

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

216974Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

IND 131330

MEETING MINUTES

Entasis Therapeutics, Inc.
Attention: Marie Minassian
Director, Regulatory Strategy and Submissions
35 Gatehouse Drive
Waltham, MA 02451

Dear Ms. Minassian:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for sulbactam-durlobactam intravenous.

We also refer to the teleconference between representatives of your firm and the FDA on March 25, 2022. The purpose of the Pre-NDA meeting was to discuss the contents of your planned NDA submission for sulbactam-durlobactam for the treatment of infections in adults due to *Acinetobacter baumannii-calcoaceticus* complex, including multidrug-resistant and carbapenem-resistant strains.

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

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

Sincerely,

{See appended electronic signature page}

Peter Kim, MD, MS
Director
Division of Anti-Infectives
Office of Antimicrobials
Center for Drug Evaluation and Research

Enclosures: Meeting Minutes
Preliminary response document dated March 22, 2022



MEMORANDUM OF TELECONFERENCE

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: March 25, 2022, from 1:00 PM to 2:00 PM, EDT

Application Number: IND 131330
Product Name: Sulbactam-durlobactam intravenous

Indication: Treatment of infections in adults due to *Acinetobacter baumannii-calcoaceticus* complex (ABC), including multidrug-resistant and carbapenem-resistant strains.

Sponsor Name: Entasis Therapeutics, Inc.
Regulatory Pathway: 505(b)(2) of the Federal Food, Drug, and Cosmetic Act

Meeting Chair: Peter Kim, MD, MS, Director
Meeting Recorder: J. Christopher Davi, MS, Senior Regulatory Project Manager

FDA ATTENDEES (Division of Anti-Infectives*)

*Unless otherwise noted

Peter Kim, MD, MS, Division Director
Dmitri Iarikov, MD, PhD, Deputy Director
Thomas Smith, MD, Medical Team Leader
Mayurika Ghosh, MD, Medical Reviewer
Terry Miller, PhD, Pharmacology/Toxicology Team Leader
Owen McMaster, PhD, Pharmacology/Toxicology Reviewer
Avery Goodwin, PhD, Clinical Microbiology Team Leader
Simone Shurland, PhD, Clinical Microbiology Reviewer
Xiaohui (Tracey) Wei, PhD, Clinical Pharmacology Reviewer
Daniel Rubin, PhD, Biostatistics Team Leader (Acting)
Cheryl Grandinetti, PharmD, Office of Scientific Investigation (OSI) Reviewer
Abimbola Adebawale, PhD, Associate Director for Labeling
Maureen Dillon-Parker, MS, RAC, Director, Regulatory Project Management Staff
Gregory F. DiBernardo, Chief, Project Management Staff
J. Christopher Davi, MS, Senior Regulatory Project Manager

SPONSOR ATTENDEES (Entasis Therapeutics, Inc.)

Manos Perros, PhD, President and Chief Executive Officer
David Altarac, MD, MPA, Chief Medical Officer
Shruta Rege, PhD VP, Head of Regulatory Affairs and Pharmacovigilance Operations
Marie Minassian, PharmD, Director, Regulatory Affairs

Matt Ronsheim, PhD, Chief, Pharmaceutical Sciences and Manufacturing Officer
John O'Donnell, BS, VP, Head of DMPK and Pharmacology
Alita Miller, PhD, VP, Head of Biology
Drew Lewis, MD, MTM&H, FACP VP, Clinical Development
Khurram Rana, PharmD, Director, Clinical Scientist
Melissa Steidler, MPH, Associate Director, Pharmacovigilance Operations
Nicole C. Close, PhD, President and Principal Biostatistician, EmpiriStat (consultant)

1.0 BACKGROUND

Entasis Therapeutics, Inc., (Sponsor) requested a type B, pre-NDA meeting on January 26, 2022, which was granted by the Division of Anti-Infectives (Division) on February 1, 2022. The purpose of the meeting was to discuss the contents of the Sponsor's pending NDA submission for sulbactam-durlobactam intravenous, to be submitted pursuant to the 505(b)(2) regulatory pathway. The Sponsor provided briefing materials for the meeting on February 23, 2022, and DAI provided preliminary responses to the questions included in the briefing document on March 22, 2022. Discussion points generated from the preliminary responses are provided herein.

2.0 DISCUSSION

- The Division opened the discussion and informed the Sponsor that feedback regarding question #1 (bioavailability/bioequivalence) would be provided as a post-meeting note* to the minutes. The Sponsor acknowledged this.

****Division Post Meeting Note:*** *Your proposed drug product (sulbactam and durlobactam powder for IV infusion) does not meet the requirement for a waiver for the submission of evidence of in vivo bioavailability or bioequivalence under 21 CFR 320.22(b)(1), because your drug product does not contain the **same active and inactive ingredients** at the same concentration as the proposed listed drug, Unasyn. However, in your future NDA, you could submit information and data to support the establishment of a bridge between your proposed drug product and the proposed listed drug based on 21CFR 320.24(b)(6). The data and information to support the bridge will be reviewed as part of the NDA review.*

- The Sponsor informed the Division that they had recently completed their phase 3 trial as outlined in the briefing package. The Sponsor indicated that they were targeting an NDA submission at the end of June 2022.
- Regarding the clinical pharmacology comment from the Division in the March 22, 2022, preliminary responses (kidney transporter organic anion transporter – OAT1), the Sponsor discussed their summary of transporter interaction assessments to date. The Sponsor stated that sulbactam and durlobactam are not likely to inhibit OAT1 based on the in vitro data.

With regards to the potential drug interactions for sulbactam and durlobactam being the substrates of OAT1, the Sponsor added that renal secretion is not significant for durlobactam, hence the likelihood for durlobactam being a substrate of the OAT1 transporter is low. However, in vitro data and clinical exposures of sulbactam demonstrate it to be a substrate of OAT1. Given that no drug-drug interactions have been observed with co-administration of sulbactam and durlobactam, and that the Unasyn labeling includes the information that sulbactam co-administered with inhibitors of OAT1, such as probenecid, may lead to increased exposures of sulbactam, the Sponsor has no plans to evaluate in vivo interactions and will include information similar to that in the Unasyn labeling into the proposed draft prescribing information for sulbactam-durlobactam.

