CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212862Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS
IND 69580

Global Alliance for TB Drug Development
c/o Research Triangle International
Attention: Christopher Shanne
Regulatory Program Leader
3040 Cornwallis Road
P.O. Box 12194
Research Triangle Park, NC 27709

Dear Mr. Shanne:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for pretomanid (PA-824).

We also refer to the meeting between representatives of your firm and the FDA on June 01, 2018. The purpose of the meeting was to ensure the NDA content to be submitted will support a reviewable NDA submission.

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 Fariba Izadi, PharmD, Senior Regulatory Project Manager at (301) 796-0563.

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
Preliminary Comments
Slides
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: June 01, 2018
3:30 PM – 4:30 PM, EST

Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1311
Silver Spring, Maryland 20903

Application Number: IND 69580
Product Name: Pretomanid (PA-824)
Indication: Treatment of Tuberculosis
Sponsor/Applicant Name: Global Alliance for TB Drug Development

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

FDA ATTENDEES
Abimbola Adebowale, PhD Associate Director for Labeling
Lynette Berkeley, PhD, MT (ASCP) Clinical Microbiology Reviewer
Dakshina Chilukuri, PhD Clinical Pharmacology Reviewer
Philip Colangelo, PharmD, PhD Clinical Pharmacology Team Leader
Edward Cox, MD, MPH Office Director, Office of Antimicrobial Products (OAP)
Jane Dean, RN, MSN Senior Regulatory Project Manager
Karen Higgins, Sc.D Statistics Team Leader
Dmitri Iarikov, MD, PhD Deputy Director
Ameet Joshi, PharmD Regulatory Project Manager, Office of Surveillance and Epidemiology (OSE)
Dorota Matecka, PhD CMC Lead
Owen McMaster, PhD Pharmacology/Toxicology Reviewer
Terry Miller, PhD Pharmacology/Toxicology Supervisor
Deborah Myers, RPh, MBA Safety Evaluator, Division of Medication Error Prevention and Analysis (DMEPA)
Sumathi Nambiar, MD, MPH Director
Elizabeth O’Shaughnessy, MD Clinical Reviewer
Shrikant N. Pagay, PhD Product Quality Reviewer
Jacquelyn Rosenberger, PharmD Regulatory Project Manager
Daniel Rubin, PhD Statistics Reviewer

Reference ID: 4283201
BACKGROUND

On March 30, 2018, RTI international submitted a request on behalf of Global Alliance for TB Drug Development (TB Alliance) for a Pre-NDA meeting to ensure the NDA content to be submitted will support a reviewable NDA submission. The Division sent Preliminary Comments (appended) to the Sponsor on May 30, 2018 via email. During the meeting, the Sponsor presented slides that are appended to the meeting minutes.

DISCUSSION

- TB Alliance provided an update regarding issues discussed at the April 30, 2018, meeting between TB Alliance and the Office of Pharmaceutical Quality (OPQ). TB Alliance stated they have been in frequent contact with [redacted] and a data integrity audit is in progress following the detailed protocol that had been previously discussed with the Office of Process and Facilities (OPF). The results of the audit will be submitted as soon as available and the chemistry, manufacturing, and control (CMC) issues will not be a rate limiting step for the NDA submission.
- The Division stated that OPF is still reviewing the data package provided by TB Alliance before the CMC meeting. Comments will be sent to TB Alliance as follow-up to the meeting minutes as soon as the review is completed.
TB Alliance provided clarification for question 1 and noted that approximately 2/3rds of patients in the Nix-TB trial have XDR-TB and the remainder are intolerant or have nonresponsive MDR-TB. They stated that as of the cutoff date of March 26, 2018, more than 90 of the 109 patients in Nix-TB will have 6 months of exposure to pretomanid in combination with bedaquiline and linezolid (BPaL). At the time of the NDA submission, all 109 subjects will have 6 months of exposure to BPaL.

TB Alliance stated that the Nix-TB clinical study report (CSR) containing data on the first 45 patients will be submitted shortly. The Division clarified that this CSR does not have to be submitted prior to the NDA. TB Alliance noted that the integrated summary of safety (ISS) that will be submitted as part of the initial NDA will contain data on more than 90 patients with 6 months of exposure to pretomanid. The CSR addendum that will be submitted as a standalone report in the initial NDA submission will include data on all 109 patients with 6 months of exposure to pretomanid. TB Alliance will confirm if a corresponding dataset to the CSR addendum will be submitted in the initial NDA submission. All the data will be integrated into the ISS in the 120-day safety update.

TB Alliance described animal studies that provide data to support the contribution of each of the 3 individual drugs, B, Pa, and L to the regimen. The studies evaluated contributions for the bactericidal activity and sterilizing activity. All three drug products are needed to attain bactericidal activity. The Division recommended that all the data supporting the contribution of the components be included in section 2 of the eCTD submission and linked to other sections. TB Alliance acknowledged the recommendation.

