CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213972Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 129834
IND 129849

MEETING MINUTES

Iterum Therapeutics International Ltd.
c/o Iterum Therapeutics, US, Ltd.
Attention: Michael Dunne, MD
Chief Scientific Officer
20 Research Parkway, Suite A
Old Saybrook, CT 06475

Dear Dr. Dunne:

Please refer to your Investigational New Drug Applications (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for the following:

IND 129834: Sulopenem injection
IND 129849: Sulopenem etzadroxil/probenecid bilayer tablets

We also refer to the teleconference between representatives of your firm and the FDA on September 28, 2020. The purpose of the meeting was to discuss the submission of new drug applications (NDAs) for sulopenem tablets for the treatment of uncomplicated Urinary Tract Infections (uUTI) caused by sulopenem-susceptible, quinolone-resistant microorganisms in adult women, and for sulopenem injection and sulopenem tablets for the treatment of complicated Urinary Tract Infections (cUTI) caused by sulopenem susceptible, quinolone-resistant microorganisms in adults who have limited or no alternative treatment options.

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

If you have any questions, call Christopher L. Smith, PharmD, Regulatory Project Manager, at (301) 796-4851.

Sincerely,

{See appended electronic signature page}

Sumathi Nambiar, MD, MPH
Director
Division of Anti-Infectives
Office of Infectious Diseases
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type-B
Meeting Category:	Pre-NDA
Meeting Date and Time:	September 28, 2020, 1:00-2:00 PM EDT
Meeting Location:	Teleconference
Application Numbers:	IND 129834 IND 129849
Product Names:	Sulopenem injection Sulopenem etzadroxil/probenecid bilayer tablets
Indications:	Uncomplicated Urinary Tract Infections (uUTI) Complicated Urinary Tract Infections (cUTI)
Sponsor Name:	Iterum Therapeutics International, Ltd.
Regulatory Pathways:	505(b)(1) for sulopenem injection 505(b)(2) for sulopenem etzadroxil/probenecid bilayer tablets
Meeting Recorder:	Christopher L. Smith, PharmD

FDA ATTENDEES:

Office of Infectious Diseases (OID)

John Farley, MD, MPH	Director

Division of Anti-Infectives (DAI)

Sumathi Nambiar, MD, MPH	Director
Carmen DeBellas, PharmD	Chief, Regulatory Project Management Staff
Christopher Smith, PharmD	Regulatory Project Manager
Dmitri Iarikov, MD, PhD	Deputy Director
Avery Goodwin, PhD	Clinical Microbiology Team Leader
Karen Higgins, ScD	Statistical Team Leader
Zhixia (Grace) Danielsen, PhD	Clinical Pharmacology Team Leader
Mukil Natarajan, MD	Clinical Reviewer
Terry Miller, PhD	Pharmacology/Toxicology Team Leader
Cristina Miglis, PharmD	Clinical Pharmacology Reviewer
Daniel Rubin, PhD	Statistical Reviewer
Peter Kim, MD, MS	Clinical Team Leader
James Wild, PhD	Pharmacology/Toxicology Reviewer

Dorota Matecka, PhD	Product Quality Team Leader

SPONSOR ATTENDEES

Iterum Therapeutics International, Ltd.

Karthik Akinapelli	Programming Lead
Steve Aronin, MD	Senior Medical Director
(b) (4) PhD	Consulting Statistician
Mike Dunne, MD	Chief Scientific Officer
Corey Fishman	Chief Executive Officer
Cynthia Morris	Director, Regulatory Operations
Katherine S. Takaki, PhD	Vice President, Regulatory Affairs
Michael Zelasky, MS	Head of Biostatistics
(b) (4) PhD	Principal consultant, (b) (4)

1.0 BACKGROUND

Sulopenem injection and Sulopenem etzadroxil/probenecid bilayer tablets (sulopenem tablets) are being developed by Iterum Therapeutics International Ltd. (the Sponsor) for the treatment of uUTI, cUTI and complicated Intrabdominal Infections (cIAI). On July 31, 2020, the Sponsor requested a Type B Pre-NDA meeting to discuss the submission of NDAs for sulopenem tablets for the treatment of uUTI caused by sulopenem-susceptible, quinolone-resistant microorganisms in adult women, and for sulopenem injection and sulopenem tablets for the treatment cUTI caused by sulopenem susceptible, quinolone-resistant microorganisms in adults who have limited or no alternative treatment options.

The Division sent preliminary comments to the Sponsor on September 24, 2020. The Sponsor provided responses to the comments on September 25, 2020. The topics discussed at the meeting are captured as "Meeting Discussion." Slides containing discussion points were presented at the meeting (appended).

2.0 DISCUSSION

1. Does the Division agree that the superiority results in the population of patients in IT001-301 with baseline pathogens resistant to quinolones, supported by additional efficacy observations in IT001-301 and IT001-302, along with the combined safety experience from IT001-301, IT001-302 and IT001-303, constitutes substantial evidence for the safety and efficacy of sulopenem etzadroxil/probenecid for the treatment of adult women with uUTIs due to quinolone-resistant pathogens?

FDA Response:
The determination of substantial evidence of effectiveness and adequate safety to support a labeled indication for the treatment of adult women with uUTI due to quinolone-resistant pathogens will be determined during the review of the NDA(s). We will need to evaluate the study data prior to deciding on the appropriate indication. Data provided in the background package suggest efficacy of sulopenem etzadroxil/probenecid for the treatment of uUTI due to quinolone-resistant pathogens. We remain concerned with the discordant results between the quinolone-susceptible and non-susceptible populations and will need to understand the reasons for this finding during the review. While it is premature to discuss labeling, it will be important that labeling reflect that the data do not support efficacy in patients with uUTI due to quinolone-susceptible isolates. Additionally, as uUTI is typically treated empirically, labeling will have to define the limited population for whom the drug would potentially be indicated.

Meeting Discussion: The Sponsor began the discussion by stating that their intention was to submit an NDA for the uUTI indication. In response to the Division's question regarding the geographic distribution of subjects enrolled in the Phase 3 uUTI trial (Study 301), the Sponsor stated that 60% of subjects were from the United States and 40% were from Russia and the Ukraine. The Division requested additional information regarding microbiologic eradication in each arm and noted that Table 5 of the briefing document presented results for overall success and clinical success in the micro-MITTR population and asked for information on the microbiological outcomes. The Sponsor agreed to provide these results after the meeting. The Sponsor explained that mild symptoms were the main reason for the higher rate of unresolved symptoms/new symptoms observed in the sulopenem arm as compared to the ciprofloxacin arm in the micro-MITTS population.

