CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216483Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 118650

MEETING PRELIMINARY COMMENTS

UTILITY therapeutics Limited
c/o Kleinfeld, Kaplan and Becker
Attention: Daniel Dwyer
1850 M Street, N.W., Suite 800
Washington, D.C. 20036

Dear Mr. Dwyer:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for pivmecillinam hydrochloride (HCl) tablets.

We also refer to your September 24, 2021, correspondence, received September 24, 2021, requesting a meeting to discuss the format and content of the planned new drug application for the treatment of uncomplicated urinary tract infections.

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 Jacquelyn Rosenberger, PharmD, RAC, Regulatory Project Manager, at (301) 796-9179.

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

U.S. FOOD & DRUG ADMINISTRATION

PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: December 06, 2021, 11:00 AM – 12:00 PM, EST
Application Number: IND 118650

Product Name: pivmecillinam hydrochloride (HCl) tablets
Indication: Treatment of uncomplicated urinary tract infections (uUTI)

Sponsor Name: UTILITY therapeutics Limited
Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetic Act

Introduction:
This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for December 06, 2021, between UTILITY therapeutics Limited and the Division of Anti-Infectives. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda. Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

Preliminary Comments:

1. **Does the Agency agree with the Utility's assessment of the clinical studies it considers "covered" and "not covered" regarding financial disclosure?**

   FDA Response:
   We agree.

2. **Does the Agency agree with the robustness analyses as outlined in Section 5.5.4.3 and Appendix 2A?**

   FDA Response:
   We agree with the general approach to the efficacy analysis which appears to adequately address the Division's previous advice (included in the Division's response to Question 1 in the meeting package for the April 6, 2021 meeting).

However, we may have additional comments upon review of how these analyses will be performed.

We also note that study populations and analysis methodologies (e.g., handling of missing data, measures used, and win criteria) for each of the studies are not entirely clear. We recommend that an estimand framework according to the ICH E9 addendum be specified for each of the three primary efficacy studies, clearly indicating the treatment, population, variable of interest, intercurrent event handling and summary measure for all estimands of interest (e.g., primary estimand, secondary and supportive estimands).

3. **Does the Agency agree that the proposed analyses of rates of TEAEs per total person-time exposure (ie, event rates divided by the number of weeks of the total AE reporting period) is appropriate?**

FDA Response:
We agree. Please provide the overall rate of adverse events (number of patients with adverse event per total number of patients) in the individual pools (proportion adjusted for pooling) in addition to the rates of TEAEs per total person-time exposure.

4. **Does the Agency agree with the proposal of case narratives and CRF's that will be provided in the NDA?**

FDA Response:
This appears to be acceptable. Please submit a dataset that includes all treated patients from the three primary efficacy studies including only variables depicting the patient ID and treatment assignment. We will take a 10% random sample of these patients and request that case report forms (CRFs) for these patients be included in the NDA.

5. **In the 120-Day safety update, UTILITY plans to include any new safety data found in a literature search as stated above covering the period 30 June 2021 to the NDA submission date. Does the Agency agree to this approach?**

FDA Response:
We agree.

Additional comments:

Clinical

1. In section 5.5.5 of the briefing package, you have stated that the primary population the for safety analysis (Safety Population) will include all females ≥18 years (b) (4)

[redacted] (b) (4)

2. Clarify if the Vik 2018 study will be included in the safety analysis.

3. We understand that the primary efficacy endpoint is at the TOC visit defined as 7 to 15 days after the start of study drug. Clarify when the test of cure visit will be for subjects who received the drug for 7 days.

4. Submit a Reviewers Guide that includes, but is not limited to the following:
   a. description of files and documentation
   b. description of selected analysis datasets
   c. key variables of interest, including efficacy and safety variables
   d. SAS codes for sub-setting and combining datasets
   e. coding dictionary used
   f. methods of handling missing data
   g. list of variables contained in every dataset
   h. listing of raw data definitions
   i. analysis data definitions
   j. annotated CRF (the annotated CRF should contain links connecting to the document that defines the variable name and lists the data sets that contain the specific item).