With regards to question 2, TB Alliance stated that they will provide a summary of the published data for historical controls in July 2018. They have also obtained access to patient level historical control data that will be further analyzed for comparison to the population enrolled in the Nix-TB trial. The Division stated that they are willing to review TB Alliance’s analyses of the data and provide feedback prior to the NDA submission.

TB Alliance noted that with regards to the Division’s response to question 7, the plan is to include case narratives, although the ability to provide adverse event data in studies not sponsored by TB Alliance is limited. TB Alliance explained that not all case narratives have investigator’s differential diagnosis and work-up for causality. The Division acknowledged that case narratives may vary in the level of detail included.

TB Alliance stated that with regards to question 12, there are plans to determine the in vitro half maximal inhibitory concentration (IC50) and inhibitory constant (Ki) of OAT3 (organic anion transporter) along with precautions for increased systemic exposure to drug substrates of OAT3. TB Alliance noted they have not seen any effects from increased exposure to pretomanid.

The Division stated that the in vitro IC50 and Ki estimates will determine if additional in vivo drug-drug interaction (DDI) studies may be needed. The Division noted that there is the option to either conduct a DDI study or to contraindicate the concomitant use of pretomanid and drug substrates of OAT3; the IC50 and Ki information will not be useful for labeling.

TB Alliance inquired as to whether an agreement could be made to submit DDI data post NDA submission. The Division replied that sometimes agreements could be made to receive DDI data after the NDA submission, however, those drugs would be
The Division recommended using pravastatin for in vivo DDI study and to avoid methotrexate. TB Alliance stated they will submit the IC$_{50}$ and $K_i$ data to the Division prior to the NDA submission and agree with contraindicating the drugs until the completion of DDI studies.

- The Division asked if pretomanid will be administered with food. TB Alliance replied that the food effect for pretomanid is not major; however, given that bedaquiline is administered with food, the combined regimen will also be administered with food. The Division advised TB Alliance to complete exposure-response studies with efficacy and safety outcomes to better interpret the increase in systemic exposure of pretomanid when given with food.

- The Division inquired about the plans for the semen analysis study. TB Alliance replied that they are drafting a protocol and the study will be started this year in the USA; however, the study results will be available after the NDA submission.

- The Division asked if TB Alliance intends to submit the NDA as a rolling submission. TB Alliance responded they may submit portions of the application before the December 2018 target date and will provide the Division with a more specific timeline July 2018. TB Alliance stated that the last portion of the NDA will most likely be the CMC section.

- The Division asked if a patient who dies before 6 months of BPaL exposure be considered a treatment failure. TB Alliance replied that such patient will be considered a failure.

**DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION**

- The content of a complete application was discussed.

- 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.

In addition, we note that a chemistry pre-submission meeting was held on April 30, 2018. We refer you to the minutes of that meeting for any additional agreements that may have been reached.

**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** and **Pregnancy and Lactation Labeling Final Rule** 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 (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

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

**SUBMISSION FORMAT REQUIREMENTS**

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

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

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

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

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

<table>
<thead>
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<th>Site Name</th>
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<th>Drug Master File Number (if applicable)</th>
<th>Manufacturing Step(s) or Type of Testing [Establishment function]</th>
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Corresponding names and titles of onsite contact:

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<th>Site Name</th>
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OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent.
with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bio research Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bio research Monitoring Technical Conformance Guide Containing Technical Specifications:


Preliminary Questions & FDA Responses

Clinical

Question 1

Does the Agency agree:

a. the requirements of the Agency’s Draft Guidance for Industry regarding Pulmonary Tuberculosis (2013) have been adhered to, and the total exposure of pretomanid, including exposure to pretomanid in combination with bedaquiline and linezolid (BPaL), adequately characterizes the safety and efficacy profiles of pretomanid in combination with bedaquiline and linezolid in XDR-TB and TI/NR MDR-TB subjects?

b. the pretomanid clinical development program supports the proposed dosing regimen and indication to permit filing and review of the NDA?

FDA Response: The proposed clinical development program for pretomanid may support the filing and review of the NDA. The safety database appears adequate. We note that in the completed and ongoing Phase 2 and 3 studies, 656 patients with DS-TB and 99 subjects with MDRTB (other than in Nix-TB) were exposed to pretomanid with other anti-TB drugs as of March 26, 2018. In Nix-TB, 90 of 109 patients with intolerant/nonresponsive MDRTB will have 6 months of exposure to BPaL at the time of filing. Please provide the number of patients and the duration of exposure to pretomanid for DS-TB and MDRTB patients over various timeframes for example, 1, 3, 6 months, and > 6 months expected at the time of NDA submission in a tabular format.

We note that the cut-off date of the CSR addendum for Nix-TB will be as close as possible to the filing date. Please clarify if the CSR addendum will be included in the initial NDA submission or if you intend to submit it after the filing date.

