DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 201699

WRITTEN REQUEST

Merck Sharp & Dohme Corp
Agent for Cubist Pharmaceuticsls, LLC
Attention: Sandra Lynn Wood, Ph.D.
Director, Global Regulatory Affairs
PO Box 1000 Mailstop UG2CD-48
351 North Sumneytown Pike
North Wales, PA 19454

Dear Dr. Wood:

Reference is made to your January 23, 2018 Proposed Pediatric Study Request for fidaxomicin oral tablets and oral suspension.

BACKGROUND:
Dificid (Fidaxomicin) is a macrolide antibacterial drug which was approved by the FDA on 27 May 2011 for the treatment of *Clostridium difficile*-associated diarrhea in adults (CDAD). CDAD is a toxin mediated disease caused by *C. difficile*, an anaerobic bacterium producing pathogenic enterotoxins. Clinical manifestations of CDAD range from asymptomatic carriage or mild, self limited diarrhea to fulminant colitis, toxic megacolon, intestinal perforation and death.

The incidence of CDAD in the pediatric population has been increasing. Estimated incidence of CDAD in individuals under 18 years of age is approximately 24,000 cases per year; mortality rate is estimated at 3.8%.[1] The only drug approved for treatment of CDAD in children <18 years of age is oral vancomycin.

Fidaxomicin has been studied in pediatric subjects from 6 months to less than 18 years of age with CDAD in a phase 2 open label, safety, tolerability, and pharmacokinetic (PK) study that evaluated the extent of systemic exposure of fidaxomicin following the administration of doses given every 12 hours for 10 consecutive days. This study is not included in this written request since it has already been completed and the final study report submitted. (b) (4)

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[1] Kim J, Smathers SA, Prasad P, Leckerman KH, Coffin S, Zaoutis T. Epidemiological features of *Clostridium difficile*-associated disease among inpatients at Children's Hospitals in the United States, 2001-2006. Pediatrics 2008;122(6):1266-70.

[redacted] (b) (4)

We agree that neonates and infants less than 6 months of age may be excluded from the proposed study due to high rates of *C. difficile* colonization and co-infection with other diarrheal pathogens which makes the diagnosis of CDAD and evaluation of treatment outcomes in this population difficult.

To obtain needed information on the safety and efficacy of fidaxomicin in treatment of CDAD in the pediatric population, 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 studies*:

Based on review of the available nonclinical toxicology data no additional animal studies are required at this time to support the clinical studies described in the written request.

- *Clinical study:*

A phase 3, multicenter, investigator-blind, randomized, parallel group study to investigate the safety and efficacy of fidaxomicin oral suspension or tablets taken q12h, compared to vancomycin oral liquid or capsules taken q 6h, for 10 days in pediatric subjects aged 6 months to less than 18 years, with CDAD.

Efficacy in children 6 months to <18 years of age will be supported by extrapolation of efficacy from trials in adults and assessment of clinical efficacy in children.

- *Objective of the study:*

To investigate the safety and efficacy of fidaxomicin oral suspension or tablets as compared with oral vancomycin in the treatment of CDAD in children from 6 months to < 18 years of age.

- *Patients to be Studied:*

  Age group in which study(ies) must be performed:

Children 6 months to <18 years of age

- *Number of patients to be studied:*

At least one hundred thirty-five eligible subjects must be enrolled and randomized to either fidaxomicin or vancomycin in a 2:1 ratio (approximately 90 randomized to fidaxomicin and 45

to vancomycin), stratified by age at enrollment (from 6 months to < 24 months, ≥ 2 years to < 6 years, ≥ 6 years to < 12 years, and ≥ 12 years to < 18 years). At least 21 subjects will be enrolled into each age group (i.e., a minimum of 14 randomized to fidaxomicin and 7 to vancomycin).

- *Representation of Ethnic and Racial Minorities:*

The study 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:*

Pharmacokinetic Endpoints:
For subjects receiving fidaxomicin, two blood samples will be taken on any day between Day 5 and 10 inclusive. One sample should be collected within 30 minutes pre-dose and another between 1 to 5 hours post-dose. For all subjects a stool sample will be taken between Day 5 and 10 inclusive, within 24 hours of a dose.

Palatability:
Acceptance of formulation at first administration of study drug and at Day 7 (± 1 day) in all subjects receiving fidaxomicin oral suspension and vancomycin oral liquid should be recorded.

Efficacy Endpoints:
The primary efficacy endpoint will be investigator-assessed clinical response (at End of Treatment (EOT)+2 days).

Important secondary endpoints must include
- Sustained clinical response at the End of Study (EOS) (EOT +30 days)
- Sustained clinical response 14 days after Confirmation Clinical Response (EOT +16 days)
- Time to resolution of diarrhea (TTROD)
- Recurrence of CDAD during or at the end of the Follow-up period.
- Time to recurrence during or at the end of the Follow-up period.

Safety Endpoints:
Safety outcomes must include:
a) Deaths
b) Serious adverse events (SAEs)
c) AEs leading to premature discontinuation of study treatment
d) Treatment-emergent AEs
e) Changes in vital signs, body weight, hematology, and blood chemistry parameters

- *Known Drug Safety concerns and monitoring:* The adverse reactions such as nausea, vomiting, gastrointestinal hemorrhage, anemia, neutropenia, abnormal elevated liver tests, and isolated instances of serious hypersensitivity reactions have been reported with the use of fidaxomicin and will be monitored throughout the study.

- *Extraordinary results:* In the course of conducting the study, 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/ route of administration/regimen

Subjects from 6 months to <6 years of age: Fidaxomicin oral suspension by mouth, 32 mg/kg/day with a maximum dose of 400 mg/day, divided in 2 doses/day for 10 days.

Subjects aged ≥ 6 years to < 18 years: Fidaxomicin 200 mg tablet, by mouth, 2 times daily, for 10 days.

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 conduct the requested study using a commercially marketable, age-appropriate 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.

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

The proportion of subjects with confirmed clinical response (primary efficacy endpoint) must be summarized within each treatment arm by age group along with exact 95% confidence intervals (CIs).

The secondary efficacy endpoints of recurrence of CDAD and sustained clinical response (at 16 days after EOT and at EOS) must be summarized in the same manner as the primary efficacy endpoint.

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(ies)*:

You must submit proposed pediatric labeling to incorporate the findings of the study(ies). Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that fidaxomicin 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 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 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 https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM312964.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 https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm333969.pdf.

- *Timeframe for submitting reports of the study:*

Reports of the above study(ies) must be submitted to the Agency on or before **July 31, 2019**. 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(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 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, CDER, FDA, Document Control Room, Metro Park North VII, 7620 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 Fariba Izadi, PharmD, Regulatory Project Manager, at 301-796-0563.

Sincerely,

{See appended electronic signature page}

Edward Cox, MD, MPH
Director
Office of Antimicrobial 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/

EDWARD M COX
05/16/2018