The Division inquired as to whether the case report forms (CRFs) captured the investigator's assessment of the need for treatment of unresolved symptoms. The Sponsor stated that investigator discretion was a common reason and that there are limitations to understanding what factors drove investigator decision making. The Division explained that in the NDA, it would be important to clearly describe why some patients received rescue therapy and some did not. The Sponsor stated that they will review CRFs as well as outcomes at the final visit for additional information. The Sponsor clarified that there was no predefined set of drugs designated for rescue therapy in the micro-MITTR population. The Division stated that it would be helpful to know how many subjects in each arm had a history of recurrent UTI and how many of those individuals contributed to the failures observed in the study. The Sponsor stated that many subjects likely had a history of UTI, and the Sponsor would look into it.

2.

A. Does the Division agree that the results of study IT001-302, supported by additional efficacy observations in IT001-301, along with the combined safety experience from IT001-301, IT001-302, and IT001-303, could constitute sufficient evidence of the safety and efficacy of sulopenem etzadroxil/probenecid for oral step-down treatment of adults with cUTIs?

B. If the Division does not agree to consider an NDA application based on Question 2a, does the Division agree that the results in the population of patients in IT001-302 with baseline pathogens resistant to quinolones, supported by additional efficacy observations in IT001- 301 and IT001-302, along with the combined safety experience from IT001-301, IT001-302, and IT001-303, constitutes sufficient evidence of the safety and efficacy of sulopenem etzadroxil/probenecid for oral step-down treatment of adults with cUTIs due to quinolone resistant pathogens to warrant inclusion of an appropriately limited patient population for this indication in the proposed NDA?

C. Does the Division agree that it would be appropriate to request approval for oral step-down treatment of adults with cUTIs due to quinolone-resistant pathogens under the LPAD pathway at the time of submission given that treatment of complicated urinary tract infections with an oral agent would address a significant, serious, unmet medical need in the quinolone resistant patient population?

Meeting Discussion: The Sponsor referred to slides 9 and 10 that provided clarification for any questions remaining about Table 7 in the briefing document and acknowledged that subgroups were defined based on a combination of baseline susceptibility and oral stepdown therapy received. The Sponsor referred to favorable results observed in the cUTI study (Study 302) in patients with ciprofloxacin-resistant isolates who received step down therapy with sulopenem tablets. The Division replied that the results seen in this subgroup of ciprofloxacin-resistant isolates were not observed in the overall primary analysis population. The Sponsor acknowledged that the study did not meet the primary endpoint and inquired about a path forward. The Division stated that they would be willing to discuss the design of a future cUTI trial and asked the Sponsor to submit proposals. The Sponsor acknowledged the Division's comment and agreed to provide some proposals.

3. Does the Division agree that the results of study IT001-302 in patients treated with intravenous sulopenem, supported by additional efficacy observations in IT001-301, along with the combined safety experience from IT001-301, IT001-302, and IT001-303, constitute sufficient evidence of the safety and efficacy of sulopenem for initial treatment of adults with complicated urinary tract infections

due to pathogens known or suspected to be resistant to quinolones to warrant inclusion of this limited patient population for this indication in the proposed NDA under the LPAD pathway?

FDA Response for Questions 2 and 3:

- As the prespecified primary analysis in Study IT001-302 was: (1) unable to demonstrate noninferiority to the ertapenem control group (and in fact demonstrated statistical inferiority), and (2) there are limitations to exploratory analyses of additional endpoints and subgroups, we do not think the data can support a labeled indication for cUTI as proposed. If you are interested in pursuing an indication for cUTI, we recommend that you conduct an additional trial in cUTI. We are willing to work with you on designing a future cUTI trial. Regarding approval under the LPAD pathway, as noted in the guidance (https://www.fda.gov/media/113729/download), the LPAD pathway provision does not alter FDA approval standards under the FD&C Act. Also, the LPAD pathway should not be used to salvage a trial that fails to demonstrate its objective (e.g., the LPAD pathway is generally not appropriate for submission of results of subpopulations from trials failing to meet their primary endpoint) or an inadequately designed development program.[1]

- In Table 7 of your briefing document there appeared to be significantly different rates of ciprofloxacin susceptibility for patients in the sulopenem and ertapenem groups. Clarify whether the “Patients with ciprofloxacin susceptible isolates” in this table were classified using only baseline susceptibility data or depended on any post-randomization variables such as the oral therapy received.

Meeting Discussion: The Division inquired if the Sponsor intends to submit an NDA for uUTI. The Sponsor replied they intend to submit an NDA and they will keep the Division updated on the timeline. The Division asked if the Sponsor intends to request the NDA be reviewed using the LPAD pathway and advised that if the LPAD pathway is chosen, the patient population would need to be clearly defined. The Sponsor added that the application would be complete upon submission and no late components are planned. The Division noted that the Sponsor should include a justification for why a single study would be adequate and the clinical relevance of the proposed limited population indication.

4. Does the Division agree that an integrated clinical safety database including all 1863 Phase 3 subjects that received at least one dose of IV sulopenem or oral sulopenem etzadroxil/probenecid FDC tablets is adequate to support the assessment of the benefit/risk of sulopenem and sulopenem etzadroxil/probenecid FDC tablets for the intended claims?

FDA Response: The size of the safety database is acceptable.

Meeting Discussion: No discussion needed.

5. Does the Division agree with the proposals set forth in the Study Data Standardization Plan?

   FDA Response: This approach is acceptable.

   Meeting Discussion: No discussion needed.

6.
   A. Does the Division agree that the NDA for the fixed dose combination of sulopenem etzadroxil/probenecid would be appropriately submitted under Section 505(b)(2) of the Food, Drug, and Cosmetic Act?

   B. Does the Division agree with the placement of the probenecid literature review in Module 5.3.5.4 (Other Studies)?

   C. Does the Division agree that it would be appropriate to submit an NDA for IV sulopenem under Section 505(b)(1) at the same time that the NDA for sulopenem etzadroxil/probenecid is submitted to allow for simultaneous review?

   FDA Response:
   We agree that a 505(b)(2) submission would be appropriate for sulopenem etzadroxil/probenecid. The placement of the probenecid literature review within the NDA is acceptable. If you submit an NDA for IV sulopenem, it would be appropriate to submit it under Section 505(b)(1).

   Meeting Discussion: No discussion needed.

7. The sponsor will be requesting Priority Review of the sulopenem etzadroxil/probenecid marketing application based on the safety and efficacy demonstrated in the population of patients in IT001-301 with baseline pathogens resistant to quinolones, the unmet medical need addressed by the product in this population, and the QIDP designation granted to sulopenem etzadroxil/probenecid for uUTI/cUTI. After review of the information that will be provided in the Briefing Document, does the Division have any additional questions or suggestions related to this Priority Review so the sponsor may be best prepared to support an expedited review?