As discussed previously, it will be important that the NDA clearly outlines the added contribution of the three components to the full regimen. Though the evidence of activity of each of the three agents alone is supportive, we are most interested in the contribution of the components as part of the combination. This can be best seen by the following comparisons:

- Contribution of Pa shown by comparing PaBL with BL
- Contribution of B shown by comparing PaBL with PaL
- Contribution of L shown by comparing PaBL with PaB

We understand that there are no clinical trials including EBA trials that assess any of the above comparisons. However, information from in vitro and animal studies can be of use. Supportive information can come from cross-study comparisons, for example, comparing subjects from Nix-TB with the MDR-TB subjects from NC-005 might be informative in assessing the contribution of L. Additional supportive information can come from assessing lower order comparisons, for...
example in NC-001, comparison of BPa vs. B can allow for the assessment of what Pa contributes when given with B.

**Question 2**

**Does the Agency agree with the proposed approach to the identification of historical control data?**

**FDA Response:** The proposed approach to the identification of historical control data is in principle acceptable, but the comparability of historical patients and Nix-TB patients will be assessed during review of the NDA. We request that you provide a summary of your review of the published outcome data in XDR-TB subjects prior to submission of the NDA. This will allow us to provide feedback on your approach and help facilitate our review of the NDA.

**Question 3**

**Does the Agency agree with the proposed structure of Module 2.7.3 and the assessment that an ISE is not warranted?**

**FDA Response:** This plan is acceptable.

**Question 4**

**Does the Agency agree that the clinical summary of safety can be submitted in 2.7.4, and a separate ISS is not required?**

**FDA Response:** This plan is acceptable.

**Question 5**

**Does the Agency agree with the plan for integrating and pooling the clinical safety data in support of the pretomanid NDA?**

**FDA Response:** The pooled safety analyses groups described in Table 4 are acceptable. We request that the NDA include an analysis of hepatic safety across the clinical development program for pretomanid that summarizes the entire hepatic safety database, the portfolio of clinical trials, dosing of pretomanid, other anti-TB drugs used in combination, duration of treatment, monitoring protocols, methods of DILI detection, and management of patients. A case summary and analysis of each case of clinically significant liver injury should be included. We also request a comprehensive report of hepatic safety for the Nix-TB study in the addendum to the CSR. Please see the attached instructions on how to submit eDISH for graphic analysis of both the clinical trial populations as well as individual hepatic cases of interest. The information should be patient-specific, and should be included in the narratives. For patient-level narrative content and formatting (all cases of interest with ALT > 5X ULN or elevations of ALT> 3X ULN and bilirubin >2X ULN) please refer to Tabs “Narrative SAS Data” and “Narrative PDF file” in the eDISH Data Specifications.

As agreed to previously, safety data for the long-term use of linezolid from published literature should be included in the NDA.

**Question 6**
Does the Agency agree:

a. with the current strategy of a safety data cut-off date of 26 Mar 2018 for the analyses of the Nix-TB and ZeNix studies in addition to all completed studies to support NDA filing, assuming a submission date in Q4 2018?

b. that the Nix-TB CSR addendum, containing a later data cut-off for safety and efficacy, can be submitted and reviewed as a stand-alone document in the NDA?

c. with the planned 120-day safety update to the safety database with data from Nix-TB and ZeNix, and submission of individual study information from SimpliciTB and the ongoing non-TB Alliance sponsored studies?

d. with the planned 120-day efficacy update to include data from Nix-TB, and that no 120-day efficacy update is required for ZeNix and SimpliciTB?

**FDA Response:** The proposed plan is acceptable.

**Question 7**

Does the Agency agree with the proposed plan for submission of narratives of all SAEs, AEs leading to discontinuations, and pregnancies in support of the pretomanid NDA from completed studies of pretomanid and Nix-TB, and CIOMS for SAEs and pregnancies for ZeNix and non-TB Alliance sponsored studies?

**FDA Response:** The proposed plan is acceptable. Please also include narratives and case report forms for patients who experience adverse events of special interest such as patients who fulfill criteria for Hy’s Law. Please ensure that case narratives provide the investigator’s differential diagnosis and work-up to assess causality.

**Question 8**

Does the Agency agree with the proposed electronic data submission plan regarding database format (Legacy/SDTM/ADaM) for the individual study databases that will be included in the NDA?

**FDA Response:** From a technical standpoint the proposed electronic data submission plan is acceptable. A Waiver Request is necessary if data are submitted in SDTM-IG 3.1.1 format. For more information please refer to [Guidelines for requesting waiver to current supported clinical study data standard versions](#).

**Question 9**

Does the Agency agree with the proposed electronic data submission plan regarding database format for the integrated safety database that will be included in the NDA?

