

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

219491Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



IND 118958

MEETING MINUTES

Entasis Therapeutics, Inc.
Attention: Marie Minassian
Senior Director, Regulatory Operations
930 Winter Street, Suite 1500
Waltham, MA 02451

Dear Marie Minassian:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for zoliflodacin (ETX0914, previously AZD0914).

We also refer to the teleconference between representatives of your firm and the FDA on September 10, 2024. The purpose of the meeting was to discuss plans for a New Drug Application (NDA) for zoliflodacin for the treatment of uncomplicated gonorrhea caused by *N. gonorrhoeae* in adults and adolescents.

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Alison Rodgers, Senior Regulatory Project Manager, at 301-796-0797.

Sincerely,

{See appended electronic signature page}

Peter Kim, MD, MS
Director
Division of Anti-Infectives
Office of Infectious Diseases
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: September 10, 2024, 4:00 – 5:00 PM
Meeting Format: Teleconference

Application Number: IND 118958
Product Name: Zoliflodacin (ETX0914, previously AZD0914)
Indication: Treatment of uncomplicated gonorrhea caused by *N. gonorrhoeae* in adults and adolescents

Sponsor Name: Entasis Therapeutics, Inc.
Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetic Act

Meeting Chair: Peter Kim, MD, MS
Meeting Recorder: Alison Rodgers

FDA ATTENDEES

CDER Participants:

Office of Infectious Diseases (OID)

Adam Sherwat, MD Deputy Director

Division of Anti-Infectives (DAI)

Peter Kim, MD, MS	Director
Mukil Natarajan, MD	Deputy Director for Safety
Jae Ho Hong, MD	Medical Officer
Shayna Dooling, MD	Medical Officer
Avery Goodwin, PhD	Clinical Microbiology Team Leader
Simone Shurland, PhD	Clinical Microbiology Reviewer

Office of Pharmacology/Toxicology for Infectious Diseases

Terry Miller, PhD Deputy Director

Division of Pharmacology/Toxicology for Infectious Diseases (DPT-ID)

Amy Nostrandt, DVM, PhD	Pharmacology/Toxicology Team Leader
Amy Ellis, PhD	Pharmacology/Toxicology Reviewer

Office of Biostatistics (OB), Division of Biometrics IV (DBIV)

Daniel Rubin, PhD	Secondary Statistics Reviewer
Jie Cong, PhD	Statistics Reviewer

Office of Clinical Pharmacology (OCP), Division of Infectious Disease Pharmacology (DIDP)

Abhay Joshi, PhD

Clinical Pharmacology Team Leader

Tajhia Whigham, PharmD

Clinical Pharmacology Reviewer

Office of Regulatory Operations for Infectious Diseases (ORO-ID)

Maureen Dillon-Parker, MS, RAC Director

Division of Regulatory Operations for Infectious Diseases (DRO-ID)/Anti-Infectives (AI)

Gregory DiBernardo

Chief, Regulatory Project Management Staff,
Anti-Infectives

Dheera Semidey, PharmD

Acting Chief, Regulatory Project Management
Staff

Alison Rodgers

Senior Regulatory Project Manager

Hany Meskelu, PharmD

Regulatory Project Manager

Claire Starling, MPH

Regulatory Project Manager

Faith Jones

Regulatory Information Specialist

Office of Pharmaceutical Quality (OPQ)

Dorota Matecka, PhD

Product Quality Team Leader

Jessica Zarenkiewicz, PhD

Product Quality Reviewer

Katherine Windsor, PhD

Product Quality Reviewer

Office of Scientific Investigations (OSI)

Phillip Kronstein, MD

Lead Medical Officer, Team Leader

John Lee, MD

Medical Officer, OSI Reviewer

Office of Surveillance and Epidemiology (OSE)

Amy Chung, PharmD, MS, BCPS Safety Regulatory Project Manager

Division of Medication Error and Prevention Analysis

Deborah Myers, RPh, MBA

Safety Evaluator

Division of Risk Management

Brad Moriyama, PharmD, BCCP

Reviewer

SPONSOR ATTENDEES**Entasis Therapeutics, Inc.**

David Altarac, MD, MPA

Chief Medical Officer

(b) (4)

Principal Biostatistician (Consultant)

Kajal Larson, PhD

Senior Director, Clinical Pharmacology &
Clinical Development

Drew Lewis, MD, MTM&H, FACP

Vice President, Clinical Development

Sarah McLeod, PhD

Senior Director, Clinical Microbiology

Marie Minniassian

Senior Director, Regulatory Operations

Jennifer Morgan, MPH

Executive Director, Program Management &
Clinical Supply

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Shruta Rege, PhD

Senior Vice President, Regulatory Affairs & Development Operations

Other Attendees

Carolyn Deal, PhD

Chief, Enteric and Sexually Transmitted Infections Branch, Division of Microbiology and Infectious Disease (DMID), National Institute of Allergy and Infection Diseases (NIAID)

Tammy Pillay, BPharm, MPRM

Head of Regulatory Affairs, Global Antibiotic Research and Development Partnership (GARDP)

Alison Luckey, MD, FFPM

Senior Medical Lead, GARDP

1.0 BACKGROUND

On June 12, 2024, Entasis Therapeutics, Inc. (Sponsor) submitted a request for a Pre-NDA meeting (teleconference) to discuss plans for an NDA for zoliflodacin for the treatment of uncomplicated gonorrhea caused by *N. gonorrhoeae* in adults and adolescents. The Division granted the September 10, 2024, meeting on June 20, 2024. The Sponsor submitted a briefing package on July 30, 2024.

The Division sent Preliminary Comments to the Sponsor on September 5, 2024. On September 6, 2024, the Sponsor submitted their responses to the Division's preliminary comments and communicated that they planned to discuss Question 1 during the meeting.

The question and discussion points from the meeting are captured below. The complete question/response preliminary communication document and the Sponsor's slides are attached.

2.0 DISCUSSION

Sponsor Question 1

Substantial evidence of effectiveness and characterization of the safety profile for zoliflodacin for the treatment of uncomplicated gonorrhea will be derived from:

- Robust safety and efficacy data from a single large, multicenter, adequate, and well-controlled Phase 3 trial (Study STI_Zoli001), where zoliflodacin met its safety and efficacy objectives, as well as supporting data provided from a Phase 2 trial (Study DMID 14-0014)
- Safety data on zoliflodacin collected from eight clinical studies, including six Phase 1 studies, one Phase 2 trial, and one Phase 3 trial
- A comprehensive nonclinical assessment, including microbiology data, primary and secondary PD, safety pharmacology, drug interactions, PK, and toxicology data as well as genotoxicity, reproductive, and developmental toxicity

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- PK/PD data with a population PK model utilizing data from Phase 1 and Phase 3 trials to determine the probability of target attainment (PTA)

Does the Agency agree that the data from the pivotal Phase 3 trial and supporting evidence from the Phase 2 trial and from the nonclinical package are adequate for the Agency's review of the NDA for zoliflodacin?

Division Response to Question 1:

We agree that the data from the phase 3 trial, the phase 2 trial, and the nonclinical package are sufficient for a review of the NDA; however, whether the single adequate and well-controlled phase 3 trial plus proposed confirmatory evidence are sufficient to demonstrate substantial evidence of effectiveness will be a review issue. We note that zoliflodacin met the NI margin of 12% in the pivotal trial, but zoliflodacin was nominally statistically inferior to the control regimen in the trial. Whether the results will translate into an adequate treatment effect size will be a review issue and could potentially impact the labeled indication (patient population, limitations of use), if approved. Please refer to the October 11, 2022, meeting with GARDP, which discussed a limited use population. We also refer you to the guidance on Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence, September 2023, available at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/demonstrating-substantial-evidence-effectiveness-one-adequate-and-well-controlled-clinical> for the types of confirmatory evidence recommended to demonstrate substantial evidence of effectiveness. The list of nonclinical pharmacology/toxicology studies provided on pages 60-64 of the briefing document to support the zoliflodacin IND and upcoming NDA appears complete and appropriate. We do not anticipate that any additional studies of this type would be needed, with the possible exception of studies that could be necessary to qualify impurities if any new concerns/issues are identified.

