with the proposed labeling changes you believe are warranted based on the data derived from these studies.
When submitting the reports, 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 Act, 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:

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

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website.[9]

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

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

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
Director
Office of Infectious Diseases
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE: Pediatric Written Request – Amendment 1

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
04/29/2022 03:46:56 PM