**FDA Response:** Your plan is acceptable. In the ISS datasets (ADAE etc.), please make a variable corresponding to each of the four pooled groups described in Table 4. Each subject in the ISS should have a value “yes or no” for each of these variables to signify if they belong to the pooled group (Y) or do not (N). All four variables should be added to all ISS datasets.
Please ensure that your ISS analysis data reviewer’s guide includes a summary of the pooled studies, for example you could use table 4 with information on the pooled analysis variable name included in an additional column.

Please provide a treatment emergent flag variable in the ISS adverse event dataset where each Adverse Event has a value of ‘Y’ if it was treatment emergent, or a value of ‘N’ if it was not.

**Question 10**

Does the Agency agree with the proposed MedDRA standardized coding plan?

**FDA Response:** The proposed plan is acceptable.

**Question 11**

Does the Agency agree with the proposed programming code submission strategy for the key phase 3 studies and the ISS/2.7.4?

**FDA Response:** The proposal is acceptable.

**Clinical Pharmacology**

**Question 12**

Does the Agency agree that no additional DDI studies are required for filing the NDA for marketing authorization?

**FDA Response:** We note that your in vitro studies showed that pretomanid is an inhibitor of the renal transporter, OAT3, and thus, the potential for an interaction between pretomanid and OAT3 substrates exists. Please clarify how you plan to mitigate this interaction between pretomanid and substrates of OAT3.

**Microbiology**

**Question 13**

Does the Agency agree that the program of pretomanid preclinical and clinical microbiology studies conducted is sufficient to support review of the NDA for marketing authorization?

**FDA Response:** Yes, we agree.

**Question 14**

Does the Agency agree with the approach to provide MIC data obtained primarily using the REMA and MGIT methods to support a provisional breakpoint for pretomanid?

**FDA Response:** Results from both the REMA and the MGIT tests are acceptable for providing provisional breakpoints for pretomanid.
Nonclinical

Question 15
Does the Agency agree that the nonclinical program conducted is sufficient to support review of the NDA for marketing authorization?

FDA Response: The nonclinical program conducted is sufficient to support review of the NDA.

Regulatory

Question 16
Does the Agency agree with the proposed indication statement and dosing and administration statement for pretomanid, bedaquiline, and linezolid, for the pretomanid label?

FDA Response: It is premature to comment on the descriptions of the indication and dosing and administration sections in the label. We may recommend revisions to these sections of the label based on our review of the data.

Question 17
Does the Agency agree that the pretomanid program meets the criteria for a priority review of the NDA planned to be submitted Q4 2018?

FDA Response: A priority review would be granted for the indication that has a QIDP designation.

Question 18
Does the Agency agree to consider a future request for rolling submission and rolling review for the NDA?

FDA Response: It is acceptable to submit some sections of the NDA once it is available and complete under a rolling review submission. However, the review clock would not start until the final portion of the application is submitted. Agreements need to be made on the timing of the subsequent portions of the application. Please provide a timeline for the sections of the NDA to be submitted in the rolling submission. For additional information regarding the agreement on the proposal, portions of an application eligible for early submission, commencement of review and calculation of review time please refer to the FDA Guidance for Industry, Expedited Programs for Serious Conditions below.

Additional Comments
1. If you intend to have a proprietary name for this product, we recommend you submit a request for a proposed proprietary name review as soon as possible. If you require information on submitting a request for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:
   • Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
Clinical Pharmacology

2. Please plan to include exposure-response analyses for both efficacy and safety endpoints of pretomanid in your NDA.

3. We would like to remind you that if your clinical trial tablet formulation and the to-be-marketed tablet formulation of pretomanid are different, then a relative BA study is required to bridge the two formulations.

Clinical

4. General Study Information:
   a. Please submit a rationale for assuming the applicability of foreign data in the submission to the U.S. population in your NDA application.
   b. Please provide a statement of Good Clinical Practice for each Phase 2 and Phase 3 study used to support the NDA application. If this information is in the Clinical Study Report, please provide the section and page number with a hyperlink to the Clinical Study Report.
   c. Please provide the summary of the information regarding Financial Certifications and Disclosures in a tabular format if possible. A sample table is provided to be modified as you wish.

<table>
<thead>
<tr>
<th>Study No. (include eCTD link for CSR)</th>
<th>Study Title</th>
<th>Sponsor</th>
<th>Name of Principal Investigator Name of Sub-Investigators (Include eCTD link to relevant forms and disclosures for each study/investigator)</th>
<th>Financial Disclosure Obtained? (Indicate Yes/No)</th>
</tr>
</thead>
</table>

Prescribing Information

5. 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 PLLR Requirements for Prescribing Information and Pregnancy and Lactation Labeling Final Rule 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 (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.
To facilitate the review process and provide additional ease for our review, please include the following in the NDA:

### Tables and Datasets

- A table of normal ranges for laboratory tests in the clinical study report for each trial. Flag out of range laboratory values in the laboratory datasets.