Sponsor Response to Question 1:

The pivotal Phase 3 trial assessed if zoliflodacin was non-inferior to the comparator (combination ceftriaxone (IM, 500 mg) & azithromycin (oral, 1 g). The results showed that zoliflodacin achieved a clinically meaningful treatment effect (>90%) and met the pre-specified non-inferiority margin (NIM). Although the study was designed with the 12% NIM, a narrower 10% NIM was achieved. The pre-specified NIM was selected based on clinical and statistical considerations to help to ensure that any observed differences within this range would not lead to a clinically meaningful loss of efficacy. Confirmatory substantial evidence of efficacy was observed in the micro-ITT evaluable population, and in all pre-specified secondary endpoints.

Zoliflodacin has the potential to address growing public health concerns, including the following benefits:

- Zoliflodacin is a first-in-class, single-dose, oral antibiotic for the treatment of uncomplicated gonorrhea
- Zoliflodacin is a new chemical class with a differentiated mode of inhibition against bacterial type II topoisomerases, resulting in no cross-resistance to other antibiotics, including fluoroquinolones
- Zoliflodacin demonstrates potent in vitro activity against contemporary clinical isolates of *Neisseria gonorrhoeae*, including multidrug-resistant and extensively drug-resistant isolates.
- No emergence of resistance following treatment with zoliflodacin has been detected

Meeting comments:

- The Sponsor thanked the Division for the preliminary comments and stated that they would like to better understand the Division's response to question 1 and the data that should be included in the NDA.
- The Division responded that they agree with the Sponsor's plan to submit data from the phase 2 and phase 3 trials and the proposed nonclinical package and that these will be sufficient to initiate review of the NDA. The remaining question regarding whether the single adequate and well-controlled phase 3 trial plus proposed confirmatory evidence are sufficient to demonstrate substantial evidence of effectiveness will be a review issue. The Division noted that the Global Antibiotic Research and Development Partnership (GARDP) had previously mentioned a proposed limited use or limited population indication for the drug product and that zoliflodacin is not intended to be a broad first line treatment in comparison to the current use of ceftriaxone.
- The Sponsor asked how the product would be positioned if it is approved. The Sponsor stated that discussion around a limited use or limited population indication focused on a 12% non-inferiority (NI) margin and that the Division had previously stated if a narrower margin is achieved, a broader indication could be considered. The Sponsor stated that they will submit the NDA for the indication: "treatment of uncomplicated gonorrhea infection caused by *Neisseria gonorrhoeae* in adults and adolescents," and that individual treatment decisions will be based on individual treatment parameters. The Sponsor noted that their pivotal trial did not study a limited population.
- The Sponsor emphasized the public health need for new alternative treatments for gonorrhea as there is emerging resistance to multiple antibacterial drugs.
- The Sponsor asked if the Division's comments regarding treatment effect size were from a clinical or statistical standpoint. The Division acknowledged that the Sponsor met the 12% and 10% NI margins, but that zoliflodacin was nominally statistically inferior to the comparator regimen of ceftriaxone plus azithromycin and the Division considers this a review issue. The Division stated that they understand that ceftriaxone is the current standard of care, and that gonorrhea develops resistance over time. The Division noted that submitting the phase 2

study data will be helpful as a component of the proposed confirmatory evidence, and the Division will review these data with the phase 3 data.

- The Division encouraged the Sponsor to include in the NDA a comprehensive discussion of the proposed confirmatory evidence for demonstrating substantial evidence of effectiveness to be used in combination with the Phase 3 trial data.
- The Division inquired whether the Sponsor is planning to propose any risk evaluation and mitigation strategies (REMS). The Sponsor stated that they are not planning for REMS.
- The Sponsor noted that a November 18, 2024, Chemistry, Manufacturing and Controls Pre-NDA meeting is scheduled.
- The Sponsor stated that they expect to submit the NDA in the 1st quarter 2025.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

4.0 ACTION ITEMS

- The Division will issue meeting minutes within 30 days.

5.0 ATTACHMENTS AND HANDOUTS

- Division's Preliminary Meeting Comments dated September 5, 2024
- Sponsor's Response to Preliminary Meeting Comments dated September 12, 2024

OTHER IMPORTANT APPLICATION INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. The Sponsor stated that there will not be any minor application components submitted after submission of the original application.
- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.
- A preliminary discussion was held on the need for a REMS, other risk management actions and, where applicable, the development of a Formal Communication Plan and it was concluded that the application will not include a REMS or other risk management action.

Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

In addition, we note that a chemistry pre-submission meeting is scheduled for

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November 18, 2024. A summary of agreements reached at that meeting will be documented in the respective meeting minutes.

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.¹ In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.²

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information³ and Pregnancy and Lactation Labeling Final Rule⁴ websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for

¹ <https://www.fda.gov/media/86340/download>

² <https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development>

³ <https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information>

⁴ <https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule>

human drug and biological products.

- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug’s use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

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Silver Spring, MD 20993
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- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.
- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).
- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).
- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission “**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**” in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, “Product name, NDA/BLA 012345, Establishment Information for Form 356h.”

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h⁵ and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*⁶. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions*, and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*, be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested

⁵ <https://www.fda.gov/media/84223/download>

⁶ <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and>

information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.⁷

⁷ <https://www.fda.gov/media/85061/download>



IND 118958

MEETING PRELIMINARY COMMENTS

Entasis Therapeutics, Inc.
Attention: Marie Minassian
Senior Director, Regulatory Operations
930 Winter Street, Suite 1500
Waltham, MA 02451

Dear Marie Minassian:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for zoliflodacin (ETX0914, previously AZD0914).

We also refer to your June 12, 2024, correspondence, received June 12, 2024, requesting a meeting to discuss plans for a new drug application (NDA) for zoliflodacin for the treatment of uncomplicated gonorrhea caused by *N. gonorrhoeae* in adults and adolescents.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, an electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with FDA policy, you should not make audio or visual recordings of the discussion at this meeting. Consistent with 21 CFR 10.65(e), the official record of this meeting will be the FDA-generated minutes.

If you have any questions, contact Alison Rodgers, Senior Regulatory Project Manager, at 301-796-0797 or alison.rodgers@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Gregory DiBernardo
Chief, Regulatory Project Management Staff
Anti-Infectives
Division of Regulatory Operations
for Infectious Diseases
Office of Regulatory Operations
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE:

Meeting Preliminary Comments



PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: September 10, 2024, 4:00 – 5:00 PM
Meeting Format: Teleconference

Application Number: IND 118958
Product Name: zoliflodacin (ETX0914, previously AZD0914)

Indication: Treatment of uncomplicated gonorrhea caused by *N. gonorrhoeae* in adults and adolescents
Sponsor Name: Entasis Therapeutics, Inc.

Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetic Act

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting (teleconference) scheduled for September 10, 2024, from 4:00 to 5:00 PM, between Entasis Therapeutics, Inc., and the Division of Anti-Infectives. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda. Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

On June 12, 2024, Entasis Therapeutics, Inc. (Sponsor) submitted a request for a Pre-NDA meeting (teleconference) to discuss plans for an NDA for zoliflodacin for the treatment of uncomplicated gonorrhea caused by *N. gonorrhoeae* in adults and adolescents. The Division granted the September 10, 2024, meeting on June 20, 2024. The Sponsor submitted a briefing package on July 30, 2024. The Sponsor's final meeting questions and the Division's responses are outlined below.