The Division acknowledged the points regarding OAT1 and informed the Sponsor that they (Division) agreed with the Sponsor's assessment and their March 23, 2022, response to the Division's preliminary comments. The Division added that additional comments and/or information requests may be forthcoming on the subject during the NDA review.

- Regarding the random sample/datasets, the Sponsor inquired as to the purpose of the Division's request. The Division informed the Sponsor that it is desirable to have a portion of the datasets for review before the submission of the NDA to ensure all elements are present to perform a meaningful analysis. The Division indicated that they typically also request a subset of randomly generated subject IDs with corresponding case report forms (CRFs). The Sponsor wished to clarify if this was for all studies, or just for the phase 3 study. The Division confirmed the later to be the case. The Sponsor estimated that they could provide the information in approximately 30 days. The Division indicated that this was acceptable.
- The Division referred the Sponsor to the section on Discussion of the Content of a Complete Application, included in the preliminary responses provided on March 22, 2022. The Division asked if the Sponsor was planning to submit any elements of the application after the official submission date. The Sponsor indicated that prior agreements have been made to submit toxicology final study reports within 60-days of the submission, along with stability data but that there were no other elements that would be pending upon submission. The Division acknowledged this.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed and has been summarized above. The Sponsor is directed to the meeting minutes from the March 24, 2022, chemistry, manufacturing and controls (CMC) meeting for a summary of agreements.
- In addition to the final report for the single toxicology study discussed at the CMC meeting, the Sponsor will submit an additional list of non-clinical reports that they propose to provide in draft form after the NDA is submitted. Upon review of this list, the clinical Division will advise if the submission of these additional reports after the NDA submission is acceptable.
- 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.
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. Please refer to the meeting minutes from the March 24, 2022, CMC meeting for information regarding agreements for late submission that have been reached to date.

Prominently identify each submission containing your late component(s) with the following wording in bold capital letters at the top of the first page of the submission:

NDA NUMBER: LATE COMPONENT - NONCLINICAL
NDA NUMBER: LATE COMPONENT - QUALITY

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:

- 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.

30 ATTACHMENT

- Division’s Preliminary Responses dated March 22, 2022

-End

IND 131330

MEETING PRELIMINARY COMMENTS

Entasis Therapeutics, Inc.
Attention: Marie Minassian
Director, Regulatory Strategy and Submissions
35 Gatehouse Drive
Waltham, MA 02451

Dear Ms. Minassian:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for sulbactam-durlobactam intravenous.

We also refer to your January 26, 2022, correspondence, received January 26, 2022, requesting a pre-NDA meeting to discuss the contents of your planned NDA submission for the treatment of infections in adults due to *Acinetobacter baumannii-calcoaceticus* complex (ABC), including multidrug-resistant and carbapenem-resistant strains.

Our preliminary responses to your meeting questions are enclosed.

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

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

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

Sincerely,

{See appended electronic signature page}

Gregory F. DiBernardo
Chief, Project Management Staff
Anti-Infectives Group 2
Division of Regulatory Operations for
Infectious Diseases
Office of Regulatory Operations
Center for Drug Evaluation and Research

ENCLOSURE: Preliminary Meeting Comments



PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: March 25, 2022, from 1:00 to 2:00 PM, EDT

Application Number: IND 131330
Product Name: Sulbactam-durlobactam intravenous
Indication: Treatment of infections in adults due to *Acinetobacter baumannii-calcoaceticus* complex (ABC), including multidrug-resistant and carbapenem-resistant strains

Applicant Name: Entasis Therapeutics, Inc.
Regulatory Pathway: 505(b)(2) 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 scheduled for March 25, 2022, between Entasis Therapeutics, Inc. and the Division of Anti-Infectives (DAI). 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. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda. It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the 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

Entasis Therapeutics, Inc. (the Sponsor) requested a Type-B, pre-NDA meeting on January 26, 2022, to discuss the contents of the planned NDA submission. DAI granted the meeting on February 2, 2022, and the Sponsor provided the necessary background materials on February 22, 2022. Responses to the questions provided in the briefing materials are provided below (*italics*).

2.0 PRELIMINARY RESPONSES TO QUESTIONS

Question 1: Entasis's proposed regulatory pathway for sulbactam-durlobactam is a 505(b)(2) application, as previously discussed with the Agency ([FDA Reference ID 4001166](#)). Based on FDA's guidance (Applications Covered by Section 505(b)(2)), Entasis intends to rely on the Agency's finding of safety for sulbactam, one of the active ingredients of sulbactam-durlobactam, based on the information in the Summary Basis of Approval (SBA) and US Prescribing Information of the listed product ampicillin sodium/sulbactam sodium (Unasyn®) as well as published literature for studies not conducted by Entasis. In the NDA for sulbactam-durlobactam, Entasis will provide full reports of nonclinical and clinical data of safety and effectiveness of the other active ingredient durlobactam (either studied alone or in combination with sulbactam). Does the Agency agree on the regulatory filing strategy for this application?

Division Response: *If you intend to rely, in part, on information required for approval that comes from studies not conducted by you or for you, or for which you have not obtained a right of reference (e.g., reliance on the FDA's finding of safety and/or effectiveness for a listed drug or published literature), then your marketing application will be a 505(b)(2) application.*

In your background package (i.e., Tables 14, 15, 16, and 17 in Section 5.2), you are proposing to reference information from the Summary Basis of Approval (SBA) for NDA 050608 (Unasyn) for support of safety and/or effectiveness in your future NDA submission. "Full reports of investigations" of safety and effectiveness are required to be submitted for approval of 505(b)(1) and 505(b)(2) NDAs. The SBA, however, does not constitute full reports of investigations. See 21 C.F.R. 314.430(e)(2). A 505(b)(2) applicant that seeks to rely upon the Agency's finding of safety and/or effectiveness for a listed drug may rely on FDA's finding of safety and effectiveness as reflected in the FDA-approved labeling for the listed drug.

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate.

You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g., by trade name(s)).

In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

*Refer to the **505(b)(2) REGULATORY PATHWAY** section below for information about submitting a 505(b)(2) NDA.*

Question 2a: Entasis plans to include the efficacy data from the single phase 3 trial in Modules 2.5 and 2.7.3; and therefore, does not plan to include a separate Integrated Summary of Efficacy (ISE) in the application. The safety data of sulbactam-durlobactam from all eight clinical studies will be included in Module 2.7.4 as well as in an Integrated Summary of Safety (ISS). Does the Agency agree on the placement of this information in the eCTD?