- An electronic submission of a site level dataset to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the NDA review process. Please refer to the draft “Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link [http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf](http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf)) for the structure and format of this dataset.

- Separate tables for patients with discontinuations of drug, discontinuations from the study, and withdrawal from the study for any reason, along with study ID, patient ID, demographics, study arm, study day of discontinuation of drug or from study, or withdrawal, reason for this disposition, and AE (if present).

- An interactive table or dataset that contains all subjects that were unblinded. The table or dataset should include the unique subject ID, the treatment received, who was requesting unblinding, date of unblinding, and the reason for unblinding.

- An interactive table detailing all the tables and figures featured in the main clinical efficacy and safety sections of the NDA. The table should contain the following:
  
  a. Title of the table or figure in the NDA
  
  b. A page number hyperlinked to the location of the table or figure
  
  c. A name hyperlink to the SAS code (and/or macros) used to create the table or figure
  
  d. Names of the datasets used to create the table or figure (hyperlinks are useful but not necessary).
  
  e. For derived (analysis) datasets used to conduct your analyses, you should indicate the tabulation datasets from which the information was derived.

- An interactive table that contains a list of all subjects for whom you submitted a CRF, narrative, or adjudication package(s).

- An algorithm which clearly explains how findings from all primary and secondary analyses were produced (e.g. dataset, variable names and programming steps used). This will minimize potential discrepancies between Reviewer and Sponsor analyses.
Meeting Minutes and Other Documents

- All DSMB meeting minutes and recommendations throughout the trial. A tabulated summary of changes for each protocol version along with the date of implementation, and the number of subjects enrolled at the time.

- A tabulated summary of meetings with FDA during the development program of pretomanid along with the meeting minutes of each; ensure that these are bookmarked.

- All meeting minutes of all groups with any responsibility for the management of the trial, e.g., Executive Committee, Clinical Endpoint Committee, Steering Committee and DSMB. Please include agendas and all data/slides presented to the Committee. Please indicate if the meeting was opened or closed. For those meetings that were cancelled or meetings where no minutes were taken, please include a place holder for that meeting noting such and signed by a member of the clinical team. Please also ensure that these packages come with a table of contents and are bookmarked by date.

- All newsletters and all other communications to investigational sites and national coordinators from the group(s) responsible for the conduct of your trial. Please bookmark the newsletters by date.
About eDISH Data Requirements

The FDA's scientists created a software solution for the detection of drug-induced liver injury (DILI), which has been well received by the liver community in the U.S. The developers of eDISH designed unique requirements for the data input for eDISH to use. Over time, the eDISH-DATA Requirements prove to be adaptive to new challenges in science, flexible for continued development of the tool, and straightforward for data preparation. The data manager must ensure the data to be submitted to the FDA are constructed to exactly follow the specifications.

Modified: 10/06/2016
## Liver Data Requirement

<table>
<thead>
<tr>
<th>Requirement</th>
<th>Standard variable</th>
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<th>Variable type</th>
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**Note:** ALT, BILI, AST, and ALP should include data collected from both central labs and local labs. In addition, the data should include records from the screening period.

Total Daily Dose must include (1) the first day dose, (2) the last of dose, (3) doses at Date of Exam. Enter value zero for suspended dose.
### Demography Data Requirement

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### On-Demand Viral Load Data Requirement

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<tr>
<td>Required</td>
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<tr>
<td>Required</td>
<td>VLSTRESN</td>
<td>Viral load Numeric Result in log10 IU/mL</td>
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Note: The viral load data are only needed for drugs used to treat chronic viral hepatitis C or B
**Narrative SAS Data Requirement**

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</thead>
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<td>2. USUBJID (Required): Unique subject identifier within the submission (Char)</td>
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<tr>
<td>3. NARRAT1* (Required): Clinical Narrative, first part (Char, length&lt;=200)</td>
</tr>
<tr>
<td>4. NARRAT2* (Required): Clinical Narrative, continued (Char, length&lt;=200)</td>
</tr>
<tr>
<td>5. NARRAT3* (Required): Clinical Narrative, continued (Char, length&lt;=200)</td>
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<tr>
<td>...</td>
</tr>
<tr>
<td>n. NARRAT_n* (Required): Clinical Narrative, last part (Char, length&lt;=200)</td>
</tr>
</tbody>
</table>

*: Requirements for Variable NARRATI* - To the medical writer:

The eDISH program is intended primarily as a medical diagnostic tool, which requires additional supplementary information beyond what may have been specified in the study protocol. We realize that it is simply not possible at the time of writing protocols to anticipate every possible adverse effect that might occur, every medical problem that may occur. So when something unexpected does happen and the responsible physician-investigator gathers extra information, asks more questions, does unscheduled studies, or makes more observation in follow-up, they should be reported and included in the narrative. Ideally, the narrative should be written by the investigator at the site, but if not they should at least be consulted. Study investigators must be physicians, for good reason: they are responsible for the safety of the research subjects, and for taking correct and appropriate action to deal with problems. Correct treatment depends on correct diagnosis, and physicians uniquely are trained in the art and skill of making medical differential diagnosis. If they hear hoofbeats, it is unlikely that they were caused by zebras, but they have to look to see if they aren’t horses. What they look for, and find, and conclude, must be entered into the narratives if they are to be useful.