2.0 DISCUSSION

Regulatory

Question 1:

Substantial evidence of effectiveness and characterization of the safety profile for zoliflodacin for the treatment of uncomplicated gonorrhea will be derived from:

- Robust safety and efficacy data from a single large, multicenter, adequate, and well-controlled Phase 3 trial (Study STI_Zoli001), where zoliflodacin met its safety and efficacy objectives, as well as supporting data provided from a Phase 2 trial (Study DMID 14-0014)
- Safety data on zoliflodacin collected from eight clinical studies, including six Phase 1 studies, one Phase 2 trial, and one Phase 3 trial
- A comprehensive nonclinical assessment, including microbiology data, primary and secondary PD, safety pharmacology, drug interactions, PK, and toxicology data as well as genotoxicity, reproductive, and developmental toxicity
- PK/PD data with a population PK model utilizing data from Phase 1 and Phase 3 trials determine the probability of target attainment (PTA)

Does the Agency agree that the data from the pivotal Phase 3 trial and supporting evidence from the Phase 2 trial and from the nonclinical package are adequate for the Agency's review of the NDA for zoliflodacin?

FDA Response:

We agree that the data from the phase 3 trial, the phase 2 trial, and the nonclinical package are sufficient for a review of the NDA; however, whether the single adequate and well-controlled phase 3 trial plus proposed confirmatory evidence are sufficient to demonstrate substantial evidence of effectiveness will be a review issue. We note that zoliflodacin met the NI margin of 12% in the pivotal trial, but zoliflodacin was nominally statistically inferior to the control regimen in the trial. Whether the results will translate into an adequate treatment effect size will be a review issue and could potentially impact the labeled indication (patient population, limitations of use), if approved. Please refer to the October 11, 2022, meeting with GARDP, which discussed a limited use population. We also refer you to the guidance on Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence, September 2023, available at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/demonstrating-substantial-evidence-effectiveness-one-adequate-and-well-controlled-clinical> for the types of confirmatory evidence recommended to demonstrate substantial evidence of effectiveness.

The list of nonclinical pharmacology/toxicology studies provided on pages 60-64 of the briefing document to support the zoliflodacin IND and upcoming NDA appears complete and appropriate. We do not anticipate that any additional studies of this type would be

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needed, with the possible exception of studies that could be necessary to qualify impurities if any new concerns/issues are identified.

Microbiology

Question 2:

In accordance with prior guidance from the Agency (IND 139105, email communicated dated 27 February 2024), Entasis plans to submit the following surveillance data in the initial NDA:

- In vitro activity of zoliflodacin and comparator agents against *N. gonorrhoeae* isolates collected from the last three years (2020-2022) (100 isolates each year). These *N. gonorrhoeae* isolates were obtained from the CDC.
- In vitro activity of zoliflodacin and comparator agents against an additional 25 *N. gonorrhoeae* isolates from the CDC collected in 2022 from female patients.
- In vitro activity of zoliflodacin and comparator agents against 50 isolates collected in 2023 from three different states in the US (MI, NY, MN) through the contract research organization (b) (4)

Does the Agency agree with Entasis's plan for the submission of surveillance data to support review of the NDA?

FDA Response: *The proposal appears reasonable.*

Question 3:

Entasis plans to submit the microbiology information under the designated eCTD sections in Modules 2, 4 and 5 as follows:

- Module 2.7.2.4: Microbiology information
- Module 2.7.3 (Summary of Clinical Efficacy): A summary of the efficacy information from the Phase 3 trial and the clinical microbiology findings from the Phase 3 trial
- Module 4.2.1.1 (Primary pharmacodynamics) and Module 5.3.5.4 (Other Study Reports and Related Information): Microbiology study reports

Does the Agency agree on the eCTD placement of the microbiology information?

FDA Response: *We agree.*

Clinical Pharmacology**Question 4:**

The clinical pharmacology program consisted of six Phase 1 studies and one Phase 3 trial and aimed to describe PK of zoliflodacin to support dose selection during clinical development and for approval. Key findings regarding the metabolism of zoliflodacin are summarized below:

- The SAD study (Study D4930C00001, powder for suspension) showed that primary exposure parameters generally increased as the dose increased, with a geometric mean fraction of the dose excreted in urine (% fe) of approximately less than 5% across all doses.
- The human ADME study (Study D4930C00003, powder for suspension) showed that approximately 80% of the dose (with approximately 1.5% as parent drug) was recovered in feces, indicating that unabsorbed drug, biliary excretion and/or efflux is a major route of elimination; 18% of the dose was recovered in urine, with only approximately 2.5% of the dose being recovered in urine as parent drug.
 - Metabolites identified in the feces accounted for 56% of the approximately 80% of the dose excreted; major metabolites (>5% of dose) included M17, M15, M13, M29, and M30 (see Section 5.2.1.2).
- Non-clinical studies conducted in rodents with and without 1-aminobenzotriazole (ABT) established that metabolites characterized in the human ADME study were derived from both CYP and non-CYP mechanisms, with the fraction metabolized by non-CYP mechanisms being estimated to be at least 25%.
 - Intravenous (IV) administration of [¹⁴C] zoliflodacin in bile-duct cannulated (BDC) rats demonstrated 54.8, 14.9, and 24.4% of the dose was excreted in the bile, feces, and urine, respectively, suggesting biliary excretion and efflux into the gut are important for the elimination of zoliflodacin, in addition to its metabolism.
- The metabolite profile in the feces of humans and BDC rats are similar with several metabolites generated via reductive metabolism by the gut flora, suggesting unabsorbed zoliflodacin and/or effluxed drug undergoes extensive non-hepatic metabolism in the gut.
- In vitro, CYP reaction phenotyping suggested CYP-mediated metabolism of zoliflodacin is likely mediated by CYP3A4/5 enzymes (68.4%) with lesser contributions from CYP1A2 (14.1%) and CYP2C9 (10.0%).

The totality of the clinical and non-clinical metabolism data indicates that a significant portion of zoliflodacin metabolism occurred via reduction in the gut following efflux of zoliflodacin in addition to CYP-mediated metabolism in the liver.

The FDA Guidance *Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling* (May 2003) states that a hepatic impairment study may not be needed for single dose drugs. Further, at a Type C Meeting on January 24, 2014 (IND 118958, Reference ID: 3457429), the Agency concurred that because zoliflodacin is being developed as a single dose regimen for the indication of uncomplicated gonorrhea, renal and hepatic impairment studies are likely not necessary, but final decisions would be based on the results of the proposed ADME study. Although the results of the ADME study showed that a substantial portion of the parent drug is metabolized and eliminated via CYP and non-CYP-mediated pathways and efflux, with minimal renal elimination, no overt safety signal was observed during the clinical development program of zoliflodacin. Therefore, based on the totality of the data for this single dose drug, Entasis determined that renal and hepatic impairment studies are not needed.

Does the Agency agree with Entasis's assessment that clinical renal and hepatic impairment studies are not required?

FDA Response: *We agree.*

Question 5:

Study STI_Zoli003 was a Phase 1, single dose, open-label, randomized study in healthy subjects evaluating two parallel cohorts: Cohort 1 was a BE/FE study and Cohort 2 was a DDI study. The DDI cohort demonstrated that co-administration of itraconazole, a strong CYP3A4 inhibitor, at steady state, increased the AUC_{0-∞} of single 3 g oral dose of zoliflodacin by approximately 1.38-fold, while C_{max} was essentially unchanged.

Data from Studies D4930C00001, D4930C00003, STI_Zoli003, and STI_Zoli001 were used to build a PBPK model to understand the DDI potential with respect to CYP3A4 inhibitors and inducers. Similar to the clinical study (STI_Zoli003), the PBPK model predicted that the fraction metabolized via CYP3A4 was approximately 31% and that the AUC of zoliflodacin would increase by 1.40- and 1.48-fold with the strong CYP3A4 inhibitors, itraconazole and ritonavir, respectively.

Therefore, having verified the PBPK model with clinical DDI data, and given that the zoliflodacin AUC_{0-∞} increased by less than 1.5-fold, Entasis determined that no additional CYP3A4 inhibitor clinical studies are necessary.

Does the Agency agree with this strategy?

FDA Response:

It is premature to provide a definitive answer pending review of the DDI Study STI_Zoli003 report. Based on the summary information presented from DDI Study STI_Zoli003, we agree that an additional CYP3A4 inhibitor clinical study may not be necessary.