Division Response: *We agree. Also see our response to 8b. We agree that a separate ISE is not needed.*

Question 2b: Entasis is planning to submit the microbiology information under the designated eCTD sections in Modules 2 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 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?

Division Response: *Yes, we agree.*

Question 3: Entasis is planning to submit a priority review application at the time of NDA submission based on the unmet need and the favorable benefit-risk profile of sulbactam-durlobactam. Does the Agency agree?

Division Response: *Yes. If priority review is requested, the Division will make the ultimate determination of the review status (i.e., Priority vs. Standard) of the application by the filing date, 60 days after the application is received.*

Question 4: Does the Agency deem that an advisory committee meeting will likely not be conducted based on the information and data provided?

Division Response: *It is premature to make a determination as to whether or not the application will be the subject of an Antimicrobial Drugs Advisory Committee meeting. We anticipate that this determination will be made at the time of NDA filing.*

Question 5: A population PK model for sulbactam and durlobactam has been completed using data from six phase 1 studies, one phase 2 trial, and one phase 3 trial, and incorporating a full covariate analysis to identify patient factors associated with the PK of both drugs. Entasis intends to leverage the population PK model to PK-PD analyses for safety and PK-PD target attainment determination in support of the clinical dose and dose adjustment based on renal function in the targeted patient population. Does the Agency agree with this strategy?

Division Response: *We agree with your general strategy. We may provide comments on your population PK model and PK/PD target attainment analyses as needed, as we delve deeper into the data during the review of the NDA.*

Question 6: Entasis plans to provide the safety and efficacy data for sulbactam-durlobactam for the proposed indication from the phase 3 trial and supporting data from in vitro and animal models of infection and PK/PD target attainment analyses. Does the Agency agree that the data from the pivotal phase 3 trial and supporting evidence from the nonclinical package are adequate for the Agency's review of the NDA for sulbactam-durlobactam?

Division Response: *We agree that the phase 3 data and supporting nonclinical package are adequate for an NDA review. The proposed non-clinical microbiology studies and the pharmacology and toxicology data in the nonclinical package appears adequate for the Agency's review of the NDA. Additionally, we agree with the proposed strategies from a Clinical Pharmacology perspective.*

Question 7: Entasis plans to include the data from the pre-specified, statistically significant primary efficacy endpoint of 28-day all-cause mortality in the CRABC m-MITT population as well as data from the following important pre-specified statistically and clinically meaningful efficacy endpoints in Section 14 of the proposed Prescription Drug Labeling:

- 14-day all-cause mortality in the CRABC m-MITT population
- A Kaplan-Meier curve demonstrating time to death by Day 28

- Clinical cure rate at end-of-treatment, test-of-cure, and late follow-up visit
- Microbiological response at end-of-treatment, test-of-cure, and late follow-up visit

Entasis will provide data from the primary safety objective of incidence of nephrotoxicity as measured by the RIFLE criteria in Section 14 of the Prescription Drug Labeling and include a cross-reference in the ADVERSE REACTIONS Section 6 of the proposed Prescription Drug Labeling. All relevant safety data, including the most common adverse reactions, serious adverse reactions and adverse reactions leading to discontinuation will be presented in Section 6 of the proposed Prescription Drug Labeling. Does the Agency agree with the inclusion of this clinically important information from the prespecified endpoints in the proposed label of the intended NDA for sulbactam-durlobactam to guide prescribers and healthcare practitioners in the safe and effective use of sulbactam-durlobactam?

Division Response: *The content of labeling will be determined at the time of NDA review. Clinical studies that prospectively evaluate an important safety endpoint may be presented in Section 14. However, presentation of these data in Section 14 usually requires Type I error control in the prespecified statistical analysis plan and robust results. We agree with the presentation of safety data in Section 6, as proposed. We note that you did not specify how to control multiplicity to test the secondary efficacy endpoints in the SAP and the study was not designed to rigorously establish superiority to the active control for these endpoints. Therefore, it is likely that only descriptive results for some clinically important secondary endpoints could be presented in Section 14.*

Questions 8a to 8g: A total of eight clinical studies in adult subjects were conducted in support of the sulbactam-durlobactam clinical program, including six phase 1 studies, one phase 2 trial, and one phase 3 trial. The data from these studies will be included in the ISS. In total, 380 subjects have been exposed to sulbactam-durlobactam or durlobactam alone. Of these, 181 subjects received the proposed dose of sulbactam-durlobactam based on renal function. Please refer to [Appendix B](#) for the ISS Statistical Analysis Plan (SAP) and the shell tables/listings/figures.

Question 8a: Does the Agency consider the size of the safety database acceptable in the assessment of the benefit-risk of sulbactam-durlobactam?

Division Response: *In general, a safety database for a drug that is the subject of a streamlined development program should include at least 300 patients at the dose and duration of therapy proposed for marketing. This safety database could include patients from all phases of clinical development and include patients who do not have an unmet medical need.*

With a small safety database, there may be uncertainties about findings of a potential serious risk and during the NDA review, the FDA may determine that a postmarketing study or clinical trial is needed to further characterize the risk (Refer to Antibacterial Therapies for Patients With an Unmet Medical Need for the Treatment of Serious Bacterial Diseases Guidance for Industry, August 2017).

Question 8b: Does the Agency agree with the ISS pooling strategy for the six phase 1 studies, one phase 2 trial, and one phase 3 trial and the intended sulbactam-durlobactam dose and duration pools, respectively, as presented in the ISS SAP Section 2.1 and in Tables 2-2 (a-d)?

Division Response: *We recommend that you not pool the safety data in the Integrated Summary of Safety (ISS). Since the ATTACK trial represents the patient population, dosage, duration of the drug and the indication you are seeking, we recommend that you present the safety data from the ATTACK trial separately (Part A and Part B combined as well as separately) rather than pooling it with the phase 1 and phase 2 trials, which represent different populations.*

Question 8c: Does the Agency agree with the definitions and presentation format for the analysis groups and period of treatment as presented in the ISS SAP Section 2.3?

Division Response: *We agree. We do not recommend pooling the phase 2 and 3 studies.*

Question 8d: Does the Agency agree with the proposed subgroups to be used for stratified analyses of the phase 2/3 pooling group by age at screening, gender, race, ethnicity, BMI group, geographic region, and renal impairment as presented in the ISS SAP Section 3 and in Table 3-1?