Statistics

5. We recommend that you include a brief algorithm in the Reviewer Guide of your NDA submission which describes how results from all primary, secondary and major safety analyses were derived (e.g., the dataset and names of variables used). This would help to limit potential discrepancies between Reviewer and Sponsor analysis results. In addition, SAS programs can be provided. Please ensure that ADaM datasets with define.xml and define.pdf will be submitted for each study. Study analysis datasets should be traceable to the tabulation datasets. If the ADaM datasets were created based on CRF raw data, please also submit the CRF raw data as well. Note that we may need to further address issues regarding data analysis after the NDA is submitted.

6. Page 25 of the submission states “A summary of changes to the efficacy analyses in the SAP (Version 3.0 to Version 4.0) is provided (Appendix 2).” However, Appendix 2 shows Changes from Version 2.0 (Feb 10, 2021) to Version 3.0 (Aug 24, 2021) of the SAP. Please clarify.

Chemistry, Manufacturing, and Controls (CMC):

7. We note that pivmecillinam hydrochloride drug substance is being added to the drug product in its salt form. As noted in the September 7, 2018, CMC comments for IND 118650, we remind you that the drug product strength should be expressed in terms of pivmecillinam, rather than the hydrochloride salt. Refer to the following Guidance for further recommendations: Naming of Drug Products Containing Salt Drug Substances. (https://www.fda.gov/media/87247/download)

8. We note that you intend to reference a drug master file (DMF) for pivmecillinam HCl drug substance and will provide the applicable Letter of Authorization (LOA) for the DMF in the NDA. Note that a copy of the relevant LOA should also be provided in the DMF.

   We encourage you to work with the DMF holder to ensure that the content of the DMF is adequate to support your NDA submission. Refer to the September 7, 2018, CMC comments for IND 118650 for relevant drug substance considerations. For example, regulatory starting materials should be appropriately selected and justified per the principles of ICH Q11 and the associated Q&A document.

   For ease of review, we request that you include the following information for the pivmecillinam HCl drug substance under Module 3 of the NDA:

   - A summary of drug substance properties under 3.2.S.1.3.
   - A tabular summary of any specified drug substance impurities under 3.2.S.3.2.
   - The current release specification for the drug substance under 3.2.S.4.1.
   - Any analytical methodology used to release drug substance for use in your drug product under 3.2.S.4.2 and related method validation/verification information under 3.2.S.4.3.
   - An analysis of three representative batches of drug substance under 3.2.S.4.4 (any drug substance lots used to manufacture the exhibit drug product lots should also be included in this summary).
   - The current drug substance retest period and storage conditions under 3.2.S.7.1.

9. As recommended during the October 31, 2018, pre-NDA meeting, we encourage you to request a CMC-dedicated pre-NDA meeting to discuss issues related to product quality and to ensure that adequate and sufficient product quality information is submitted in the NDA.

3.0 ADDITIONAL APPLICATION INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our October 14, 2021, 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]

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.

[1] https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm

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 Information[4] and Pregnancy and Lactation Labeling Final Rule[5] 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

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[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

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

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

MANUFACTURING FACILITIES

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

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

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the 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 356h[6] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[7]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

[6] https://www.fda.gov/media/84223/download
[7] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and

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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/

GREGORY F DIBERNARDO
12/02/2021 01:54:07 PM

IND 118650

MEETING MINUTES

UTILITY therapeutics Limited
c/o Kleinfeld, Kaplan and Becker
Attention: Dan Dwyer
U.S. Agent
1850 M Street, N.W., Suite 800
Washington, D.C. 20036

Dear Mr. Dwyer:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for pivmecillinam hydrochloride (HCl) tablets.