Clinical

Question 6:

The substantial evidence for efficacy will be derived from the single robust Phase 3 trial (Study STI_Zoli001); therefore, Entasis does not plan to include a separate Integrated Summary of Efficacy (ISE). Entasis plans to describe the efficacy data from the single pivotal Phase 3 trial and from a supportive Phase 2 trial (Study DMID 14-0014) in Modules 2.7.3, Summary of Clinical Efficacy and 2.5, Clinical Overview.

Does the Agency agree with this approach and the placement of this information in the eCTD?

FDA Response: *We agree with your approach.*

Question 7:

A total of eight clinical studies were conducted in support of the zoliflodacin clinical program, and include six Phase 1 studies, one Phase 2 trial, and one Phase 3 trial (see Section 5.2). The safety data from these studies will be summarized in Module 2.7.4, Summary of Clinical Safety. In total, 995 subjects have been exposed to zoliflodacin in the clinical program, with 619 exposed in the pivotal Phase 3 trial (Study STI_Zoli001) at the intended dose of 3 g.

Does the Agency agree that the size of the zoliflodacin safety database is acceptable?

FDA Response: *The size of safety database appears acceptable pending full review of the safety data submitted in the NDA.*

Question 8:

The substantial evidence for safety will be derived from the single robust Phase 3 trial (Study STI_Zoli001); therefore, Entasis does not plan to include a separate Integrated Summary of Safety (ISS). Safety data from all eight clinical studies will be summarized in Modules 2.7.4, Summary of Clinical Safety and 2.5, Clinical Overview.

Does the Agency agree with this approach and the placement of this information in the eCTD?

FDA Response:

We agree with your proposed approach and the placement of the safety information in the eCTD. We recommend that you submit narratives and case report forms for all serious adverse events, pregnancies, deaths, and adverse events leading to treatment withdrawal or study discontinuation. You may submit a 10% random sample of the case report forms.

Question 9:

To facilitate a thorough risk/benefit assessment, Entasis intends to present aggregate data using the following six Standardized MedDRA Queries (SMQ) in the safety summary: Acute renal failure (Broad), Drug related hepatic disorders - comprehensive search (Narrow), Haematopoietic leukopenia (Broad), Cardiac arrhythmias (Broad), Hypersensitivity (Narrow), and Pseudomembranous colitis (Broad).

Does the Agency agree with this strategy to present aggregate data for the safety summary?

FDA Response:

Your proposal is acceptable. In addition to your proposed safety summary, we also recommend you present aggregated data for the following SMQs: tendinopathies and ligament disorders, peripheral neuropathy, and convulsions. Also, present aggregated data for following adverse events: sleep disorders and disturbances, anxiety disorders and symptoms, and depressed mood disorders and disturbances to evaluate any similarities or differences from other topoisomerase inhibitors.

Question 10:

A pivotal Phase 3 trial (Study STI_Zoli001) evaluated the efficacy and safety of a single oral dose of zoliflodacin compared to a combination of a single IM dose of ceftriaxone and a single oral dose of azithromycin in the treatment of patients with uncomplicated gonorrhea.

Entasis plans to include the data from the primary efficacy endpoint of microbiological cure at test of cure (TOC) at the urogenital site among participants included in the micro-ITT (urogenital) population, (b) (4)

in Section 14 of the proposed label.

Does the Agency agree with the inclusion of this clinically important information in the proposed label of the intended NDA for zoliflodacin to guide prescribers and healthcare practitioners for the safe and effective use of zoliflodacin for the treatment of uncomplicated gonorrhea?

FDA Response:

We note that you did not specify [REDACTED] (b) (4) [REDACTED] and the study was not designed to rigorously establish non-inferiority or superiority versus the active control for these endpoints. The inclusion of this proposed information in the product labeling will be a review issue.

Additional Comments:**Product Quality/Chemistry, Manufacturing and Controls (CMC):**

We have the following comments for consideration as you prepare for submission of an NDA:

1. Please refer to the following guidance for further information regarding recommended microbiological controls for your process: *Guidance for Industry- Microbiological Quality Considerations in Non-Sterile Drug Manufacturing* (2021).
2. We remind you that specified and unspecified impurities in the drug substance and drug product should be controlled per ICH Q3A, Q3B, and M7, as applicable, considering the proposed maximum daily dose.
3. Specific acceptance criteria should be set for all tests in the drug product specification currently listed as "Report Results" including water content, reconstitution time and XRPD/crystallinity. These limits should be justified based on product development data.
4. As previously recommended, conduct and submit a risk assessment for the presence of elemental impurities as described in the ICH guidance Q3D Elemental Impurities.
5. In addition, conduct and submit a risk assessment for the presence of residual solvents as described in the ICH guidance Q3C Residual Solvents
6. We also remind you to maintain awareness of potential nitrosamine impurities in your API and drug product throughout product development and consider the recommendations in the "FDA Guidance for Industry: Control of Nitrosamine Impurities in Human Drugs."
7. We strongly recommend you request a pre-NDA CMC-dedicated meeting to discuss any outstanding product quality issues and to ensure that sufficient and complete CMC information is submitted in the NDA.

Regulatory:

In response to your Priority Review inquiry shared via email to the DAI Regulatory Project Manager we note the following. Priority review may be granted when a drug is intended to treat a serious condition and if approved would provide a significant improvement in safety or effectiveness over currently available treatments. Additionally, a product that has been designated as a Qualified Infectious Disease Product may be granted a priority review. A determination for priority review is made within 60 days of the NDA submission. Submit your justification for priority review with your NDA.

Clinical Pharmacology:

At the time of NDA submission, for clinical pharmacology studies, submit tables summarizing the bioanalytical methods and the life-cycle information using the templates available in the 'Bioanalytical Methods Templates' Technical Specifications Document (<https://go.usa.gov/xVsdJ>) and submit the tables in the Appendix of the Summary of Biopharmaceutics located in eCTD 2.7.1.

3.0 ADDITIONAL IMPORTANT APPLICATION INFORMATION**DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION**

As stated in our June 20, 2024, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA VII. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at [FDA.gov](https://www.fda.gov).¹

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived,

¹ <https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm>

deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.² In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.³

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information⁴ and Pregnancy and Lactation Labeling Final Rule⁵ websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.

² <https://www.fda.gov/media/86340/download>

³ <https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development>

⁴ <https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information>

⁵ <https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule>

- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug’s use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h⁶ and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*⁷. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions*, and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*, be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA

⁶ <https://www.fda.gov/media/84223/download>

⁷ <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and>

investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.⁸

REAL-WORLD EVIDENCE

CDER strongly encourages sponsors to include information in their submission cover letters that identifies uses or proposed uses of real-world evidence (RWE) to support a regulatory decision regarding product safety and/or effectiveness. For recommendations on specific information to include in submission cover letters, see the guidance for industry *Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drug and Biological Products*.⁹ For questions or clarification, contact cdermedicalpolicy-realworldevidence@fda.hhs.gov.

-End.

⁸ <https://www.fda.gov/media/85061/download>

⁹ <https://www.fda.gov/media/124795/download>

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/

GREGORY F DIBERNARDO
09/05/2024 09:25:34 AM

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 118958

MEETING MINUTES

Entasis Therapeutics
c/o MMS Holdings, Inc.
Attention: Roberta Krieger, MS
Regulatory Strategist
6880 Commerce Blvd.
Canton, MI 48187

Dear Ms. Krieger:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ETX0914 (b) (4) for Oral Suspension.

We also refer to the teleconference held between representatives of your firm and the FDA on January 20, 2016. The purpose of the End-of-Phase 2 meeting was to discuss the Phase 3 study for ETX0914.

A copy of the official minutes of the teleconference is enclosed your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Alison Rodgers, Regulatory Project Manager, at (301) 796-0797.