Division Response: *We agree. Please present the subgroup analysis for the phase 3 trial separately and combined with phase 2.*

Question 8e: Laboratory values will be normalized using common standard reference laboratory ranges as presented in Section 6.3.3 and in Appendix 1 of the ISS SAP. Does the Agency agree with the normalization strategy proposed?

Division Response: *We agree.*

Question 8f: Does the Agency agree with the format and presentation of the lab parameters as presented in the ISS SAP Sections 6.3.3, 6.3.4, and 6.3.5?

Division Response: *We agree.*

Question 8g: Subjects participating in crossover trials will be counted in each of the pertinent treatment columns of the relevant summary tables (ISS Section 2.3). Does the Agency agree with this strategy for presenting data from the crossover trial?

Division Response: *We agree.*

Question 8h: In consideration of the potential risks or safety concerns based on the Drug Class for sulbactam-durlobactam, we are including seven targeted SMQs for risk-benefit consideration. For the ISS, Entasis intends to present the following seven Standard MedDRA Queries (SMQ) in the safety analysis: Drug related hepatic disorders - comprehensive search (SMQ), Hypersensitivity (SMQ), Acute renal failure (SMQ), Infective pneumonia (SMQ), Sepsis (SMQ), Pseudomembranous colitis (SMQ), and Convulsions (SMQ). Does the Agency agree with this strategy and the proposed seven SMQs?

Division Response: *We agree.*

Question 9: Entasis has made sulbactam-durlobactam available through an expanded access program (EAP) for patients in the United States with immediate life-threatening or serious infections with *A. baumannii* including multidrug-resistant and carbapenem-resistant strains. To date, sulbactam-durlobactam has been made available to seven patients in this program. The safety data obtained from the sponsor-investigators will be provided as individual safety narratives in Module 2.7.4. Does the Agency agree with this strategy?

Division Response: *We agree.*

Additional Comments:

Clinical:

- *We recommend that you provide a random sample of the datasets so we can provide feedback.*
- *Provide copies of individual case report forms for each patient who died during a clinical study, had a serious adverse event or who did not complete the study because of an adverse event, whether believed to be drug related or not, including patients receiving reference drugs or placebo.*

Clinical Pharmacology:

- *You reported that durlobactam and sulbactam are substrates of the kidney transporter organic anion transporter 1 (OAT1) based on the in vitro study. Provide any data or plan to further assess the drug-drug interaction (DDI) risk of sulbactam/durlobactam in humans due to interaction with OAT1.*

Refer to the following FDA guidance regarding the DDI assessments:

<https://www.fda.gov/media/134582/download> and

<https://www.fda.gov/media/134581/download>.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our February 2, 2022, 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 VI. 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.¹

In addition, we note that a chemistry pre-NDA meeting is scheduled for March 24, 2022. A summary of agreements reached at that meeting will be documented in the respective meeting minutes.

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.

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

U.S. Food and Drug Administration

Silver Spring, MD 20993

www.fda.gov

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 draft 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.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and

² When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

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>

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Silver Spring, MD 20993

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- 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.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER’s standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.⁶

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.⁷

⁶ <http://www.fda.gov/ectd>

⁷ <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway>

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 356h⁸ and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*⁹.

⁸ <https://www.fda.gov/media/84223/download>

⁹ <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and>

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.

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999).¹⁰ In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at Regulations.gov).¹¹

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. by trade name(s)).

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If FDA has approved one or more pharmaceutically equivalent products in one or more NDA(s) before the date of submission of the original 505(b)(2) application, you must identify one such pharmaceutically equivalent product as a listed drug (or an additional

¹⁰ We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

¹¹ <http://www.regulations.gov>

listed drug) relied upon (see 21 CFR 314.50(i)(1)(i)(C), 314.54, and 314.125(b)(19); see also 21 CFR 314.101(d)(9)). If you identify a listed drug solely to comply with this regulatory requirement, you must provide an appropriate patent certification or statement for any patents that are listed in the Orange Book for the pharmaceutically equivalent product, but you are not required to establish a “bridge” to justify the scientific appropriateness of reliance on the pharmaceutically equivalent product if it is scientifically unnecessary to support approval.

If you propose to rely on FDA’s finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA’s consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA’s finding of safety and/or effectiveness for a listed drug(s) or on published literature (see table below).

In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA’s finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the “bridge” that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying the source of supporting information in your annotated labeling, we encourage you to include in your marketing application a summary of the information that supports the application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA’s previous finding of safety and effectiveness for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)
<i>(1) Example: Published literature</i>	<i>Nonclinical toxicology</i>
<i>(2) Example: NDA XXXXXX “TRADENAME”</i>	<i>Previous finding of effectiveness for indication A</i>
<i>(3) Example: NDA YYYYYY “TRADENAME”</i>	<i>Previous finding of safety for Carcinogenicity, labeling section B</i>

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a “duplicate” of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA’s policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

Please be advised that the Agency does not make exclusivity determinations pursuant to sections 505(c)(3)(E) and (j)(5)(F) of the Federal Food, Drug, and Cosmetic Act, and 21 CFR 314.108, until after approval of an NDA. As described at 314.50(j), an applicant should include in its NDA a description of the exclusivity to which the applicant believes it is entitled. FDA will consider the applicant’s assertions regarding exclusivity in the review of the application. Please also note that the New Molecular Entity (NME) determination for an application is distinct from and independent of the New Chemical Entity (NCE) determination and any related exclusivity determinations.

FDA has made a preliminary determination that the application for this product would be reviewed as a new molecular entity (NME) and therefore subject to the Program, under PDUFA VI. Please note that this is a preliminary determination, based on information available to FDA at this time, and will be re-evaluated at the time your application is submitted. This determination is based on our understanding of the active moiety (21 CFR 314.108(a)) and whether another marketing application containing the same active moiety is approved or marketed. Please also note that the NME determination for an application is distinct from and independent of the new chemical entity (NCE) determination and any related exclusivity determinations, which are made after approval of an NDA.

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 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*.¹²

-END

¹² <https://www.fda.gov/media/85061/download>
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/s/

GREGORY F DIBERNARDO
03/22/2022 04:08:27 PM

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/

PETER W KIM
04/11/2022 08:58:34 AM



IND 131330

MEETING MINUTES

Entasis Therapeutics
c/o MMS Holdings, Inc.
Attention: Roberta Krieger, MS
Regulatory Strategist
6880 Commerce Boulevard
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 Sulbactam-ETX2514, Powder for Injection.