We also refer to the teleconference between representatives of your firm and the FDA on April 06, 2021. The purpose of the meeting was to obtain feedback on the planned NDA submission of pivmecillinam HCl tablets for the treatment of uncomplicated urinary tract infections (uUTI).

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 Jacquelyn Rosenberger, PharmD, RAC, Regulatory Project Manager, at (301) 796-9179.

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
- Sponsor Slides

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: April 06, 2021, 10:00 AM – 11:00 AM, EDT

Application Number: IND 118650
Product Name: Pivmecillinam hydrochloride (HCl) tablets
Indication: Treatment of uncomplicated urinary tract infections (uUTI)
Sponsor Name: UTILITY therapeutics Limited

Meeting Chair: Sumathi Nambiar, MD, MPH
Meeting Recorder: Jacquelyn Rosenberger, PharmD, RAC

FDA ATTENDEES - Division of Anti-Infectives

Timothy Bensman, PharmD, PhD	Clinical Pharmacology Reviewer
Maureen Dillon-Parker, MS, RAC	Chief, Regulatory Project Management Staff
Amy Ellis, PhD	Nonclinical Pharmacology/Toxicology Reviewer
Mayurika Ghosh, MD	Clinical Reviewer
Avery Goodwin, PhD	Clinical Microbiology Team Leader
Karen Higgins, ScD	Statistical Team Leader
Dmitri Iarikov, MD, PhD	Deputy Director
Seong H. Jang, PhD	Clinical Pharmacology Team Leader
Jiajun Liu, PharmD, MSc	Pharmacometrics Reviewer
Terry Miller, PhD	Nonclinical Pharmacology/Toxicology Team Leader
Sumathi Nambiar, MD, MPH	Director
Jacquelyn Rosenberger, PharmD, RAC	Regulatory Project Manager
Daniel B. Rubin, PhD	Statistical Reviewer
Jalal Sheikh, PhD	Clinical Microbiology Reviewer
Thomas Smith, MD	Clinical Team Leader

SPONSOR ATTENDEES – Utility therapeutics Limited

Tom Hadley	President and CCO
Morten Sommer, PhD	Founder and Board Director
Ian Friedland, MD	Head of Medical
Anne Santerre Henriksen, PhD	Executive Vice President
Nina Kromann	Head of CMC
Lutz Wevelsiep, PhD	Vice President of Regulatory Affairs
Anita Das, PhD	Head of Biostatistics

[redacted] (b) (4)	Consultant PK/PD
Claus Maxel Henriksen	Head of Project Management

1.0 BACKGROUND

On December 31, 2020, UTILITY therapeutics Limited, submitted a request for a Pre-NDA meeting to obtain feedback on the planned NDA submission of pivmecillinam HCl tablets for the treatment of uUTI. The meeting was granted on January 21, 2021, for April 06, 2021, and the briefing package was received on March 19, 2021. The Division sent preliminary comments to the Sponsor on April 02, 2021, these comments are noted below as **"FDA response"**. The Sponsor provided slides in response to the preliminary comments on April 05, 2021 (appended). The discussion that took place during the meeting is captured as ***"Meeting Discussion".***

2.0 DISCUSSION

1. **Does the Agency agree that the studies that were re-analyzed based on patient-level data are adequate to support FDA review of a potential NDA submission for pivmecillinam in the treatment of uUTI?**

   FDA Response:
   It is difficult to fully assess the adequacy of these historical trials until we conduct a full review of study data during the NDA review. As noted in our previous communications, given the age of these trials and the limitations as outlined in your briefing package, we continue to recommend that you conduct a prospective randomized trial in uUTI. Your overall package will be stronger with the results of a current uUTI trial.

   We understand that you have re-analyzed data from the trials using different criteria which better conform to the current FDA guidance for uUTI. Note that it is important to provide analyses for both the reassessment and original results as we will look for consistency of results. Additional analyses should also address the robustness of findings to the methods used to extract data from the original studies. For example, how would study findings be affected by alternative approaches in specifying exclusion criteria or defining study outcomes or analysis sets?