Sincerely,

{See appended electronic signature page}

Sumathi Nambiar, MD, MPH
Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: End-of-Phase 2

Meeting Date and Time: January 20, 2016, 10:00 – 11:00 AM
Meeting Location: Teleconference

Application Number: 118958
Product Name: ETX0914 (b) (4) for Oral Suspension
Indication: Treatment of uncomplicated gonorrhea
Sponsor/Applicant Name: Entasis Therapeutics

Meeting Chair: Sumathi Nambiar MD, MPH
Meeting Recorder: Alison Rodgers

FDA ATTENDEES

Division of Anti-Infective Products

Alma Davidson, MD, Clinical Reviewer
Maureen Dillon-Parker, Chief, Project Management Staff
Amy Ellis, PhD, Pharmacology and Toxicology Reviewer
Avery Goodwin, PhD, Clinical Microbiology Team Leader (Acting)
Felicia Griffin, PhD, Statistical Reviewer
Yang He, PhD, Clinical Pharmacology Reviewer
Karen Higgins, ScD, Statistics Team Leader
Seong Jang, PhD, Clinical Pharmacology Team Leader (Acting)
Sumathi Nambiar, MD, MPH, Director
Alison Rodgers, Regulatory Project Manager
Hala Shamsuddin, MD, Clinical Team Leader
Simone Shurland, PhD, Clinical Microbiology Reviewer
Joseph Toerner, MD, MPH, Deputy Director for Safety
Rama Yasaei, Intern
Ping Zhao, PhD, Physiologically-based Pharmacokinetics Reviewer
Luning Zhuang, PhD, Clinical Pharmacology Reviewer

Office of Antimicrobial Products

John Farley, MD, MPH, Deputy Director

Division of Medical Errors and Prevention

Deborah Myers, PharmD, Safety Evaluator

SPONSOR ATTENDEES

Entasis Therapeutics (Entasis)

Robin Isaacs, MD, Chief, Medical Officer

John Mueller, PhD, Vice President, Projects and Early Clinical Development

John O'Donnell, BS, Director DMPK

Kenneth Lawrence, BS, PharmD, Associate Director, Development Operations

(b) (4)

National Institute of Allergy and Infectious Diseases (NIAID)

Sexually Transmitted Diseases Branch, Division of Microbiology and Infectious Diseases

Carolyn Deal, PhD, Branch Chief,

Jill Long, MD, Medical Officer

BACKGROUND

The original IND for this product was submitted on August 8, 2013, by AstraZeneca Pharmaceuticals, LP, for the treatment of uncomplicated *Neisseria gonorrhoeae* infection. Ownership of the IND was transferred to Entasis on May 20, 2015. The name of the product was changed from AZD0914 to ETX0914.

The Sponsor submitted a request for an End-of-Phase 2 meeting on October 8, 2015, and a briefing package on December 17, 2015. The Division sent preliminary comments to the Sponsor on January 15, 2016. The Sponsor submitted comments and requested further discussion of the Division's responses to questions 4, 1a, 2, and 5 (in that order) on January 19, 2016. The format provides for the meeting discussion points in the order requested by the Sponsor. The complete document containing the Sponsor's original questions, Division's responses, and Sponsor's comments submitted on January 19, 2016 is appended.

DISCUSSION

Sponsor Question 4

With respect to drug-drug interaction (DDI) studies:

4a. Does the FDA concur that no DDI studies are required to support the licensure of ETX0914 as a single dose for the treatment of uncomplicated gonorrhea?

4b. Does the FDA concur that patients with HIV infection on treatment can be enrolled in the Phase 3 study?

Meeting Comments:

- The Division confirmed that they had reviewed the Sponsor's comments regarding question #4. While the Division agreed that CYP3As were not responsible to 100% of metabolites, the Division requested that the Sponsor provide more detail regarding its

in vitro phenotyping results. The Sponsor responded that they had used standard methodology and typical controls. The Sponsor agreed to provide the study report to the Division for review.

- The Division requested further explanation of the Sponsor's statement that the formation of the M3 metabolite occurs through a non-P450 mediated metabolic pathway. The Sponsor responded that they had provided the urine profile and can send the fecal profile and human absorption, distribution, metabolism, and excretion (ADME) report.
- The Division requested that the Sponsor provide the quantitative or semi-quantitative metabolic scheme. This information will help to eliminate the Division's concern regarding the predominant involvement of the enzyme. The Sponsor agreed to provide the information.
- The Sponsor agreed to submit the following documents to the IND within the next four weeks: Human ADME Clinical Study Report, Summary of P450 and non-P450 metabolic pathways, in vitro metabolism phenotyping results, and human metabolic scheme based on ADME results. The Division stated that they would review the information within one to two weeks and respond to the Sponsor as needed.

Discussion of the physiologically based pharmacokinetic (PBPK) Modeling Analysis

Meeting Comments:

- The Sponsor requested clarification of the Division's comment regarding PBPK modeling analysis. The Division responded that in the meeting package, the Sponsor states that PK extrapolation from adults to adolescents is supported by allometric and/or PBPK modeling. However, no further information was provided. The Division requested information to support this statement. At the current stage, any results from PBPK modeling would be helpful as no population PK data are available from the adolescent population. The Sponsor agreed to submit the data to the IND within the next four weeks.

Sponsor Question 1

With respect to dose selection for the Phase 3 study:

1a. Does the FDA agree that the efficacy and the safety data from the interim analysis of approximately 80% of evaluable patients enrolled in the ongoing Phase 2 study will inform the Phase 3 dose? Based on these data, the Sponsor proposes to study (b) (4) orally as a single dose in the Phase 3 study.

Meeting Comments:

- The Sponsor clarified that the oral suspension used in the Phase 2 study is not available anymore. The Sponsor stated that data from the Thorough QT (TQT) study will be provided and asked if this would be satisfactory. The Division agreed that this would be

acceptable and requested that the Sponsor provide the report of the TQT study. The Sponsor asked if a summary document of the pharmacokinetic portion of the TQT study would be sufficient. The Division agreed.

- Regarding PK/PD target attainment analysis (PTA), the Sponsor stated that they have not seen isolates with MIC>0.25 mcg/mL in their study and asked if the Division had any additional comments. The Division clarified that the Sponsor's PK/PD target analysis result is acceptable at the current dose and anticipated MIC, but the concern is that bacterial resistance could potentially increase in the future and the currently proposed dose of (b) (4) may not be sufficient.
- The Sponsor stated that they will not finalize the dose until efficacy and microbiology data from the Phase 2 study are fully analyzed.

Sponsor Question 2

With respect to the overall ETX0914 clinical development program:

2a. Does the FDA concur with the proposed design of the Phase 3 study?

Meeting Comments:

- The Sponsor stated that it would be very challenging to conduct a double-blind study due to logistical issues. They maintained that only an open-label study can be done, and asked if an open-label design is acceptable. The Division requested clarification of the logistical issues involved in conducting a double-blind study.
- The Sponsor responded by first confirming that the current Phase 2 study is being conducted according to the Division's requirement that all of the data remain blinded until after the database has been locked. This is the model for the Phase 3 study. The Sponsor explained that asking patients to receive both oral medication and a placebo injection would probably adversely affect enrollment as many patients have received injections in the past and would not wish to be given another intramuscular injection. The Sponsor noted that Institutional Review Boards (IRBs) may have concerns about the inclusion of a placebo injection.
- The Division stated that it understands the Sponsor's concerns about conducting a double-blind study, but explained that the problem with an open-label study in this situation is that there is a negative feeling toward the control which might bias the study results. The Division asked the Sponsor to provide information in the protocol for how the bias might be addressed. The Division recommended that the Sponsor follow all randomized patients whether they receive the test drug or not, collect outcomes, and conduct a sensitivity analyses. The Sponsor agreed. The Sponsor stated that they will blind as much of the study as possible. The Division reminded the Sponsor that it is their risk if they choose to conduct an open-label study because it is a trial design with added biases that may affect the interpretation of the study results.

2b. Does the FDA concur with the enrollment of adolescents (b) (4) into the Phase 3 program?