   FDA Response: We have no additional questions.

Meeting Discussion: No discussion needed.

8. After review of the information that will be provided in the Briefing Document, does the Division agree with the format and content of the proposed NDA as described in the draft Table of Contents?

   FDA Response: The draft Table of Contents is acceptable.

   Meeting Discussion: No discussion needed.

   Additional Comments to Sponsor
   Clinical Pharmacology
   1. In your End of Phase 2 meeting package, you stated that your additional planned Phase 1 studies include a hepatic impairment study. Comment on the status of this study.
   2. You state that the target attainment analyses included in your pre-NDA briefing package are based on T_{free}>MIC and the distribution of MICs observed in the Phase 3 studies. Confirm these data are from actual and not simulated Phase 3 patients and that food intake was recorded in these studies. Additionally, clarify why you have only presented target attainment analyses for single dose administration.

   Meeting Discussion: The Sponsor stated that a Phase 1 hepatic impairment study was not conducted. The Division agreed that this study was not necessary, and no further discussion was needed based on the information provided in the Sponsor's response to the Division's preliminary comment.

   The Sponsor explained their rationale for target attainment referring to slide 11 and noted that the MIC distribution used in the target attainment simulation was based on actual MIC data from the Phase 3 studies. However, the target attainment, as such, is based on simulations. The Sponsor also stated that food intake was recorded in the Phase 3 studies.

   The Division agreed with the overall plan and inquired about how many patients had oral step-down therapy with and without food in Study 302 (cUTI). The Sponsor stated that approximately half of the study participants took the study therapy with food. This significantly reduced the occurrence of diarrhea and, subsequently, discontinuation rates.

   The Division stated that these data will be useful in determining the extent of food effect on clinical outcomes in patients with cUTI.

   The Sponsor commented on the differences between MICs that are based on serum concentrations of antibacterial drugs and urine-specific MICs based on

concentrations of antibacterial drugs in the urine and asked the Division if breakpoints for the uUTI indication should be based on urine concentrations. The Division noted that further internal discussion regarding this question would be required. The Division expressed concern that even in the presence of high urinary concentrations of sulopenem, asymptomatic bacteriuria was observed. The Sponsor acknowledged that further conversation would be valuable and explained that the asymptomatic bacteriuria was related to recolonization from the vaginal mucosa.

Pharmacology/Toxicology

1. Before submitting the NDA, submit a list of all the nonclinical studies that will be included in the NDA submission.
2. Final, complete study reports for all nonclinical safety pharmacology, pharmacokinetic, and toxicology studies including those submitted in INDs 73463 and 77881 should be included in your NDA submission.

Meeting Discussion: No discussion needed.

Statistics:

1. For the micro-MITTS and micro-MITTR populations of IT001-301, please present the proportion of subjects in each treatment group at the TOC visit who met the overall success criterion of "resolution of the symptoms of uUTI present at trial entry and no new uUTI symptoms," and also the proportion in each treatment group who met the overall success criterion of "The patient has received no rescue therapy for uUTI."

   Meeting Discussion: The Sponsor referred to information provided on slide 3.

2. Clarify whether any patients in IT001-301 developed pyelonephritis.

   Meeting Discussion: The Sponsor referred to information provided on slide 8.

3.0 ADDITIONAL APPLICATION INFORMATION (not discussed at the meeting)

DISCUSSION OF THE CONTENT OF A COMPLETE 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.

- 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.

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*.[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]

[1] 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.

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

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 Information[3] and Pregnancy and Lactation Labeling Final Rule[4] 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
- 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.

[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

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).[5] 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.[6]

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 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

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

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)**
(1) Example: Published literature	*Nonclinical toxicology*
(2) Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication A*
(3) Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section B*

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.

4.0 ATTACHMENT

Sponsor’s Slide Presentation

11 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

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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
10/27/2020 05:36:06 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 129834
IND 129849

MEETING MINUTES

Iterum Therapeutics US Inc.
Attention: Michael Dunne, MD
20 Research Parkway, Suite G
Old Saybrook, CT 06475

Dear Dr. Dunne:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for the following:

IND 129834 CP 70429 (sulopenem)
IND 129849 PF 03709270 (sulopenem etzadroxil)

We also refer to the meeting between representatives of your firm and the FDA on July 21, 2017. The purpose of the meeting was to discuss the clinical development program for sulopenem and sulopenem etzadroxil.

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

If you have any questions, call Carmen DeBellas at (301) 796-1203.

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
Meeting Slides

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	End of Phase 2
Meeting Date:	July 21, 2017
Application Numbers and Product Names:	IND 129834 CP 70429 (sulopenem) IND 129849 PF 03709270 (sulopenem etzadroxil)
Indication:	Complicated Urinary Tract Infections (cUTI) Complicated Intra-abdominal Infections (cIAI) Uncomplicated Urinary Tract Infections (uUTI)
Sponsor Name:	Iterum Therapeutics US Inc.

FDA ATTENDEES

Office of Antimicrobial Products

Edward Cox, MD, MPH	Director Office of Antimicrobial Products (OAP)
Sunita Shukla, MPH, Ph.D.	Associate Director for Regulatory Science, (OAP)
Carmen DeBellas, PharmD	Chief Project Management Staff
Seong Jang, PhD	Clinical Pharmacology Team Leader
Peter Kim, MD, MS	Clinical Reviewer
Sumathi Nambiar, MD, MPH	Director
Joseph Toerner, MD, MPH	Deputy Director for Safety
Sonia Pahwa, PhD	Clinical Pharmacology Reviewer
James Wild, PhD	Pharmacology/Toxicology Reviewer
Avery Goodwin, PhD	Clinical Microbiology Reviewer
Karen Higgins, ScD	Statistics Team Leader
Terry Miller, PhD	Pharmacology/Toxicology Team Leader
Dmitri Iarikov, MD, PhD	Acting Deputy Director
Thomas Smith, MD	Clinical Team Leader
Fang Li, PhD	Pharmacometrics Reviewer
John Lazor, PharmD	Director, Division Clinical Pharmacology 4

SPONSOR ATTENDEES

Iterum Therapeutics US Inc.

Michael Dunn, MD	Chief Scientific Officer
Sailaja Puttagunta, MD	Vice President, Clinical Development
(b) (4), PhD	Clinical Pharmacologist (b) (4)

BACKGROUND

Iterum Therapeutics US Inc. submitted a Type B End of Phase 2 meeting request on April 27, 2017 followed by the meeting package on June 20, 2017 to discuss further development of sulopenem and sulopenem etzadroxil (collectively referred to as "sulopenem" unless otherwise specified). FDA sent Preliminary Comments to Iterum Therapeutics US Inc. on July 17, 2017.