   We also recommend that further analyses be conducted to address the potential effect of study limitations on efficacy and safety findings in order to better establish the robustness of the overall evidence. For example, how could the absence of exact CFU counts post-baseline have affected estimates of overall response in the Vik and Menday studies? Also, how would the assumption that the rescue therapy used by Day 7 affect the assessment of clinical cure in the Vik study?

Meeting Discussion: *No further discussion needed.*

2. **Can the Agency confirm that the proposed efficacy and safety tables and listings from the analysis of clinical studies are complete for FDA review of a potential NDA?**

FDA Response:
Please see response to Question 1. Regarding the safety analysis, the data from these studies have limitations, as noted in your briefing package. Some considerations for submission of safety data include:

- Submit sample datasets for review prior to submitting the NDA.
- Clarify the criteria for prolongation of antibacterial therapy beyond 3-5 days.
- Provide a table with all individual studies including study design (including randomization ratios), sample sizes, patient population (including the proportion of elderly patients), treatment groups, doses and dosing schedule, and study site location (foreign vs. domestic).
- Use the total person-time exposure for each treatment group and calculate the rate of the adverse events per period of exposure (number of patients with adverse event per total person-time exposure), rather than the overall rate of adverse events (number of patients with adverse event per total number of patients).
- Conduct a selective exploration of less frequent adverse events which may be drug-related (e.g., rash).
- Conduct explorations of adverse events (e.g., symptoms of carnitine depletion or acute porphyria) which may be triggered by pivmecillinam.
- Provide percent distribution of patients within treatments by age, gender, race as well as weight (if available).
- Provide explorations for hepatotoxicity, QTc prolongation effect (if any), and *C. difficile* colitis.
- Provide post marketing adverse event data including adverse event data from literature and any pregnancy and human reproduction data.
- As communicated to you in July 2019, we recommend that as a supplementary safety assessment, the major outcomes in safety pools be analyzed with adjustment for randomization ratios as unadjusted combining of studies with different randomization ratios can confound safety assessments.

Meeting Discussion:
The Sponsor acknowledged the limitations of their data. In regard to submission of sample datasets suggested by the Division, the Sponsor asked if these should include safety and efficacy data. The Division replied that the datasets should contain both safety and efficacy data so more informative feedback could be provided. The Division noted that the data cannot be fully assessed until the NDA is under review.

Regarding the criteria for prolongation of antibacterial therapy beyond 3-5 days, the Sponsor inquired if the criteria should be established now and asked for clarification on the criteria being requested. The Division clarified that this was in the context of a clinical trial. The proposed duration in the meeting package is 3-7 days and the Division asked the Sponsor to clarify if the duration is contingent on the resolution of symptoms.

The Sponsor asked about the expectations of explorations of adverse events (AEs). For the rare AEs, a summary of the incidence can be presented with a narrative. The narrative should include onset of the AE, whether the treatment was discontinued, seriousness of the AE, potential causality to the drug, and outcome. The Division stated that they understand that the safety data are limited and some of the studies did not assess rare AEs, such as QTc prolongation. The Division also noted that any postmarketing safety information would be helpful as well. The Sponsor asked if they could refer to the information in approved labeling. The Division replied that foreign labeling could be submitted with English translation as needed as part of the review package. The Division noted that the safety data will be reviewed in totality and that it would be helpful to provide a comprehensive safety package with postmarketing and literature review.

3. **Does the Agency agree that a 200 mg tid dosing regimen for a treatment duration of 3 to 7 days is adequately justified based on the re-analysis of the 4 primary efficacy and safety studies as well as the estimation of PTA in the PK/PD analysis (see also Question 4)?**

FDA Response:
Refer to the response to Question 1. Whether the proposed dose and duration is justified based on the primary efficacy studies will be determined during the review of your application.