Meeting Comments:

- The Sponsor requested clarification on how to conduct sparse PK sampling, as patients want to get in and out of the study center as quickly as possible due to the social stigma of a sexually transmitted disease. The Division responded that sparse sampling in adolescents is necessary in order to provide PK information for this population, given that currently such information is not available. The Sponsor stated that it will be difficult to enroll adolescents if they must have parental consent. The Division stated that it understands the Sponsor's concerns about sparse PK sampling of adolescents, but recommended that the Sponsor try to collect PK data in order to evaluate drug-drug interactions in patients receiving anti-HIV drugs that are CYP3A modifiers. The Division strongly recommended sparse PK sampling in the proposed Phase 3 study because the population PK or PBPK modeling approach should be validated with patient PK data. The Division clarified that it may not require PK samples in all patients, and suggested that the Sponsor could collect PK samples from patients in a few sites. The Sponsor asked if collecting PK on 20-30 patients from a few sites would be acceptable. The Division requested that the Sponsor submit a plan for sparse PK sampling and focus on patients receiving anti-HIV drugs that are CYP3A modifiers in the proposed Phase 3 study. The Sponsor agreed to provide a plan for sparse sampling when they submit their Phase 3 protocol.

Sponsor Question 5

The Sponsor requests general guidance on the Pediatric Study Plan (PSP) that will be submitted within 60-days after the End-of-Phase 2 meeting.

Meeting Comments:

- The Sponsor asked if the Division could suggest any strategies for enrolling adolescents in a clinical trial for a gonococcal infection, as the Sponsor is concerned that requiring parental consent will be a barrier to enrolling this population. The Division responded that it understands the difficulties of enrolling adolescents in the trial and suggests enrolling as many adolescents as possible. The Division asked the Sponsor to share any difficulties it encounters trying to enroll this population with the Division for further discussion.
- The Sponsor stated that they will submit an initial Pediatric Study Plan (iPSP) and asked if the PeRC was likely to accept a small number of adolescent patients. The Division explained that it has usually been able to work with the PeRC and that the iPSP timeline allows for discussion in order to reach an agreement on the number of adolescent subjects.

ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

ACTION ITEMS

- The Sponsor will submit to the IND within the next four weeks: Human ADME Clinical Study Report, Summary of P450 and non P450 metabolic pathways, in vitro metabolism phenotyping results, human metabolic scheme based on ADME results, and results of PBPK modeling.
- The Sponsor will submit a summary document containing the pharmacokinetic portion of the TQT study.
- The Sponsor agreed to provide a plan for sparse sampling when they submit their Phase 3 protocol.
- The Sponsor will submit an iPSP within 60 days of this meeting.

ATTACHMENTS AND HANDOUTS

- Communication of January 19, 2016 [Questions/responses]

General Application Information

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at

301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to:
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions “shall be submitted in such electronic format as specified by [FDA].” FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf>). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See <http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf>), as well as email access to the eData Team (cdet-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a [Study Data Standards Resources](#) web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, [Study Data Standards Resources](#) and the CDER/CBER Position on Use of SI Units for Lab Tests website found at <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm>.

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

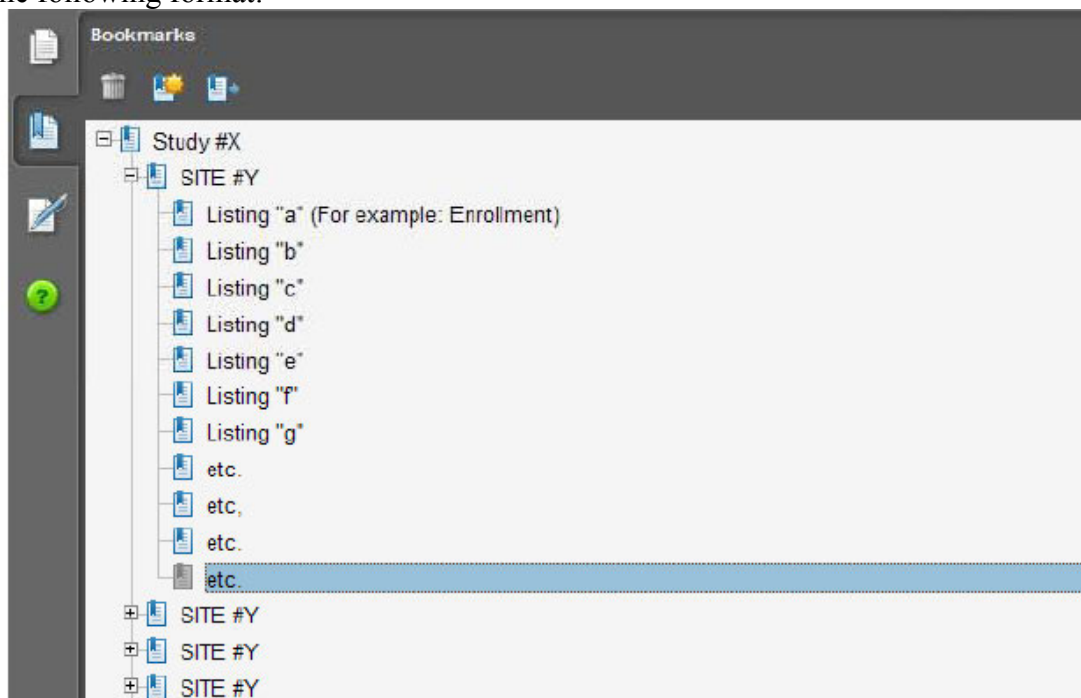
This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
 - a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
 - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
 - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as “line listings”). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
 - b. Subject listing for treatment assignment (randomization)
 - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

Attachment 1

Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

- A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item ¹	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

- B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



- C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

¹ Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page
(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population
5. A brief description of the study design (e.g., placebo or active controlled)
6. Specific concerns for which you anticipate the Division will have comments
7. For changes to protocols only, also include the following information:
 - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
 - Other significant changes
 - Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

SPONSOR'S ORIGINAL QUESTIONS, DIVISION'S PRELIMINARY RESPONSES SENT TO SPONSOR ON JANUARY 15, 2016, AND SPONSOR'S COMMENTS SUBMITTED ON JANUARY 19, 2016

IND 118958 – ETX0914 – Entasis list of EOP2 questions

A. Question 1

With respect to dose selection for the Phase 3 study:

1a. Does the FDA agree that the efficacy and the safety data from the interim analysis of approximately 80% of evaluable patients enrolled in the ongoing Phase 2 study will inform the Phase 3 dose? Based on these data, the Sponsor proposes to study (b) (4) orally as a single dose in the Phase 3 study.

FDA Response:

Based on the interim analysis of efficacy and safety data of the Phase 2 study, and assuming that the analysis of the complete data is similar to the interim analysis, the proposed (b) (4) oral single dose of ETX0914 as the oral suspension appears reasonable. However, there is lack of bridging data/information between the oral suspension used in the Phase 2 study and the proposed Phase 3 formulation. Thus, in order to determine the dose of Phase 3 formulation, we recommend you provide additional information (see our response to the Question 1b below).

We also note that the range of MIC₉₀ values for ETX0914 was up to 0.25 mcg/mL, and that the probability of PK/PD target attainment falls sharply for isolates with MIC $\geq$ 0.5 mcg/mL. Thus we are concerned that emerging resistance may render the (b) (4) dose less effective in the future.

Entasis Response:

Thank you for your response. Entasis proposes to provide the Agency a brief summary of results from the completed thorough QT study for comment prior to finalization of the dose for Phase 3. An information amendment will be submitted to the IND.

Your comment concerning PK/PD target attainment in the setting of emerging resistance is noted. We would propose to discuss this further at the teleconference.

1b. Does the FDA agree that the Phase 3 dose will be finalized based on the relative bioequivalence study of the Phase 3 formulation? The Sponsor will provide these data to FDA for review prior to initiation of the Phase 3 study.

FDA Response:

The proposed PK assessment in the planned TQT study appears acceptable to assess PK of the proposed Phase 3 formulation, but is not adequate to evaluate the relative bioavailability with the oral suspension. Thus, we recommend you conduct an additional PK study to evaluate the relative bioavailability of the proposed Phase 3 formulation compared with the oral suspension formulation prior to the Phase 3 study, in order to support the dose of the proposed Phase 3 formulation. Alternatively, prior to conducting the proposed Phase 3 study, the planned TQT study needs to be completed to obtain the PK and safety information of the proposed Phase 3 formulation.