DISCUSSION

The meeting began with the Sponsor describing their clinical development plans. The Phase 3 uncomplicated UTI (uUTI) study discussion began with the definition of clinical success. The Sponsor indicated that defining clinical success as resolution of the symptoms of uUTI may be challenging because some patients, despite significant clinical improvement and successful microbiologic response, may still report some residual symptoms and therefore be categorized as failures. Defining clinical success as resolution of symptoms may result in lower cure rates and increase the sample size for the trial. The Sponsor pointed out that recent trials for cUTI have used both cure and improvement to demonstrate clinical success. The Sponsor also noted that the use of nonsteroidal anti-inflammatory drugs can confound assessment of clinical symptoms and make the distinction between resolution and improvement of symptoms less relevant.

The Division emphasized that clinical response should be defined as resolution of symptoms of uUTI present at trial entry. The Division suggested moving the primary endpoint evaluation to Day 10-12 post-randomization to allow sufficient time for resolution of symptoms. The Sponsor stated they would evaluate if this change was feasible.

The Sponsor enquired about the inclusion of organisms resistant to the comparator in the primary analysis population for the uUTI trial. The Division responded that for a noninferiority (NI) trial it is essential that only patients with organisms susceptible to the proposed comparator be included in the efficacy analysis. The Sponsor asked what happens when the population with pathogens resistant to the comparator is a small subset of the population enrolled. The Division reiterated that in an NI trial, it is essential that patients in the comparator group receive effective therapy and also noted that as susceptibility information is collected at baseline conducting efficacy analyses in this subgroup would not compromise the statistical analysis. The Sponsor stated that the trial would be difficult to conduct operationally and the sample size would need to be increased to account for patients with resistant organisms.

The Division noted that superiority could be tested if the trial design assumes sulopenem will be superior to ciprofloxacin due to high resistance rates to ciprofloxacin. Alternatively, NI could be

demonstrated in patients with susceptible organisms and superiority in the subset of patients with resistant organisms.

The Sponsor asked what the indication would be if superiority in resistant organisms was demonstrated. The Division replied that the label would likely state: "…effective in the treatment of uUTI due to susceptible organisms…"

The Sponsor stated that if a trial using ciprofloxacin as a comparator was not feasible, the Sponsor may consider a switch to nitrofurantoin as the comparator. The Division indicated that if the Sponsor would like to use nitrofurantoin as the comparator, they would need to provide a rationale to justify the acceptability of nitrofurantoin as appropriate therapy for uUTI. The Division stated that they were willing to have a follow-up discussion on this topic, if needed.

The Sponsor agreed to a secondary endpoint to assess patients for resolution of symptoms and microbiologic success around Day 28 post-randomization.

The Sponsor and Agency discussed concerns that patients could potentially take placebo tablets before completing the three days of ciprofloxacin based on the design of the proposed blister package (see attached). The Sponsor acknowledged the concern and stated that they will continue to evaluate solutions to address this issue.

The Sponsor noted that recent studies for complicated urinary tract infections (cUTI) utilized a definition of clinical success that included both patients with complete resolution, as well as, those with significant improvement of symptoms. The Division noted that as outlined in the cUTI guidance, for drugs with only an IV formulation, such as those with recently completed trials, the primary endpoint assessment typically occurs on Day 5. In such situations, assessment of clinical success is based on resolution of all signs/symptoms with the exception of flank pain which could be improved but may not have completely resolved by Day 5. Additionally, complete resolution of all signs and symptoms, including flank pain, should be achieved at a subsequent fixed timepoint assessment that would encompass the total duration of antibacterial therapy plus an observation period of approximately 7 days after completion of antibacterial therapy. For development programs that have both an IV and oral formulation, such as sulopenem, the primary endpoint would occur at a fixed timepoint at least 5 days after completion of all antibacterial therapy (Day 17 in the current proposal). The expectation for this primary endpoint assessment is complete resolution of all signs and symptoms, including flank pain. The Sponsor stated that they understood the Agency's rationale for complete resolution of signs and symptoms by Day 17 and would incorporate the change in the cUTI protocol.

The Sponsor noted that EMA was concerned with the choice of ertapenem as a comparator in the cUTI trial because it is not approved for the treatment of cUTI in Europe and stated that they will keep the Agency abreast of further discussions with EMA.

The Sponsor agreed that the primary efficacy endpoint for clinical success in the complicated intra-abdominal (cIAI) trial should be defined as resolution of all baseline signs and symptoms of cIAI and no new symptoms from baseline to Day 28. The Sponsor added that the final blinding

plan for the IV to oral switch would ensure patients in both treatment groups would receive similar numbers of tablets.

The Sponsor addressed concerns with enrolment of patients with creatinine clearance (CrCl) <50 mL/min. These patients were initially excluded because of the precaution in the probenecid label that it is not recommended in conjunction with a beta-lactam in the presence of known renal impairment.

The Sponsor agreed to re-evaluate the use of probenecid in patients with renal impairment and allow patients with CrCl <50 mL/min in the cUTI and cIAI trials but preferred to exclude them from the uUTI trial. The Agency stated that was acceptable. The Sponsor added that due to daily variations in CrCl in patients with renal insufficiency, CrCl will be monitored at baseline and on Day 3 for the possibility of dose adjustment.

The final item for discussion was the bilayer tablet. The Sponsor stated that use of the bilayer tablet in the Phase 3 program will depend on its availability. The Sponsor stated their preference to use the individual tablets in the uUTI trial rather than wait for the bilayer tablet to be available. They proposed performing a bioequivalence (BE) study and delaying the cIAI and cUTI trials until the bilayer tablet is available. The Division stated that the Sponsor could consider switching to the bilayer tablets in the uUTI trial once they become available and BE is demonstrated.

The FDA suggested that BE of both sulopenem and probenecid should be established based on the Guidance on Bioavailability and Bioequivalence Studies submitted in NDAs or INDs (https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm389370.pdf). The Sponsor agreed to review the Guidance.

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 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 (cder-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.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. As of May 5, 2017, the following submission types: NDA, ANDA, and BLA must be submitted in eCTD format. Commercial IND and Master File submissions must be submitted in eCTD format beginning May 5, 2018. 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.

ATTACHMENTS AND HANDOUTS

The preliminary responses and Sponsor slides discussed at the meeting are attached.