We also refer to the teleconference between representatives of your firm and the FDA on November 5, 2018. The purpose of the meeting was to discuss your Phase 3 development plans for Sulbactam-ETX2514.

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

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

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
Division's Preliminary Responses dated November 1, 2018



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF TELECONFERENCE

Meeting Type: B
Meeting Category: End of Phase 2

Meeting Date and Time: November 5, 2018 from 2:00 to 3:00 PM, EST
Application Number: IND 131330

Product Name: Sulbactam-ETX2514, Powder for Injection
Indication: Treatment of *Acinetobacter baumannii* infection
Sponsor/Applicant Name: Entasis Therapeutics

Meeting Chair: Sumathi Nambiar, MD, MPH, Director, Division of Anti-Infective Products (DAIP)
Meeting Recorder: J. Christopher Davi, MS, Senior RPM, DAIP

CDER Participants: Division of Anti-Infective Products (DAIP)*

***Unless otherwise noted**

John Farley, MD, MPH, Deputy Director, OAP
Sumathi Nambiar, MD, MPH, Director
Thomas Smith, MD, Medical Team Leader
Joseph Toerner, MD, MPH, Deputy Director for Safety
Dmitri Iarikov, MD, PhD, Deputy Director
Mayurika Ghosh, MD, Clinical Reviewer
Terry Miller, PhD, Nonclinical Team Leader
Owen McMaster, PhD, Nonclinical Reviewer
Seong Jang, PhD, Clinical Pharmacology Team Leader
Xiaohui (Tracey) Wei, PhD, Clinical Pharmacology Reviewer
Karen Higgins, ScD, Statistical Team Leader
Daniel Rubin, PhD, Statistical Reviewer
Avery Goodwin, PhD, Acting Clinical Microbiology Team Leader
Simone Shurland, PhD, Clinical Microbiology Reviewer
J. Christopher Davi, MS, Senior Regulatory Project Manager
Maureen Dillon-Parker, MS, Chief, Regulatory Project Management Staff

SPONSOR ATTENDEES (Entasis Therapeutics)*

***Unless otherwise specified**

Robin Isaacs, MD, Chief Medical Officer, Entasis Therapeutics
Roberta Krieger, MS, Sponsor's Regulatory Representative, MMS Holdings Inc.
Subasree Srinivasan, MD, MPH, Senior Medical Director, Entasis Therapeutics
Emily Stone, BS, MBA, Clinical Project Manager, Entasis Therapeutics
John Mueller, PhD, Chief Development Officer, Entasis Therapeutics
Alita Miller, PhD, Senior Director Biology, Entasis Therapeutics
John O'Donnell, BS, Director DMPK, Entasis Therapeutics
Manos Perros, PhD, Chief Executive Officer, Entasis Therapeutics
Christopher M. Rubino, PharmD, Executive VP, Institute for Clinical Pharmacodynamics
Harald Reinhart, MD, Chief Medical Officer, Zai Lab

BACKGROUND

Entasis Therapeutics (Sponsor) requested a Type B, End of Phase 2 Meeting on July 25, 2018, to discuss the drug development plans for Sulbactam-ETX2514. The objective for the teleconference was to obtain input regarding the proposed Phase 3 clinical trial. The Division of Anti-Infective Products ("Division") granted the teleconference on August 13, 2018, and the Sponsor provided background information for the meeting on September 7, 2018, and subsequently on September 14, and 28, 2018. The Division provided preliminary responses to the information in the meeting briefing materials on November 1, 2018. Discussion points from the preliminary responses are provided herein.

DISCUSSION

- The Sponsor clarified the approach being used to conduct the ELF-based probability of target attainment analysis (PTA). The Sponsor stated that the systemic PK/PD targets of sulbactam and ETX2514 as determined from murine thigh infection model would be similar to those determined from the murine lung infection model, based on their experimental observations. The Sponsor stated that the ELF AUC/pMIC (potentiated MIC after adding ETX2514) targets of ETX2514 could be calculated by adjusting the plasma AUC/pMIC ratio with the mouse ELF/plasma AUC ratio (63%). The Division acknowledged this but expressed concern over a potential overestimate of the PK/PD target analysis in the ELF (i.e., based on a lower value of corrected PK/PD target and a higher plasma drug exposure in humans). The Division commented that the ELF/plasma AUC ratio of 37% in humans was low and asked the Sponsor if they performed the ELF-based PTA analysis based on the plasma PK or ELF PK. The Sponsor confirmed that they used ELF PK to conduct the ELF-based PTA analysis. The Sponsor indicated that they also considered using uncorrected AUC/pMIC for ELF-based PTA and did not observe any significant differences as compared to using corrected AUC/pMIC. The Sponsor provided the PTA with uncorrected AUC/pMIC=10 (net-stasis). The Division acknowledged these points and asked the Sponsor to provide the results for the AUC/pMIC target of 30 for 1 log kill. The Sponsor agreed to do so.