After completion of either an additional relative bioavailability study or the proposed TQT study, we will provide further comment about the dose of the proposed formulation to be evaluated in the Phase 3 study.

Entasis Response:

Direct comparison in the same study with the Phase 2 oral suspension is not possible as no Phase 2 drug substance is available.

Entasis agrees that prior to conducting the proposed Phase 3 study, the planned TQT study needs to be completed to obtain the PK and safety information of the proposed Phase 3 formulation; a brief summary of the completed thorough QT study will be provided to the IND prior to finalization of the dose for Phase 3.

B. Question 2

With respect to the overall ETX0914 clinical development program:

2a. Does the FDA concur with the proposed design of the Phase 3 study?

FDA Response:

The draft protocol that you submitted for the Phase 3 trial appears reasonable. However, we highly recommend that you include study sites that are geographically dispersed and representative of various regions in the United States, and that you especially include sites where fluoroquinolone resistance is more prevalent.

Additionally, we recommend that you consider conducting this study as a fully blinded study using a double-dummy design. Subjects assigned to arm 1 would receive an oral dose of 2 g of ETX0914 and a placebo intramuscular injection. Subjects assigned to arm 2 would receive an oral placebo and intramuscular dose of 500 mg of ceftriaxone.

Entasis Response:

Thank you for your response. Entasis does not believe that the Phase 3 study can be undertaken as a double-blind placebo-controlled study for logistical reasons. The FDA supported this view at the January 24 2014 Type C meeting; the Agency minutes state “Ideally, the trial should be double-blinded; however, we agree with an open-label design because of logistical reasons.”. In addition, we note both the recent delafloxacin and solithromycin Phase 3 studies for the treatment of gonorrhea are open-label.

2b. Does the FDA concur with the enrollment of adolescents [REDACTED] (b) (4) into the Phase 3 program?

FDA Response:

Yes, we agree. We recommend that you include a PK assessment, using a sparse PK sampling design, in all patients enrolled for the proposed Phase 3 study, including adolescents [REDACTED] (b) (4) and adults (18 years of age or older).

Entasis Response:

Thank you for your response. We would like to discuss at the teleconference your comment concerning sparse PK sampling.

2c. Does the FDA agree that the planned development will include sufficient numbers of patients to support licensure with regard to gender, race, and hepatic or renal insufficiency?

FDA Response:

While your proposal seems reasonable, it is premature to discuss whether the data are sufficient to support a potential approval.

Entasis Response:

Thank you for your response.

2d. Does the FDA concur with the proposed size of the safety database at the time of NDA submission?

FDA Response:

The proposed safety database (N= 638) appears reasonable for the (b) (4) dose assuming that the oral suspension in the Phase 2 study and the oral sachet intended to be tested in the Phase 3 study have similar bioavailability.

Entasis Response:

Thank you for your response.

2e. Does the FDA concur that the totality of the proposed clinical development program is sufficient to support licensure of ETX0914 for the treatment of uncomplicated gonorrhea?

FDA Response:

In general, an adequate and well controlled Phase 3 study with supportive data from a Phase 2 study would be acceptable to support an indication for the treatment of uncomplicated urogenital gonorrhea. Please note that the acceptability of your Phase 2 trial data will be contingent on demonstrating bioavailability of the formulations.

Entasis Response:

Thank you for your response.

C. Question 3

With respect to the design of the thorough QT study:

3a. Does the FDA concur with the proposed study design for the thorough QT study?

FDA Response: Yes, we agree.

Entasis Response:

Thank you for your response.

3b. Does the FDA concur with the proposal to evaluate the relative bioequivalence of the Phase 3 formulation in the context the thorough QT study?

FDA Response: Please see our response to the Question 1b.

Entasis Response:

Thank you for your response.

D. Question 4

With respect to drug-drug interaction (DDI) studies:

4a. Does the FDA concur that no DDI studies are required to support the licensure of ETX0914 as a single dose for the treatment of uncomplicated gonorrhea?

FDA Response:

No, we do not agree. Please see our response to Question 4b.

Entasis Response:

Thank you for your response. Our response for Question 4 is consolidated below in the response to Question 4b.

4b. Does the FDA concur that patients with HIV infection on treatment can be enrolled in the Phase 3 study?

FDA Response:

Yes, we agree that patients with HIV infection on treatment can be enrolled in the proposed Phase 3 trial. However, we have the following concerns regarding the prediction of the effect of CYP3A modulators on the exposure of ETX0914 using a PBPK modeling approach.

Figure 16 in your PBPK analysis showed that exposure of ETX0914 may be increased by about (b) (4) when co-administered with CYP3A inhibitors in subjects with (b) (4) of $f_{m,CYP3A}$ (fraction of hepatic clearance contributed by CYP3A). However, the PBPK study report also indicated that $f_{m,CYP3A}$ may be (b) (4) (item #3 of Section 6.14 Limitation of the modeling), in which a (b) (4) increase in the exposure of ETX0914 may be expected when co-administered with CYP3A inhibitors. We recommend that you provide additional information to justify in detail the choice of the value for $f_{m,CYP3A}$ in your current ETX0914 PBPK model using existing in vitro and human mass balance data.

If the information to justify current $f_{m, CYP3A}$ is acceptable, you may enroll HIV-infected patients that are on the treatment with protease inhibitors and/or integrase inhibitors. However, we recommend you modify your protocol by collecting sparse samples of ETX0914 in sufficient numbers of non-HIV patients and HIV patients receiving CYP3A inhibitor-containing regimen, and use population PK analysis to determine the effect of CYP3A inhibitors on the ETX0914 exposure. You may use your PBPK simulations to support the design of this DDI assessment. In addition, after completion of the proposed Phase 3 study, the results of the population PK analysis can be used for additional verification of your PBPK model.

If the information to justify current $f_{m, CYP3A}$ (b) (4) is not acceptable, we recommend that you conduct clinical drug-drug interaction (DDI) studies to assess need of dose adjustment when ETX0914 is co-administered with CYP3A inhibitors/inducers prior to the Phase 3 study. Depending on the results of clinical DDI studies, we recommend you propose ETX0914 dose adjustments for HIV patients receiving CYP3A inhibitor-containing antiviral regimens in the proposed Phase 3 study, using the verified PBPK model with clinical DDI data and available safety information. Please refer to the following FDA Guidance: “Drug Interaction Studies - Study Design, Data Analysis, and Recommendations for Dosing and Labeling” for study design.

We also recommend you evaluate the effect of a moderate CYP3A inducer (e.g. efavirenz) on the exposure of ETX0914 using your verified PBPK simulations. Depending on the outcome of the simulations, we may recommend you restrict enrollment of HIV patients receiving nucleoside reverse transcriptase inhibitors that are CYP3A inducers.

Entasis Response:

Thank you for your response.

With respect to the $f_{m, CYP3A}$, as outlined below, the totality of data justify the current $f_{m, CYP3A}$. We have provided a brief summary of our position to facilitate the discussion at the teleconference; figures of the metabolites structure and profiles are provided below to support our arguments. We would like to reach resolution of this issue at the teleconference; if this is not possible due to time constraints, we would like to understand

any additional materials the Agency requires for their review and the timeline for the Agency to respond in writing.

With respect to the impact of moderate inducers, we will work with (b) (4) to evaluate the requested PBPK simulations.

Fraction metabolized by CYP 3A4/5:

Initial assessment of the metabolic contribution attributed to CYP3A4/5 was completed *in vitro* following incubation of [¹⁴C]-ETX0914 with recombinant cytochrome P450 isoforms (study report KMZ227 cited in the SimCYP report). These experiments were completed at 1 and 10 μ M with the metabolism characterized by product formation with only two metabolites (M2 and M6) detected in the incubations with CYP3A4/5. At the time of IND submission and Type C interaction in January 2012 experimental results suggested 100% turnover of ETX0914 was attributed to CYP3A4/5.