CP-70429 (sulopenem) (IV)
PF-03709270 (sulopenem pro-drug) (Oral)

For the treatment of Uncomplicated Urinary Tract Infections (uUTI), Complicated Urinary Tract Infections (cUTI) and Complicated Intra-abdominal Infections (cIAI).

End of Phase-2
Meeting Briefing
Document
July 21, 2017

1. SPECIFIC QUESTIONS

We are requesting feedback from the Agency on the following questions:

5.1 Clinical Development Program

5.1.1 Question 1: Clinical Program

Does the Division agree that one adequate and well-controlled clinical trial per indication will provide adequate evidence to allow filing and review of the package in the efficacy of oral sulopenem etzadroxil for a claim of uUTI, and IV sulopenem and oral sulopenem etzadroxil for the claims of cUTI and cIAI?

Division Response:

One successful adequate and well-controlled clinical trial per indication is acceptable to support the uUTI, cUTI and cIAI indications.

Sponsor: Acknowledged.

5.1.2 Question 2: Phase 3 Registration Program

I. **Does the Agency agree that Study IT001-301, as proposed in the draft protocol, will provide adequate evidence to determine efficacy by demonstrating the non-inferiority (NI) of oral sulopenem etzadroxil (PF-03709270) co-administered with oral probenecid relative to oral ciprofloxacin for the treatment of uUTI? Could the Division please comment on specific study design features including:**

a. The proposed key inclusion criteria
b. The choice of combined clinical and microbiologic response as the co-primary endpoint, including definitions of outcome measures and the timing of measurement of the primary endpoint (Day 7)
c. The choice of the comparator of oral ciprofloxacin
d. The justification for the NI margin for the comparison of oral sulopenem etzadroxil plus oral probenecid with oral ciprofloxacin
e. Methodology for the measurement of the clinical outcome variables

Division Response:

a. Regarding your inclusion/exclusion criteria,

i. Clarify whether you intend to enroll the following groups:
    i. pregnant patients
    ii. patients with diabetes
    iii. patients with uncontrolled diabetes

Sponsor:

- We will exclude pregnant women in the uUTI study.
- We will include diabetics but the diabetes must be adequately controlled.

Division Response:

b. Ensure that you adequately address drug interactions with probenecid

Sponsor:

The probenecid package insert will be included as an attachment to the protocol but we will also add the following to the protocol:

- Exclude patients with hypersensitivity to probenecid, history of blood dyscrasias or uric acid kidney stones, acute gouty attack, patients on chronic methotrexate therapy.
- To the background information, add that (1) there is a risk of hypoglycemia in patients taking oral sulfonylureas and (2) though the clinical significance has not been established, the plasma concentrations of indomethacin, acetaminophen, naproxen, ketoprofen, meclofenamate, lorazepam, ketamine, thiopental, and rifampin can be increased.

Division Response:

c. We recommend that the responder definition used for the Day 7 primary efficacy endpoint require resolution of uUTI symptoms rather than resolution or improvement, which may make the endpoint more sensitive.

Sponsor:

There are, of course, no recent historical precedents upon which to define the primary endpoint in uUTI studies, so we acknowledge that this is an appropriate topic for discussion. There are challenges, however, with 'cure' as the only marker of clinical benefit:

- Cure vs improved is very subjective as one person's cure is another's improved, likely related to the subjective nature of pain. It is more important that response, whether cure or cure + improved, is different from failure.
- The NI margin justification would accept cure + improved to allow for a treatment effect over placebo, albeit with only the Christiaens paper for the analysis, and as a result, there is no real advantage to making the endpoint more stringent, even if that were possible.
- Using the complicated studies as a reference point, with the exception of the ceftazidime-avibactam study, in all recent complicated UTI and IAI studies responders have been defined as 'cured + improved'. There was an 'improved' caveat in the ceftazidime-avibactam study endpoint related to flank pain at Day 5, presumably related to the subjective nature of the resolution of pain and its measurement at an earlier timepoint.
- Removing 'improved' as an option in the primary endpoint lowers the point estimate, adds uncertainty related to anticipation of the point estimate of success and increases the required sample size of the study.
- We would like to discuss this topic further at the FTF meeting.

Division Response:

i. Regarding the assessment of efficacy, we note on page 27 of the protocol that, "…Concomitant systemic antibacterials are prohibited during the study, up to the TOC visit…" However, the following statement found on page 32 of the protocol states, "…If an antibiotic is given for other reasons, then the patient will not be considered a non-responder for uUTI…" Note that for the ITT analysis, if a non-study antibacterial agent with activity against the UTI pathogen(s) is taken by the patient during the study up until the primary endpoint visit, then the patient would be considered a failure

Sponsor

We understand your position but would prefer to make a patient who receives a concomitant antibiotic for an indication other than the UTI, with activity against the UTI pathogen, an indeterminate, which can be assigned to failure, as per a statistical analysis plan.

Division Response:

ii. Note that based on our current thinking and in an effort to harmonize with EMA, we are moving towards microbiologic eradication defined as < 10^3 CFU/mL instead of < 10^4 CFU/mL. Based on our analyses of completed trials in complicated UTI, the vast majority of patients achieve microbiological eradication defined as < 10^3 CFU/mL and this change should not impact your results significantly

Sponsor

We agree with this suggestion and will change the protocol.

Division Response:

iii. An assessment of continued resolution of symptoms and microbiologic success should occur at a fixed time point approximately 21 to 28 days following randomization. This is an important secondary endpoint

Sponsor

We appreciate that you are referencing the cUTI guidance document regarding the secondary endpoint timing. We were trying to efficiently align the study objectives across both the US and EU. The EMA guidance for cUTI studies does recommend that the day of evaluation for the primary endpoint occur 7 days after the last dose which would be day 12 in this study. In the Ferry study with pivmecillinam in uUTI, extending the observation period from Day 8-10 to Day 35-42 increased the response rate from 60.8% to 68.1%. Having a visit at Day 12/14 and Day 21 seems unlikely to provide a lot of additional information but we can do so if necessary. This can be further discussed at the FTF meeting.

Division Response:

d. The choice of oral ciprofloxacin as the comparator is acceptable.

Sponsor:

Acknowledged.

Division Response:

e. The justification for the NI margin for the comparison of oral sulopenem etzadroxil plus oral probenecid with oral ciprofloxacin is acceptable. However, we recommend that the primary non-inferiority analysis only be conducted in patients with ciprofloxacin-susceptible baseline pathogens

Sponsor:

We were not able to identify any precedent for excluding the resistant pathogens from the primary analysis population in these three indications. This exclusion is also problematic for a number of reasons:

- Further removes the analysis population from the ITT population
- Selects for a patient population which does not necessarily represent the target population for labelling as patients with quinolone resistant pathogens are likely to be sicker and older having been previously treated with a quinolone [Karlowsky 2006]
- Quinolone resistant pathogens are frequently resistant to other classes of antibiotics including other β-lactams. Given that sulopenem is a β-lactam, it is important to document activity against those type of β-lactamase producing organisms, including ESBL producing pathogens. Therefore, excluding quinolone resistant pathogens is counter-productive in defining the risks and benefits of sulopenem in these indications.
- Ultimately excluding quinolone resistant pathogens removes a significant population of patients for whom sulopenem is actually ideal and meeting a critical medical need in the outpatient setting.