Please be aware that we wish to use eDISH to assess the likelihood that your new compound causes liver toxicity and identifying potential "Hys Law" cases of elevated ALT or AST > 3xULN and TBL > 2xULN (or more in Gilbert syndrome) is just the first step. The next two steps are: 1) looking at all the liver test data for patients of interest over the time of observation, to appreciate the time-related elevations and which of the tests rises first, and then 2) evaluating the narrative data gathered to adjudicate the probable cause of the abnormal findings. This may require
additional questions, tests, examinations to search for the cause, and only after ruling out other
causes can a presumptive diagnosis of probable drug-related liver injury (DILI) be made. Liver
biopsy is not definitive, and there is no single test or finding that proves DILI. For the adjudication
to be successful, your investigators must search actively for the cause of all cases of elevated
ALT or AST > 3xULN and TBL > 2xULN. Finding a probable, very likely, or definite cause of the
liver injury other than the drug is very important. The eDISH system, as used by medical
reviewers at CDER, includes the capability to create time-course graphs for each subject, and to
read the narrative summaries, helping them in drawing their own conclusions as to whether the
drug may have caused the abnormal findings. We will want to review the data independently.
Estimation of the likelihood that the liver injury was caused by the drug being studied is frequently
difficult and requires information to rule out or rule in other possible causes.

Therefore, we recommend that the narratives should be written by physicians or other medical
personnel skilled in medical differential diagnosis. Pertinent negative findings should be included
in any narrative. The data that needs to be gathered by the investigator are those that can
establish or rule out other causes, such as acute viral hepatitis A or B (less often C or E), biliary
disease such as stones or tumors, cardiac failure or shock, acute alcoholic or autoimmune
hepatitis.

It is not necessary to include all subjects in this patient narrative data set.
However, make sure to include narratives for subjects with ALT or AST > 3xULN and TBL > 2xULN.
The narratives should include information described in the following points:

1. Indication
2. Subject’s medical history and concomitant medications
3. Dates and laboratory values of diagnostic tests done to evaluate liver disease including X-ray,
ultrasound, or liver biopsy
4. Time course of any signs or symptoms of liver disease, including jaundice
5. Differential diagnosis and final diagnosis of liver disease
6. The study site investigator and the sponsor’s assessment of relationship of study drug to
abnormal hepatobiliary lab results or adverse events
7. Clinical course of liver-related adverse events including treatment and outcome
8. Complete information about the resolution, or progression, of increased ALT or
total bilirubin in each of these study subjects, including time to complete resolution of
all hepatobiliary lab results, or most current available patient status for any cases in which
the events had not resolved at the time of report preparation.

9. It is also helpful to include in the narrative:
- Dose and duration of study therapy in weeks
- Laboratory values for ALT, AST, ALP, TBL and corresponding dates of measurements

The text-string lengths of the narratives commonly exceed the allowable maximal length of 200 characters.
The sponsor is recommended to create multiple character variables, NARRAT1, NARRAT2, ..., NARRAT_n to hold
the narratives. The number of narrative-holding variables is determined by the longest narrative among all
the subjects in the narrative data set.
## Requirements for Supplemental Narrative Data as PDF Files

### PDF Format for Supplemental Narratives

When the sponsor submits the clinical narratives in a SAS data set, it should be allowed to supplement narratives in PDF files. Such flexibility should add more power to eDISH in determining potential DILI.

The supplemental narratives can be submitted in the following fashion:

1. Each supplemental PDF file only represents one subject of interest. The name of the PDF file is the unique subject ID: USUBJID that is used in the data submission to the FDA.
2. No two subjects should share the same PDF file.

The supplemental narratives may include any forms of text, bullet points, tables, graphs, or other eye-catching tools that PDF format permits. However, they should be kept simple, clear, and informative.

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<thead>
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<th>Requirement</th>
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<tbody>
<tr>
<td>Each supplemental PDF file only represents one subject of interest.</td>
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<tr>
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**Note for Data Manager**

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Format of Standard Narrative Data

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<td>NARRATn* (Required): Clinical Narrative, last part (Char, length&lt;=200)</td>
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</tbody>
</table>

*Requirements for Variables NARRAT1-NARRATn - To the medical writer:

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9. It is also helpful to include in the narrative:
   - Dose and duration of study therapy in weeks
   - Laboratory values for ALT, AST, ALP, TBL and corresponding dates of measurements

Reference ID: 4283201

15 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUMATHI NAMBIAR
06/26/2018
Dear Dr. Daily:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Pretomanid (PA-824).