Additional relevant studies have been completed since the Type C interaction.

Studies were completed using CYP reaction phenotyping by substrate depletion methods and measuring intrinsic clearance (CL_{int}) in recombinant enzymes. Derived CL_{int} values were “weighted” to the relative amount of the specific isoform in the liver. This is achieved using SimCYP Inter-system Extrapolation Factors (ISEFs) along with median abundance values. The assay consists of testing a panel of six CYP isoforms: CYP1A2, 2C8, 2C9, 2C19, 2D6 and 3A4. The incubation with each CYP is analysed with LC-MS and the result is reported as percent contribution to the metabolism (from each CYP isoform, relative to the other isoforms included in the test). Positive controls with established prototypic standards were completed in parallel to verify integrity of the assay. Percent contribution was combined with predicted clearance of ETX0914 and CL_{int} estimates were determined using the retrograde calculator in SimCYP.

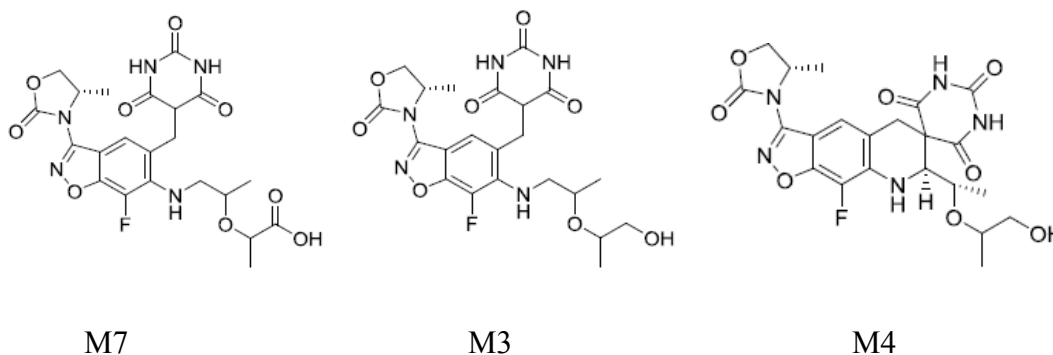
The results of these CYP reaction phenotype studies are detailed below and suggest a role for additional isoforms besides 3A which was estimated to contribute to ~68% of metabolism as assessed using recombinant CYPs (see table below). Predicted overall oral clearance agreed well with observed Phase 1 PK data and the resulting PBPK model was able to reproduce AUC and C_{max} values observed over the clinical dose range.

CYP	% Contribution	CL_{int} estimate (μ L/min/mg)
3A4	68.4	6.63
2C9	10.0	0.97
2C8	4.9	0.47

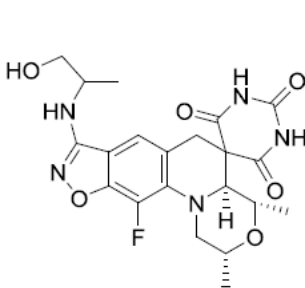
2C19	2.7	0.26
1A2	14.0	1.37
2D6	0.0	0.00

In addition to the CYP reaction phenotyping generated *in vitro*, human ADME data from subjects administered a 3 g radiolabelled dose of ETX0914 showed systemic circulation and urinary excretion of major metabolites not attributed to CYP3A4/5 mediated metabolism which appears to be confined to oxidation of the oxazolidinone moiety of ETX0914 (M2 and M6) per outcome of *in vitro* experiments using 3A4/5 recombinant enzymes. *In vivo* metabolites such as M3, M4, and M7 were observed in the plasma and urine metabolite profiles from humans and were not generated in microsomes *in vitro*, although M4 and M7 were observed in rodent hepatocytes. These same metabolites also showed no modification to the oxazolidinone structure, but rather initial oxidation of the morpholine ring and further cleavage of the tetrahydropyridine ring. Recent *in vivo* work in-house has also shown M3, M4 and M7 are formed in rodents following oral and intravenous administration of ETX0914. Interestingly pre-treatment with 1-aminobenzotriazole (a P450 inhibitor) had no effect on their appearance of M3 suggesting formation of this major metabolite occurs through a non-P450 mediated pathway. Taken collectively these data suggest a reduced role for CYP3A4/5 mediated clearance of ETX0914.

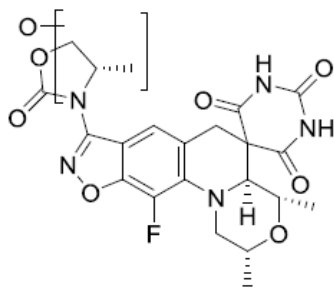
Metabolites observed in vivo only



Metabolites generated by 3A4/5 in vitro



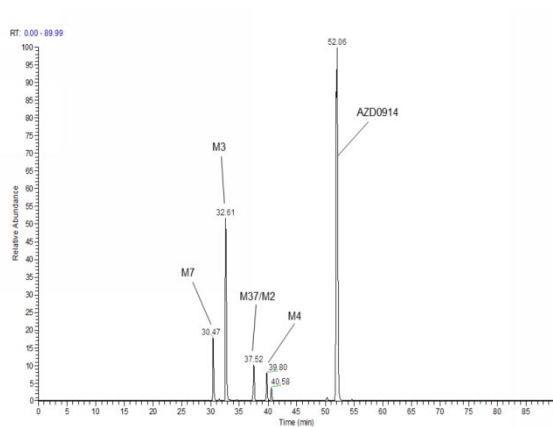
M2



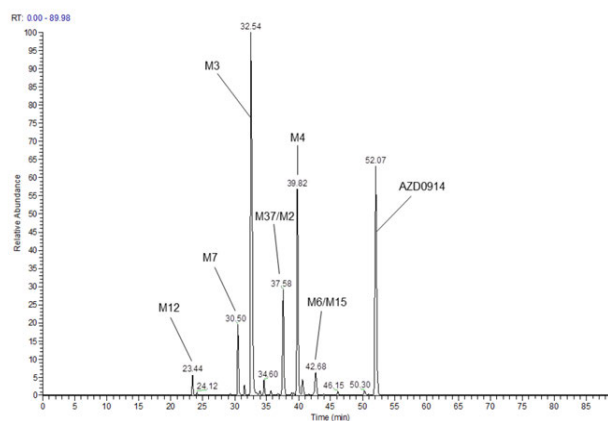
M6

¹⁴C- labelled human ADME study

Plasma profile 4 hpd



Urine profile 0-48 hpd



Additional Comments for the PBPK Modeling Analysis

- Regarding the prediction of the effect of age, please provide modeling and simulation data that support your dose recommendations (b) (4)

Entasis Response:

We would like to discuss this briefly at the teleconference in order to clarify the exact nature of the Agency request.

2. Submit model files used to generate the final simulations (e.g. drug model files, population files, and workspace files, .cmp, .lbr, and .wks). These files should be executable by the FDA reviewers using Simcyp. Software specific excel files such as parameter estimation data files and simulation outputs should be submitted as MS Excel files.

Entasis Response:

We have approached (b) (4) to assess availability of the requested datasets; if available, we will provide to the Agency.

E. Question 5

The Sponsor requests general guidance on the Pediatric Study Plan (PSP) that will be submitted within 60-days after the End-of-Phase 2 meeting.

FDA Response:

Your request of a waiver for pediatric patients below (b) (4) based on the rationale that the necessary studies are unfeasible appears reasonable. However, the Pediatric Study Plan that is to be submitted within 60 days of EOP-2 meeting will be discussed with the Pediatric Review Committee (PeRC) and a determination will be communicated to you.

Entasis Response:

Thank you for your response. In our background document for Question 2, it was stated:

“Potential barriers to the inclusion of (b) (4) patients into a clinical trial of gonococcal infection include obtaining informed consent from the patients’ parents. We would like to discuss means of addressing specific barriers to the conduct of a study of uncomplicated gonorrhea in this population.”

If time permits, Entasis would value the Agency's insights into this issue at the teleconference.

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

/s/

SUMATHI NAMBIAR
02/11/2016