Sub-group analyses in patients with ciprofloxacin-susceptible and ciprofloxacin-resistant pathogens can be included in a statistical analysis plan.

We would like to discuss this topic further at the FTF meeting.

Division Response:

f. The proposed patient symptom assessment questionnaire is acceptable.

Sponsor:

Acknowledged.

Division Response:

Additional comments:

- Clarify how you intend to ensure that patients in the comparator arm will take oral ciprofloxacin consecutively for the first 3 days and not placebo since both will be in the same blister pack

Sponsor:

The blister pack is labelled by day numbers and the patients will be instructed to take the first dose starting at Dose 1. We are considering including in the pharmacy manual a requirement for the coordinator to witness the first dose and teach the patient the sequence in which the drugs will be taken. On Day 3, the blister packs will be provided to the coordinator for inspection, at which time a compliance check, not just with the number of pills taken but the order in which they are taken, can be done.

Division Response:

- Note that since you plan to conduct an NI trial in uUTI, if the prevalence of ciprofloxacin nonsusceptible isolates is high, you may need to factor this into your calculation of sample size

Sponsor:

Please see response to item e above.

II. **Does the Agency agree that Study IT001-302, as proposed in the draft protocol, will provide adequate evidence to determine efficacy by demonstrating the non-inferiority (NI) of IV sulopenem with switch to oral sulopenem etzadroxil relative to IV ertapenem with switch to oral ciprofloxacin for the treatment of cUTI? Could the Division please comment on specific study design features including:**

a. The proposed key inclusion criteria
b. The choice of combined clinical and microbiologic response as the co-primary endpoint, including definitions of outcome measures and the timing of measurement of the primary endpoint (Day 12)
c. The choice of the comparator of IV ertapenem with switch to oral ciprofloxacin
d. Methodology for the measurement of the clinical outcome variables

Division Response:

a. Regarding the inclusion/exclusion criteria,
    i. Explain why you intend to exclude patients with CrCl < 50 mL/min

Sponsor:

The reason patients with CrCl <50 mL/min were excluded was to simplify the protocol given the precaution in the probenecid label that its use is not recommended in conjunction with a penicillin in the presence of known renal impairment. However, given that no safety concerns associated with probenecid use in patients with renal impairment were identified in a literature review, we will not exclude patients with CrCl < 50 mL/min, and plan to check sulopenem PK in these patients. We do expect however that very few patients with renal impairment of this magnitude will be enrolled in these studies given previous experience in clinical trials and the unlikelihood of patients with moderate/severe renal impairment to have cUTIs.

Division Response:

ii. Ensure that you adequately address drug interactions with probenecid

Sponsor:

Please see response to item I b above.

Division Response:

b. Regarding the primary efficacy responder endpoint, we note that based on the protocol, the primary efficacy responder endpoint visit will occur on Day 17 and not Day 12.

Sponsor:

Please disregard Day 12 in the Briefing Document as that was an error. We confirm that the primary endpoint will be assessed on Day 17.

Division Response:

c. We recommend that, in addition to microbiologic eradication, the responder definition used for the Day 17 primary efficacy endpoint requires complete resolution of cUTI symptoms rather than "resolution or significant improvement".

Sponsor:

We prefer to define clinical success as resolution/improvement for the following reasons:

- Resolution/improvement was used to define the primary endpoint in all but one recent registrational cUTI trials including ceftolozane-tazobactam and meropenem-vaborbactam cUTI studies;
    - "resolution of all symptoms except flank pain which had to be improved on Day 5" was used in the ceftazidime-avibactam cUTI trial.
- Cure vs improved is very subjective as one person's cure is another's improved. It is more important that response, whether cure or cure + improved, is different from failure.
- Endpoints related to pain can be more subjective than others. Frequency and although related to pain, dysuria should be easier to assess as cured but other pain endpoints such as suprapubic pain and flank pain, may be harder to clearly define as cured rather than significantly improved.
- Removing improved as an option in the primary endpoint lowers the point estimate and increases the required sample size of the study.
- We would like to discuss this topic further at the FTF meeting.

Division Response:

i. Note that based on our current thinking and in an effort to harmonize with EMA, we are moving toward microbiologic eradication defined as $< 10^3$ CFU/mL instead of $<10^4$ CFU/mL. Based on our analyses, this change should not impact your results significantly.

Sponsor:

We agree with this suggestion and will change the protocol.

Division Response:

d. The choice of the comparator of IV ertapenem with a switch to oral ciprofloxacin is acceptable. The sensitivity analysis considering patients as failures if it is not

possible to find an appropriate oral step-down medication is acceptable, but we recommend against this definition for the primary analysis because the endpoint could become a measure of treatment usage rather than patient response. Additionally, we note that determining whether a quinolone-resistant pathogen, based on serum concentrations, would fail to be adequately treated when the site of infection is the urinary tract is not straightforward. Therefore, the decision regarding appropriate oral step-down therapy is complex

Sponsor:

Acknowledged.

We are in the process of discussing appropriate comparators for this study with the European regulatory agencies and would like to briefly review our thoughts at the FTF meeting.

We agree that the decision regarding appropriate oral step-down therapy is complex, but prefer to not allow a step-down to ciprofloxacin in patients whose baseline pathogen is found to be resistant to ciprofloxacin, given that this could lead to poor outcomes in patients with complicated infections that may be associated with bacteremia [Wilcox 2009].

Division Response:

e. Regarding the methodology for measurement of the clinical outcome, the proposed Patient Symptom Assessment Questionnaire (PSAQ) as noted on page 62 of the protocol does not appear to assess for flank pain or tenderness. We recommend including a question to assess flank pain and tenderness.

Sponsor:

Will add flank pain or tenderness to the Questionnaire.