We also refer to the meeting between representatives of your firm and the FDA on May 25, 2016. The purpose of the meeting was to discuss the current status of the ongoing NiX-TB trial, [A Phase 3 Open-label Trial Assessing the Safety and Efficacy of Bedaquiline plus PA-824 Plus Linezolid in Subjects with Pulmonary Infection with either Extensively Drug-resistant Tuberculosis (XDR-TB) or Treatment Intolerant, Non-responsive, Multi-drug Resistant Tuberculosis (MDR-TB)]

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 Fariba Izadi, Pharm.D, Regulatory Health Project Manager at (301) 796-0563.

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
Slides
MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: End of Phase 2
Meeting Date and Time: May 25, 2016
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1313
Silver Spring, Maryland 20903

Application Number: IND 69580
Product Name: Pretomanid (PA-824)
Indication: Treatment of tuberculosis
Sponsor/Applicant Name: Global Alliance for TB Drug Development
Meeting Chair: Sumathi Nambiar, M.D., M.P.H
Meeting Recorder: Fariba Izadi, Pharm.D.

FDA ATTENDEES
Lynette Berkeley, PhD Clinical Microbiology reviewer
Elsbeth Chikhale, PhD Biopharmaceutics Team Leader
Dakshina Chilukuri, PhD Clinical Pharmacology Reviewer
Philip Colangelo, PharmD, PhD Clinical Pharmacology Team Leader (By Phone)
John Farley, MD, MPH Deputy Director, Office of Antimicrobial Products
Felicia Griffin, PhD Statistics Reviewer
Karen Higgins, Sc.D Statistics Team Leader
Fariba Izadi, Pharm D Regulatory Health Project Manager
Owen McMaster, PhD Pharmacology/Toxicology Reviewer
Dorota Matecka, PhD Product Quality Lead/CMC
Sumathi Nambiar, MD, MPH Director
Elizabeth O’Shaughnessy, MD Clinical Reviewer
Wendelyn Schmidt, PhD Pharmacology/Toxicology Team Leader
Mary Singer, MD, PhD Acting Deputy Director
Kalavati Survarna, PhD Acting Clinical Microbiology Team Leader
Maureen Dillon Parker Chief Project Management Staff
Joseph Toerner, MD, MPH Deputy Director for Safety
Yuliya Yasinskaya, MD Acting Clinical Team Leader

SPONSOR ATTENDEES
Global Alliance for TB Drug Development
Erica Egizi, MS Global Trial Manager
BACKGROUND
On April 01, 2016, RTI, on behalf of Global Alliance for TB Drug Development (TB Alliance), submitted an End of Phase 2 meeting request. The briefing package was submitted on April 28, 2016 and contained the questions noted below in **bold type**. The Division provided preliminary comments to the questions via email on May 23, 2016. These are identified as **FDA Response**. Global Alliance for TB Drug Development submitted their responses to FDA’s preliminary comments on May 24, 2016 and presented them in a slide presentation during the meeting (Attached). Meeting discussion points are captured under “Meeting Discussion.”

**Nonclinical**
1. Is the nonclinical package sufficient to support the Phase 3 study and potentially the registration of pretomanid in XDR-TB?

**FDA Response:** The microbiology and pharmacology/toxicology data are sufficient to support the Phase 3 study. Please provide a Gantt chart with your completed and planned pharmacology/toxicology studies in relation to you proposed NDA submission. We do not anticipate requesting any additional pharmacology or toxicology studies beyond those that you have planned. However, please be aware that the results of your planned studies could indicate the need for additional, follow-up studies prior to registration. The adequacy of the microbiology data for registration is a review issue.

**TB Alliance Response:** Segment III reproductive toxicity study in rats will be initiated in 2016 (final draft protocol is ready for FDA review), and carcinogenicity studies in mice and rats will be initiated 1 year before NDA filing (as agreed at STAND EOP2 meeting).

**Meeting Discussion:**
In response to TB Alliance’s request for clarification regarding the adequacy of the microbiology data, the Division stated that the results of all ongoing microbiologic studies should be submitted formally prior to submission of the NDA.

2. Based on the specific toxicities for the individual components of the proposed regimen (pretomanid, bedaquiline and linezolid) and the available clinical pharmacology data, we find no evidence to suggest that unacceptable additive or synergistic toxic effects should be expected. Thus, no additional combination toxicology or nonclinical safety pharmacology testing is planned. Does the Agency agree with this approach?
FDA Response: Yes, we agree.

Meeting Discussion: No further discussion.

Clinical

3. Does the Agency agree with the design of the protocol as a single pivotal trial to support the new drug application of pretomanid for the indication, in combination with bedaquiline and linezolid, for the treatment of pulmonary tuberculosis caused by XDR-TB, or treatment intolerant/non-responsive multi-drug resistant (MDR) pulmonary tuberculosis (TB) in adults?