- The Sponsor indicated that ETX2514 has similar plasma concentrations in healthy subjects and patients with cUTI. The Sponsor stated that they expect the ETX2514 PK in patients with HABP/VABP to be similar to that in patients with other types of infections, even though no PK data in HABP/VABP patients are available. However, the Sponsor plans a sequential review of the PK data during the Phase 3 study, since the enrollment into Part A of the study is anticipated to be slow initially. The Division asked the Sponsor to obtain PK data on at least 8 subjects with HABP/VABP in order to compare the PK in these patients with that in patients who have other types of infections. The Sponsor agreed to do so. The Division further requested that if the Sponsor were to observe any significant PK differences and accordingly change the dose, they (Sponsor) should notify the Agency. The Sponsor agreed to do so.
- Regarding the reproductive toxicity data package, the Sponsor informed the Division that they had issues with using the rat but have found a CRO to assist them with a mouse study. The Sponsor indicated that they would like to start enrolling in the Phase 3 study in March 2019, and asked the Division if they could conduct the trial concurrently with the reproductive toxicity study. The Sponsor proposed to submit the final report for the planned mouse study 3 months after starting the Phase 3 trial. The Division indicated that this would be acceptable, provided they submit finalized reports from the completed studies (e.g., rabbit study, 7-day GLP mouse study, etc.) by the end of 2018. The Sponsor agreed to do so.
- Regarding Part B of the Phase 3 study, the Sponsor indicated that their intent was to obtain data on patients who have colistin-resistant infections and/or those who are colistin intolerant. They felt that these data will be supportive and that it would be difficult to randomize to a “best available therapy” control group. The Division indicated that this is acceptable, provided it remains a supportive analysis, and that data from Part B would be difficult to interpret without a comparator group. The Division also reminded the Sponsor to provide their rationale for any dose adjustments in patients on continuous renal replacement therapy (CRRT). The Sponsor acknowledged these points.
- Regarding enrollment of patients with catheter-related bloodstream infections (CRBSI) the Division recommended that these patients should only be enrolled if there is a “paired” positive culture from a peripheral vein and the catheter, as colonization of the catheter alone could result in a false positive blood cultures. The Division added that it is important that the source of the infection be identified and noted on case report forms. The Sponsor acknowledged these points and committed to inform the clinical sites and CROs about this.
- The Division asked the Sponsor to clarify the dose selection of imipenem 1 gm intravenously (iv) every 6 hrs for the treatment of *Acinetobacter* infections instead of 500 mg iv every 6 hrs. The Sponsor stated that this was based on advice from external consultants.

- The Division and Sponsor discussed the use of the proposed rapid diagnostic device. The Sponsor noted that the device (Biofire[®]/Film Array[®]) is currently being reviewed by the Center for Devices and Radiologic Health (CDRH). They expect the proposed device to be used at some sites but not all sites for screening of patients. The Sponsor stated that if the product is approved, the product insert will be provided. If the device is not approved the Division advised that information pertaining to the device (i.e., performance characteristics) be provided in early/mid-January 2019, so that CDRH can be consulted. The Division also indicated that the device is considered a screening tool and not a companion diagnostic device. It was noted that patients enrolled in the trial and have a positive study qualifying baseline culture will be considered in the primary analysis population. The Sponsor acknowledged these points.

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-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 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 Pedsdrugs@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 (cdcr-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 started after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that started 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 started on or 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.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The [FDA Study Data Technical Conformance Guide](#) (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the [FDA Study Data Standards Resources](#) web site. When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

Additional information can be found at

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

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:

- 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.

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](https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM587505.pdf) and the CDER/CBER Position on Use of SI Units for Lab Tests website found at:

<https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM587505.pdf>.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER’s standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: <http://www.fda.gov/ectd>.

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ACTION ITEMS

- Sponsor to submit final reports for all toxicology studies by December 31, 2018
- Sponsor to submit rapid-diagnostic device information/specifications for CDRH review by January 18, 2018
- Sponsor to submit their Initial Pediatric Study Plan (iPSP) by January 4, 2019
- Sponsor was advised to request a dedicated CMC meeting

ATTACHMENTS AND HANDOUTS

- Division's Preliminary Responses dated November 1, 2018

-End

Dear Ms. Krieger,

In anticipation of our teleconference with Entasis Therapeutics on November 5, 2018 (IND 131330), the Division of Anti-Infective Products has the following preliminary responses to the questions in your briefing document dated September 14, 2018:

Question 1:

ETX2514SUL is being developed for the treatment of infections caused by ABC complex with the proposed indication “ETX2514SUL is indicated for the treatment of infections due to *Acinetobacter baumannii-calcoaceticus* complex in patients (b) (4). The Sponsor is proposing a streamlined development strategy with a single pivotal Phase 3 study in patients with hospital acquired-/ventilator-acquired bacterial pneumonia and/or with blood stream infections caused by ABC. The overall safety database at the time of NDA submission will be approximately 400 subjects/patients receiving at least one dose of ETX2514 at a dose ≥ 1 g, the proposed ETX2514 clinical dose. Does the Agency agree:

- a) That the proposed development strategy is sufficient to support approval of ETX2514SUL for the proposed indication?

Division Response: *We generally agree with your development strategy. We cannot comment on the adequacy of the data to support approval at this time. As the Phase 2 trial did not evaluate any patients with infection due to A. baumannii, the data are not helpful to the overall efficacy evaluation. For comments on the Phase 3 trial, see responses to question 3.*

- b) That the size of the pre-marketing safety database will be adequate to support a New Drug Application?

Division Response: *If no unexpected safety signals are observed, the proposed safety database (400 patients) is acceptable. The size of the safety database will ultimately depend on the identification and characterization of any safety signals that arise as the development program progresses.*

Question 2:

The dosing regimen of sulbactam 1 g plus ETX2514 1 g administered by intravenous infusion over 3 hours every 6 hours will be evaluated in the Phase 3 study. Based on the evaluation against an extensive collection of contemporary clinical *A. baumannii-calcoaceticus* complex isolates, this regimen would be expected to deliver efficacy in the target patient population, including patients with pneumonia. Does the Agency agree with the dose justification rationale for the proposed Phase 3 ETX2514SUL regimen?

Division Response: *In order to further justify the proposed Phase 3 ETX2514SUL regimen, we recommend you address the following issues related to the PK/PD target attainment analyses:*

- *Clarify how you performed the ELF PK/PD probability of target attainment analysis (PTA). Because the PK/PD target of ETX2514 was determined from a murine thigh infection model but not from a murine lung infection model, we recommend you predict ELF PTA based on the unadjusted PK/PD targets (i.e., not corrected by mice ELF/plasma AUC ratio) and ELF drug concentration-time profiles.*
- *The PK of antimicrobials in HABP/VABP patients are often different (in terms of the variability, as well as the mean PK parameter values) from those in healthy subjects and patients with other infections. We note that the PK of ETX2514SUL has not been evaluated in HABP/VABP patients. The PK simulation based on data from healthy subjects and cUTI patients may mislead the PK/PD target attainment analyses in HABP/VABP patients. We also note that you plan to collect sparse PK samples (5 samples per patient) in the first 30 patients (15 patients from ETX2514SUL group) randomized in Part A of the proposed Phase 3 study. We recommend the independent unblinded PK expert (with consultation with the DSMB if necessary) determine the PK of ETX2514 and sulbactam in these ETX2514SUL treated patients (≥ 8 patients with HABP/VABP) and assess whether the proposed dosing regimen is appropriate in HABP/VABP patients before dosing rest of the patients in the proposed Phase 3 study.*

Question 3:

Does the Agency agree with the design of the pivotal Phase 3 study including the definition of carbapenem-resistant ABC, the comparator (colistin plus imipenem/cilastatin), the dosing regimen for colistin, the definition of colistin resistance, the non-inferiority margin, and enrolment of patients with Augmented Renal Clearance (Creatinine clearance ≥ 130 mL/m²) into Part A?