III. **Does the Agency agree that Study IT001-303, as proposed in the draft protocol, will provide adequate evidence to determine efficacy by demonstrating the non-inferiority (NI) of IV sulopenem with switch to oral sulopenem etzadroxil relative to IV ertapenem with switch to a regimen of oral ciprofloxacin and metronidazole for the treatment of cIAI? Could the Division please comment on specific study design features including:**

a. The proposed key inclusion criteria
b. The choice of clinical response as the primary endpoint, including definitions of outcome measures and the timing of measurement of the primary endpoint (Day

28)

c. The choice of the comparator of IV ertapenem with switch to appropriate oral comparator
d. Methodology for the measurement of the clinical outcome variables

Division Response:

a. Regarding the inclusion/exclusion criteria,
    i. ensure that you adequately address drug interactions with probenecid

Sponsor:

Please see response to item I b above.

Division Response:

b. The primary efficacy endpoint of clinical success should be defined as resolution of all baseline signs and symptoms (not "resolution or significant improvement") of cIAI and no new symptoms from baseline to Day 28

Sponsor:

All three recent registrational cIAI trials (ceftazidime-avibactam, ceftolozane-tazobactam and eravacycline) defined clinical success as cure or improvement for the primary endpoint. We believe that it is reasonable to include the caveat of "no worse than mild" with regard to abdominal pain in a setting where patients may have had a recent surgical intervention. We will otherwise amend the primary endpoint in our protocol to require resolution of the baseline signs and symptoms. We would like to discuss this further at the FTF meeting.

Division Response:

c. The choice of the comparator of IV ertapenem with a switch to an appropriate oral comparator is acceptable. The sensitivity analysis considering patients as failures if it is not possible to find an appropriate oral step-down medication is acceptable, but we recommend against this definition for the primary analysis because the endpoint could become a measure of treatment usage rather than patient response.

Sponsor:

Acknowledged.

Division Response:

d. We are unclear what methodology for measurement of the clinical outcome variable you might be referring to in the cIAI protocol.

Sponsor:

The patient's clinical response will be assessed by the investigator based on a simple symptom review that addresses the original list of symptoms as well as other factors such as the patient being alive and the lack of any additional antibiotics or interventions. We will amend the protocol to make that clearer.

Division Response:

Additional comments:

- Per page 35 of the protocol, subjects randomized to the comparator regimen who have an organism resistant to ciprofloxacin and who meet criteria for oral step-down therapy will receive one tablet from the kit bottle twice daily and one capsule from a blister pack twice daily. Subjects randomized to the sulopenem arm and subjects randomized to the comparator without an organism resistant to ciprofloxacin appear to receive an extra blister pack. This could potentially compromise the study blind. Therefore, subjects randomized to the comparator regimen that have an organism resistant to ciprofloxacin and who meet criteria for oral step-down therapy should likely receive one tablet from the kit bottle twice daily and one capsule from each of two blister packs twice daily to avoid compromising the study blind.

Sponsor:

The concern is that there could be an unblinding if patients resistant to ciprofloxacin (who will be getting Augmentin if on comparator) will be unblinded because they will get an extra blister pack. The protocol may not be clear on the dosing arrangements at this point given that we are in the final stages of designing the actual blister packs; when available a schematic will be put into the protocol to make it clearer.

To address the concern directly:

If the organism is ciprofloxacin susceptible, both the sulopenem and comparator patients will get a metronidazole blister pack (placebo [PBO] for the sulopenem patients and active for the ciprofloxacin patients), as well as a bottle with either active sulopenem or its placebo and a blister pack with either the overencapsulated probenecid or the overencapsulated ciprofloxacin. If the organism is ciprofloxacin resistant, no metronidazole/PBO blister pack is necessary and patients will get one bottle and one blister pack, with the active sulopenem/overencapsulated probenecid or sulopenem PBO and overencapsulated Augmentin.

Division Response:

- Regarding section 8.3, "Definition of an AE," on page 45, the "events" refer to cUTI instead of cIAI

Sponsor:

That is a typo that will be corrected.

Division Response:

5.1.3 Question 3: Size of the Safety Database

Does the Division agree that the proposed clinical database will provide adequate evidence regarding the safety of IV sulopenem and oral sulopenem etzadroxil to support the benefit/risk assessment for the intended claims?

Division Response:
The proposed safety database of 1284 subjects in Phase 3 may be acceptable as long as no new safety signals are identified during your Phase 3 program.

Sponsor:

Acknowledged.

5.2: Phase 1 Studies

5.2.1 Question 4: Cardiac Safety of Sulopenem

Does the Division agree that the cardiac safety of IV sulopenem has been adequately characterized in Studies A1091001 and A7371007, thus precluding the need for conduct of an additional thorough QT study?

Division Response:
The QT Interdisciplinary Review Team is currently reviewing your submissions. We anticipate being able to respond to your question in early September 2017.

Sponsor:

Acknowledged.

5.2.2 Question 5: Dose Adjustment in Renal Failure

Given that oral sulopenem etzadroxil will only be supplied as a bi-layer tablet in combination with oral probenecid, and based on the results of the renal-impairment study (A8811009), does the Division agree that no dose adjustment is warranted for PF-03709270 in the setting of renal failure?

Division Response:

In terms of sulopenem exposure, your rationale for no dose adjustment in patients with renal impairment appears reasonable. However, probenecid exposure may potentially be increased in patients with moderate and severe renal impairment. We recommend that you address whether there are any adverse events related to elevated exposure to probenecid. Additionally, we recommend that you include patients with creatinine clearance less than 50 mL/min in the Phase 3 trials in order to conduct population PK and safety analyses as a function of renal impairment and, in turn, evaluate whether a dose adjustment in renal impairment is needed.

Sponsor:

We will prepare a thorough review of the literature for any adverse events related to the use of probenecid in patients with impaired renal function. To date, we have not identified an issue but will continue to investigate.

We will include patients with creatinine clearance less than 50 mL/min in the complicated studies but would prefer to continue to exclude them from the uUTI studies given that the pathophysiology of a uUTI infection in those patients could be very different from patients at large.

5.2.3 Question 6: Additional Phase 1 Studies

Does the Division agree that there are no additional Phase 1 studies required prior to review of the NDAs for IV sulopenem and oral sulopenem etzadroxil?

Division Response:

The planned Phase 1 studies appear reasonable. However, we strongly recommend that you evaluate safety and efficacy of the bilayer formulation in the Phase 3 trials. We recommend that you develop the new bilayer formulation before the Phase 3 trials and conduct a standard BA/BE study of the new formulation before the Phase 3 trials.

Sponsor:

We acknowledge the Division's Guidance on the use of the bilayer tablet in the phase 3 program as it would remove any downstream uncertainty related to bioequivalence of the formulations. Our hesitation initially to introduce the bilayer tablets into phase 3 directly was only related to the timing of the availability of clinical supplies. We now have some greater clarity on that process and would like to discuss some alternative options, perhaps moving forward with the uUTI program with individually dosed tablets followed by a BE study later and delaying the complicated studies until the bilayer tablets are available. Probenecid is less critical to the efficacy of sulopenem in the urine given the high sulopenem urinary levels so a BE study could be viewed differently from one in which serum levels are important. We would like to discuss this further at the FTF meeting.