Meeting Discussion: *No further discussion needed.*

4. **Does the Agency consider the approach taken by UTILITY to compare the efficacy of pivmecillinam with existing first-line uUTI treatments helpful to support the benefit-risk discussion in a potential NDA?**

FDA Response:
Your general approach to risk-benefit analyses comparing the trials from other treatments for uUTI is reasonable. Some of the risk-benefit analyses may be limited given that some of the studies were conducted several decades ago. You could additionally describe if there are any documented benefits in patients who have failed to respond to previous treatment.

Meeting Discussion: *No further discussion needed.*

5. **Does the Agency agree that the PK/PD analysis and the assessment of PTAs for different dosing regimens are adequate for FDA review of a potential NDA?**

FDA Response:
Your PK-PD investigations appear to be adequate to submit an NDA. Whether the overall PK-PD data and the assessment of PTAs are adequate to support your proposed dosing regimen will be determined at the time of NDA review.

Consider providing any mecillinam PK-PD studies conducted in the murine *Escherichia coli* thigh infection model. You provided such information at the PIND meeting (Presentation Slide 9 in October 2018) to support acute uncomplicated cystitis and urinary PK-PD targets.

Meeting Discussion: *No further discussion needed.*

6. **Does the Agency agree that the available surveillance, as well as microbiological in vitro studies, combined with the UTILITY re-analysis of the clinical studies, provide adequate support for the proposed list of susceptible pathogens?**

FDA Response:
We agree that the in vitro antimicrobial susceptibility data support the activity of mecillinam against the susceptible (b) (4) urinary pathogens.

Meeting Discussion: *No further discussion needed.*

7. **Does the Agency agree with the conclusions that the mutagenicity studies with pivmecillinam confirm absence of a genotoxic potential?**

FDA Response:
We are not able to draw conclusions from studies that we have not had the opportunity to review. Please submit the final reports for these studies as soon as they are available. Regardless of our interpretation, as long as the studies were adequate, you appear to have fulfilled the requirement that this testing be performed prior to NDA submission so that the product can be adequately labeled according to current standards.

Meeting Discussion: *No further discussion needed.*

8. **Does the Agency agree that based on UTILITY's in vitro drug-drug interaction (DDI) assessments no clinical DDI studies are required for FDA review of a potential NDA?**

FDA Response:
To support that no clinical DDI studies are required, submit additional information as follows.

When addressing the risk potential for a drug interaction with MATE1, MATE2K, or OAT3 renal transporter inhibitors (e.g., probenecid, cimetidine), include all available clinical drug-drug interaction studies. Your assessment should discuss pivmecillinam's and mecillinam's expected exposures in the presence of MATE1, MATE2K, or OAT3 inhibitors in relation to pivmecillinam's and mecillinam's safety margin and therapeutic index.

When addressing the risk potential for a gastric pH-dependent drug interaction with acid-reducing agents (ARA), you should assess its physiochemical characteristics. We refer you to the FDA draft guidance for ARAs (https://www.fda.gov/media/144026/download).

Meeting Discussion: *No further discussion needed.*

9. **Does the Agency agree that the available studies with full study reports listed for the proposed nonclinical and clinical pharmacology package are complete for FDA review of a potential NDA?**

FDA Response:
We do not anticipate that additional nonclinical pharmacology/toxicology studies will be needed to support an NDA for pivmecillinam.

The clinical pharmacology data may be enough to submit an NDA. Whether the clinical pharmacology program is adequate to support your proposed dosing regimen in the generally indicated population and any specific subpopulations based on key intrinsic factors (e.g., renal impairment) or extrinsic factors (e.g., food, DDI) will be determined at the time of NDA review.