Division Response: *Although we generally agree with the overall design of the Phase 3 trial, we have the following comments:*

- *We prefer that you limit enrollment of patients in Part A of the Phase 3 trial to those who have received no more than 24 hours of therapy before enrollment. We understand that this can pose practical challenges. However, in a noninferiority (NI) trial, use of prior effective therapy can confound the assessment of efficacy, making the trial difficult to interpret. Please make every effort to limit the use of prior effective therapy. A subgroup analysis of patients who receive less than 24 hours of prior therapy, as well as patients who receive no prior therapy will be an important secondary efficacy analyses during the NDA review.*

- Consider revising your inclusion criteria to >15% bands and respiratory rate > 25 breaths/minute to be consistent with our Draft Guidance for Industry “Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment”, May 2014, available at: <https://www.fda.gov/downloads/drugs/guidances/ucm234907.pdf>
- For a diagnosis of catheter-related bloodstream infection, we recommend paired blood samples drawn from the catheter and a peripheral vein. Please prespecify how you plan to define catheter-related bloodstream infection and steps that will be taken to ensure that assessments are uniform across study sites.
- We recommend that you consider all randomized patients to be a key secondary analysis population.
- According to the protocol, patients can be enrolled with identification of *A. baumannii* within 72 hours of randomization, even if subsequent pre-randomization cultures are negative. Noninferiority could be difficult to interpret if a large fraction of patients have negative blood cultures before randomization. Subgroup analysis of patients with negative cultures at randomization will need to be performed.
- Please clarify whether patients can be transferred from Part A to Part B based on cultures taken post-randomization, or other post-randomization criteria. If so, this could confound the efficacy assessment of Part A, and we instead recommend that patients who are currently to be switched from Part A to Part B have control group therapy switched from colistin+imipenem/cilastatin to a “best available therapy” chosen by the unblinded investigator, and that these patients be kept in the analysis of Part A.
- We do not agree with your definition of carbapenem resistant *A. baumannii*. Based on the FDA’s recommended susceptibility criteria of imipenem/cilastatin, the definition of resistance should be an MIC of ≥ 8 mcg/mL based on your proposed dosing of 1g q6h of imipenem. A dose of 500 mg q6h for imipenem can support a definition of resistance of an MIC of ≥ 4 mcg/mL. Submit the epidemiological data for the prevalence of *A. baumannii* with MIC ≥ 8 or 4 mcg/mL in the clinical trial sites you plan to use, as this may have implications for the number of patients enrolled.
- The definition of colistin resistance (>2 mcg/mL of MIC) is acceptable. However, for clarification, we recommend you define it as an MIC of ≥ 4 mcg/mL rather than >2 mcg/mL.

- *Part B of the Phase3 trial will be limited due to its uncontrolled nature. The efficacy and safety results in the non-comparative group will be difficult to interpret, due to the absence of the comparative arm, morbidity and mortality related to underlying diseases, and potentially active background therapy in some patients. We recommend that patients eligible for Part B at baseline instead be randomized to an ETX2514SUL group versus a “best available therapy” control group*

Clinical Pharmacology:

From the perspective of clinical pharmacology, your proposed dosing regimen of colistin in general, is acceptable (see additional comments below).

- *Your proposal to enroll patients with Augmented Renal Clearance (Creatinine clearance ≥ 130 mL/min/m²) into Part A is acceptable.*
- *In the briefing package you note that patients on active renal replacement therapy or acute hemodialysis will only be allowed to enroll in Part B of the study. Clarify whether these patients will be treated with colistin or not, since you did not plan to include a comparator arm in Part B. In addition, provide the rationale for your proposed dose adjustments for colistin in patients on intermittent hemodialysis and patients receiving continuous renal replacement therapy and for imipenem/cilastatin in patients receiving continuous renal replacement therapy.*
- *You have reported that ETX2514 mean recovery in urine ranged from 50 to 76% and sulbactam recovery ranged from 62 to 66% across the dosing cohorts in the FIH study. We recommend you exclude patients with severe hepatic impairment from your Phase 3 studies because the hepatic drug metabolism for ETX2514 and sulbactam appears to be substantial (i.e., >20 % of total drug clearance *) and the exact effect of hepatic impairment on the PK of ETX2514SUL is unknown.*

*** FDA guidance:** *Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling 2003*

Question 4:

The 28-day ETX2514SUL combination toxicology study in rats did not identify a NOAEL; however, the adverse changes related to the combination treatment were absent in animals treated with ETX2514 alone, were not severe, were restricted to hepatic and pulmonary inflammation that was not associated with target organ toxicity, and were completely reversible. Additionally, notable effects in rats treated with the ETX2514SUL combination were consistent with known effects of sulbactam. ETX2514SUL was generally well tolerated in the Phase 1 and Phase 2 clinical studies without evidence of pulmonary or hepatic toxicity.

The Sponsor will monitor patients in the Phase 3 study for generalized inflammation using accepted hematology (WBC and neutrophil counts) parameters, as well as monitor oxygen saturation as an indicator of pulmonary function in the patients with pneumonia. Does the agency agree that the proposed monitoring strategy is adequate to support the Phase 3 study?

Division Response: *We agree with the proposed safety monitoring in the Phase 3 trial. To evaluate for drug induced pulmonary toxicity while treating HABP/VABP patients, in addition to assessment of WBC, neutrophils and oxygen saturations you have incorporated in the protocol, consider monitoring the respiratory rate, peripheral blood eosinophilia and CXR. The investigators should be instructed to monitor subjects for dyspnea, wheezing, and cough.*

Question 5:

ETX2514 has been assessed for cardiovascular risk in *in vitro* and *in vivo* studies. No significant interactions with cardiac ion channels, including hERG, were identified at any concentrations ranging from 100 to 1000 µM. ETX2514 had no quantitative effects on any ECG parameter in telemetered conscious dogs. ETX2514SUL has been generally well tolerated in the Phase 1 and Phase 2 clinical studies. Entasis proposes to undertake a thorough QT study in parallel with the Phase 3 study.