5.3 Pre-clinical/In Vitro Data

5.3.1 Question 7: Non-clinical Safety Package

Does the Division agree that no additional preclinical studies will be required for

submission and review of the toxicology package?

Division Response:

The scope of the completed nonclinical studies with CP-70429 and PF-03709270 appears to be adequate to support the planned Phase 3 trials and marketing with the following recommendations.

1. For the combination of a late-stage entity (defined as compounds with Phase 3 or post marketing experience) and an early stage entity with clinical experience, the M3(R2) Guidance recommends that a nonclinical combination study should be conducted to support late-stage clinical trials. We recommend that a nonclinical combination study with PF-03709270 and probenecid of a duration that matches the intended clinical duration of dosing with the combination should be conducted to support Phase 3 studies and marketing of PF-03709270. The nonclinical combination study can be conducted before initiating Phase 3 trials or at the time of initiation of the first Phase 3 trial. Ideally, the nonclinical combination study should include: (1) low and high doses of PF-03709270 and probenecid administered individually and in combination, (2) encompass the planned clinical doses of the two compounds, and (3) provide plasma exposures above the exposures expected in the clinic. Guidance regarding study design will be provided by the Division upon request.

Sponsor:

Acknowledged. We will plan to conduct a 2 week toxicology study with the combination of PF-03709270 and probenecid in rats.

Division Response:

2. Pre- postnatal studies for both CP-70429 and PF-03709270 should be completed to support marketing

Sponsor:

We will conduct a Segment 3 study for both compounds.

Division Response:

3. Based on results in nonclinical studies and safety results in clinical studies, additional nonclinical studies may be recommended.

Sponsor:

Acknowledged.

5.3.2 Question 8: *In Vitro* Studies

Does the Division agree that there are no additional *in vitro* studies required to allow review of the NDA?

Division Response:

We recommend that you provide the reaction phenotyping results of sulopenem with a panel of CYP and UGT enzymes, to demonstrate if sulopenem is a substrate for CYPs or UGTs.

Sponsor:

Acknowledged.

5.4. Question 9: Equivalence of Oral Formulations

Does the Division agree with the proposed approach to demonstrate equivalence across the two oral formulations for PF-03709270 and are there any other characteristics of the comparison which may be important to consider?

Division Response:

The proposed approach to demonstrate equivalence across the two oral formulations appears to be acceptable. However, we recommend you evaluate safety and efficacy of the bilayer formulation in the Phase 3 trials (see our response to Question 6).

Sponsor:

Please see our response to Question 6.

5.5 Question 10: Microbiology Surveillance Studies

Does the Division agree that the proposed plan to include microbiology data from the upcoming Phase 3 studies in conjunction with a recently completed in vitro susceptibility study of about 1100 recent clinical isolates (2013-2015) be sufficient to support the microbiology section of the application and are there any additional microbiologic studies we should have available?

Division Response:

We agree with the proposed plan to include microbiology data from your upcoming Phase 3 trials in addition to your recently completed in vitro susceptibility data of 1100 (2013-2015) clinical isolates. For guidance concerning additional microbiologic studies, we refer you to our microbiology guidance document entitled *Microbiological Data for Systemic Antibacterial Drug Products—Development, Analysis, and Presentation Guidance for Industry*. Available at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM182288.pdf

Sponsor: Acknowledged.

5.6 Question 11: Pediatric Studies

Does the Division agree with our proposed plans for development of sulopenem for use in pediatric patients and could the Division please clarify the pathway for reaching agreement on the pediatric program and requirements under PREA, including the timing of such requirements relative to approval of the NDA?

Division Response:

Please submit your initial pediatric study plan (iPSP) to your INDs. Your iPSP will be reviewed by DAIP and the Pediatric Review Committee (PeRC). Pediatric studies of clinical effectiveness and safety should be initiated once you have preliminary evidence of efficacy and safety in adults. Your iPSP will need to address uUTI in pediatric patients.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an iPSP within 60 days of an End of Phase (EOP2) meeting. 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.

Sponsor: Acknowledged.

5.7 Question 12: Breakpoint Determination

Can the Division please clarify the approach for setting breakpoints based on urinary drug concentrations for the treatment of UTIs?

Division Response:

We note that in general, breakpoints are established by using three principles: MIC distribution patterns from large surveillance studies, clinical response data, and PK/PD characteristics of the drug. Urinary drug concentrations are important to evaluate in the context of a clinical development program for uUTI and cUTI and may be considered in the evaluation of the PK/PD characteristics of the drug. At this time, we are not setting breakpoints based on urinary concentrations of the drug for UTIs. If you want to provide a scientific rationale for determining breakpoints based on urinary concentrations, we will review it and provide feedback. Concentrations in the urine can be affected by several factors including renal function, fluid intake, etc. and will need to be taken into consideration.

Sponsor: Acknowledged. We will review the topic in more detail and will re-engage on this topic if deemed appropriate.

5.8 Regulatory Issues

5.8.1 Question 13: 505(b)(2) Application

Does the Division agree with the proposed regulatory strategy of using a 505(b)(2) application for oral sulopenem etzadroxil co-formulated with probenecid?

Division Response:
If you plan to pursue the 505(b)(2)NDA, whereby you rely in part on the Agency's previous finding of safety and efficacy of probenecid, you will need to present a systematic review and summary of the safety of probenecid from the published literature.

Sponsor: Acknowledged.

5.8.2 Question 14: QIDP status

Does the Division agree that the QIDP status granted for PF-03709270 will apply to the PF-03709270/probenecid combination tablet formulation?

Division Response:
No, a new QIDP request would need to be submitted containing clinical and microbiology information for the PF-03709270/probenecid combination formulation.

Sponsor: Acknowledged. We will submit another QIDP request shortly.

REFERENCES

1. Karlowsky J, Hoban D, DeCorby M, et al. Flouroquinolone-resistant urinary isolates of *Escherichia coli* from outpatients are frequently multidrug resistant: results from the North American urinary tract infection collaborative alliance-Quinolone resistance study. Antimicrobial Agents and Chemotherapy 2006: 2251-2254

2. Wilcox M, Tack K, Bouza E, et al. Complicated skin and skin-structure infections and catheter-related bloodstream infections: Noninferiority of linezolid in a Phase 3 study. Clinical Infectious Diseases 2009; 48:203-12

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/s/

SUMATHI NAMBIAR
08/17/2017