Meeting Discussion: *No further discussion needed.*

ADDITIONAL COMMENTS

Clinical Pharmacology

Submit the following information in your NDA:

- Population PK Reports
  - All (base, key intermediate, and final) population PK model files, parameter input files, data files, and control streams for the population PK reports and any codes (R, SAS, etc.) for PK/PD analyses;
  - The standard model diagnostic plots, tables with parameter estimates;
  - The output files for population PK models if applicable;
  - Include a USUBJID (unique subject ID) column to all the population PK datasets so that we can relate these datasets to the corresponding clinical efficacy/safety datasets.
- PK-PD Reports
  - All datasets used for the PK-PD analyses in a SAS transport file (*.xpt) format;
  - Clinical: This should include efficacy endpoints, baseline pathogen, MIC, and independent variables data;
  - Pre-Clinical: This should include data from animal infection model experiments (e.g., drug PK, bacterial burden and associated time, inoculum size, etc.) and in vitro surveillance data. Also, provide clinical or laboratory strain identification;
  - The output files for PK-PD models if applicable;
  - Include a USUBJID (unique subject ID) column to all PK-PD datasets so that we can relate these datasets to the corresponding clinical efficacy/safety datasets.
- Bioanalytical Reports
  - Submit tables summarizing the bioanalytical methods and the life-cycle information using the templates available in the 'Bioanalytical Methods Templates' Technical Specifications Document (https://go.usa.gov/xVsdJ) and submit the tables in the Appendix of the Summary of Biopharmaceutics located in eCTD 2.7.1.

Please ensure traceability of source data for any dataset constructed using output files or postprocessed results from population PK analyses (e.g., exposure-response) by providing definition files, reviewer guides, or codes utilized for dataset assembly.

Meeting Discussion:
Regarding the popPK data, the Sponsor stated they have PK data from 18 Phase 1 studies and do not have information on PK and efficacy as PK samples were not collected as part of the Phase 3 studies. The Division explained while this may be a

review issue during the NDA review, they are willing to consider evaluating a population PK model based entirely on the Phase 1 PK studies.

Statistics

1. Clarify if protocols will be available for the studies submitted. This will be important in order to assess the adequacy of how the study was conducted and to determine if the study results are consistent with the original primary analysis results as planned.

2. For the subpopulations of the micro-ITT (micro-ITTS and micro-ITTR) defined in the SAP, note that the treatment arms will no longer be comparable if subjects are excluded based on different susceptibility patterns across the arms. We recommend that these populations be based on either susceptibility to the control or susceptibility to both the test and control. If a noninferiority comparison is considered based on the Menday study, we want to make sure that the baseline pathogens for both arms are susceptible to the control.

3. The definition of microbiological response at TOC states that patients having cultures with more than two organisms at TOC are considered indeterminate. We note that if a patient had a pathogen as baseline (based on genus/species) and they continued to have that pathogen at the TOC visit, it is not clear if such a patient should be indeterminate if they had more than two other organisms as well.

Additional Meeting Discussion:
The Sponsor inquired about the next steps regarding the submission of a 'Program' application and whether the available data will be sufficient to support an NDA. The Division replied that the decision regarding adequacy of the data will be made during review of the NDA. The Division reiterated their concerns with the available data and their recommendation to conduct a new trial in uUTI. The Division also noted that any late submissions to the NDA must be agreed upon prior to the NDA submission and that the Sponsor could request a Type B Pre-NDA meeting. Agreements, on late submissions, if any, can be discussed at the meeting.

Regarding the iPSP, the Division explained that as the Sponsor must have an agreed iPSP in place prior to the NDA submission, it is important for the Sponsor to start that process as soon as possible.

***Post-meeting Note**: See the Guidance for additional information. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pediatric-study-plans-content-and-process-submitting-initial-pediatric-study-plans-and-amended*

3.0 ACTION ITEM

Action Item/Description	Owner	Due Date
Issue Meeting Minutes	FDA	May 06, 2021

4.0 ADDITIONAL APPLICATION INFORMATION (not discussed at the meeting)

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. For further guidance on pediatric product development, please refer to FDA.gov.[2]

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[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

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/s/

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