- a) Does the FDA agree that the thorough QT study can be run in parallel to the Phase 3 study?

Division Response: *The purpose of the TQT study is to guide the intensity of ECG monitoring in Phase 3 studies. If the TQT study is conducted in parallel with Phase 3, then you should collect ECGs near the end of infusion after the first dose, in all patients.*

- b) Does the FDA agree with the proposed study design of the thorough QT study, including the choice of ETX2514 supratherapeutic dose and only investigating the impact of ETX2514 on the QT interval?

Division Response: *Yes, we agree. The proposed study design and analysis plan appear acceptable to characterize the effects of ETX2514 on the QT interval.*

Additional Comments for Question 5:

- *When you submit your QT study report, please include the following items:*
 - i. *Study report(s) for any other clinical studies of the effect of product administration on the QT interval that have been performed*
 - ii. *Study report*
 - iii. *Statistical analysis plan*
 - iv. *Clinical study protocol*
 - v. *Investigator's Brochure*
 - vi. *A completed Highlights of Clinical Pharmacology and Cardiac Safety Table*
 - vii. *Annotated CRF*

- viii. *A data definition file which describes the contents of the electronic data sets*
- ix. *Electronic data sets as SAS.xpt transport files (in CDISC SDTM and ADAM format – if possible) and all the SAS codes used for the primary statistical and exposure-response analyses. Please make sure that the ECG raw data set includes at least the following: Subject ID, treatment, period, ECG date, ECG time (down to second), nominal day, nominal time, replicate number, heart rate, intervals QT, RR, PR, QRS and QTc (including any corrected QT, e.g., QTcB, QTcF, QTcN, QTcI, along with the correction factors for QTcN and QTcI), Lead, and ECG ID (link to waveform files, if applicable).*
- x. *Data set whose QT/QTc values are the average of the above replicates at each nominal time point*
- xi. *Adverse Event analysis using the MedDRA SMQ “Torsade de pointes/QT Prolongation” and include the preferred term “Seizure” by treatment and dose level.*
- *Narrative summaries and case report forms for any:*
 - xii. *Deaths*
 - xiii. *Serious adverse events*
 - xiv. *Episodes of ventricular tachycardia or fibrillation*
 - xv. *Episodes of syncope*
 - xvi. *Episodes of seizure*
 - xvii. *Adverse events resulting in the subject discontinuing from the study*
- *We are also interested in the effects of the test substance on other ECG intervals and changes in waveform morphology. Please submit PR and QRS interval data with the study report and descriptive waveform morphology changes.*
- *Submit all related ECG waveforms to the ECG warehouse (www.ecgwarehouse.com)*

Question 6:

ETX2514SUL is cleared primarily by urinary excretion. Rodent mass balance in QWBA studies is complete. The metabolite profile of ETX2514 is being investigated in an ongoing [¹⁴C]-ETX2514 rodent study and data from this study will be used to profile human plasma and urine samples from the first-in-human study. Assuming that there are no unique or disproportionate metabolites in humans relative to the rodent, the sponsor proposes to undertake a human ADME study in parallel with the Phase 3 study. Does the Agency agree with this approach and with the proposed study design of the human ADME study?

Division Response: *Yes, we agree.*

Question 7:

Does the Agency agree that the non-clinical toxicology plan (study types, study designs, and the duration of repeated-dose studies proposed to support registration) is sufficient to support approval of ETX2514SUL?

Division Response: *The adequacy of the proposed nonclinical toxicology plan to support approval of ETX2514SUL will be determined upon review of the NDA. We cannot comment on the adequacy of the data to support approval at this time. The proposed package includes pharmacokinetics, safety pharmacology, genotoxicity, repeat dose toxicology (up to 28 days in rats and dogs) and reproductive toxicology testing (in rats, rabbits and mice). If these studies are valid, they will provide sufficient information to determine if ETX2514SUL is safe for treatment durations of up to 2 weeks.*

The duration of the toxicology studies required for registration will be guided by the proposed clinical treatment duration, therefore additional toxicology studies may be needed if the treatment duration extends beyond 14 days. Information on pharmacokinetics (e.g., absorption, distribution, metabolism and excretion), in test species and in vitro biochemical information relevant to potential drug interactions should be available before large numbers of human subjects are treated for long durations (generally before phase III).

The background document indicates that “The DART study reports will be finalized and submitted to the Agency during the first half of 2019. The Phase 3 protocol requires contraceptive precautions, as these results will likely not be available at the time of the Phase 3 initiation.” While we acknowledge the challenges you have faced in selecting a second species for your embryo fetal development program, ICH M3 R2, indicates that ‘In the US, assessment of embryo-fetal development can be deferred until prior to Phase 3 for WOCBP using highly effective contraceptive methods.’ We therefore recommend that you submit at least audited draft reports for the two embryo fetal toxicity studies prior to initiation of your Phase 3 trial (See also ICH S5 (R3) “Detection of toxicity to reproduction for human pharmaceuticals.” Consult ICH M3 (R2) for additional information regarding the timing of submission of the various nonclinical studies.

Please submit final and audited draft reports for all completed nonclinical toxicology studies as soon as possible and before initiation of your planned Phase 3 trial, and a Gantt chart detailing the submission dates for planned nonclinical studies and the proposed Phase III clinical trial.

ADDITIONAL COMMENTS

Clinical Microbiology:

- *You stated that a rapid diagnostic test of respiratory samples will be used to identify patients for enrollment into the study, which is under development by BioMerieux as a component of the Biofire® pneumonia panel utilizing Film Array® 2.0 technology. Submit a detailed description of the method for review, including justification, validation of the method and performance characteristics (sensitivity, specificity, cross-reactivity, precision, reproducibility etc.) of the assay(s). If you plan to use any new assay in the trial, please submit the requisite information prior to use in the clinical trial. We will also seek input from the Center for Devices and Radiologic Health.*

Clinical Pharmacology:

- *Depending on the results from your human ADME study, consider conducting a clinical study to characterize the PK of ETX2514SUL in patients with hepatic impairment.*

We can discuss the preliminary responses above in more detail with you during our teleconference on November 5, 2018. If you have questions in the interim, I can be reached at (301) 796-0702.

J. Christopher Davi, MS, Sr. RPM, DAIP

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/

SUMATHI NAMBIAR
11/21/2018