FDA Response: In order for us to consider your proposed trial in support of the indication of XDR, and MDR TB intolerant to available therapy, you should provide:

a) Evidence of the added contribution of each component to the selected three-drug regimen. Please summarize the available data from animal and early phase human studies, organized by each component, to support the added contribution. Submit this summary data with the clinical protocol.

b) A justification for the use of a historical control, including comparability of the patient populations, endpoints, and effect size of the standard of care regimen. See additional points regarding sample size and control for the type I error in the response to your question #8

c) Discussion regarding blinded treatment assignments in your trial. If it is not possible to fully blind the study, the study should be treated as if it were a blinded study in all ways other than the physician and patient having knowledge of the treatment assignment, for example, microbiologists and central ECG readers could be blinded to the study arm to which the subject was randomized.

Meeting Discussion:
See attached Slides 7-10.

TB Alliance presented slides with data from a mouse study to describe the added contribution of each component to the selected three-drug regimen, i.e. pretomanid, bedaquiline and linezolid (JPaL). TB Alliance plans to summarize the available data from animal and early phase human studies, organized by each drug component. TB Alliance
noted that they also have EBA data in humans for 2 weeks for each of the three drugs in the regimen.

TB Alliance stated that the JPaL regimen in XDR-TB, due to the different risk-benefit balance and greater need, justifies moving forward to phase 3 without demonstrating the contribution of each drug in EBA studies alone or in combination and without phase 2 proof-of-concept clinical trials.

The Division stated that they will make a determination if the data are acceptable once it has been submitted for review.

TB Alliance stated their intent to submit an NDA for pretonamid using the JPaL regimen for the treatment of XDR-TB and MDR-TB. Results from NiX-TB and NC-007 trials in XDR-TB and MDR-TB will be available. TB Alliance also noted that some safety data for pretonamid from the STAND trial would be available for submission in the NDA for XDR-TB and MDR-TB.

TB Alliance agreed with the Division’s comment on question 3 (FDA response c), concerning the blinded treatment assignments in the trial.

4. Is the proposed size of the safety database adequate?

**FDA Response:** The proposed size of the safety database in the NiX-TB trial (n=200) combined with Study NC-007 (n=100) appears adequate to support treatment with pretomanid in combination with bedaquiline and linezolid for the indication in XDR-TB subjects unless unexpected safety signals arise during the NiX-TB and NC-007 trials. In our assessment of safety, we will evaluate all available safety data, including drug-sensitive TB trials, to assess the overall safety of pretomanid.

**TB Alliance Response:** The NiX-TB trial will stop enrolling (n=50?) when NC-007 begins enrolling, so the safety database of JPaL will be smaller, around 150 subjects. The safety database of Pa is much larger.

**Meeting Discussion:**

The Division commented that if the regimen with the highest dose of linezolid is chosen for development, the safety of linezolid at this dose for long term use would have been evaluated in a relatively small number of patients, i.e., 50 subjects from the NiX-TB trial plus 25 subjects from Study NC-007. The Division recommended that TB Alliance provide additional safety data for the long term use of linezolid from the published literature.

5. Does the Agency agree that an analysis of the endpoints at 6 months after the completion of therapy is adequate for the regulatory file, with the plan that all subjects will be followed for 24 months after the completion of therapy for a confirmatory analysis?
FDA Response: Yes, we agree.

Meeting Discussion: No further discussion.

6. Does the Agency agree with the proposed arms of the study to identify the best dose and duration for linezolid therapy in the regimen to optimize the best benefit/risk profile for this regimen in the target population?

FDA Response: The proposed doses and durations of linezolid are acceptable provided that patients are closely monitored for adverse effects. There is limited safety data for prolonged treatment with linezolid; therefore the study sites must have the necessary clinical and laboratory expertise to monitor patients and manage adverse effects of linezolid and the other study drugs.

Meeting Discussion: No further discussion.

7. Does the Agency agree with the plan

FDA Response: The dose regimen of bedaquiline in the ongoing NiX-TB trial is the approved regimen of 400 mg once daily (QD) for 2 weeks followed by 200 mg three times a week (TIW) for 22 weeks.

TB Alliance Response: 

Meeting Discussion: 
TB Alliance stated
**Statistical**

8. Does the Agency agree with the sample size chosen for the study to demonstrate that efficacy, as defined for the primary endpoint, is better than a point estimate of 50%, which is at the upper end of general historical experience?

**FDA Response:** We are unable to agree with the sample size at this point. It is important that you include in your protocol a clear discussion as to why a controlled trial cannot be conducted, why an externally controlled trial is interpretable for this trial, and a more formal data-driven justification for the chosen target of 50% based on upper end of the historical control for treatment of XDR-TB. This justification should compare the patient populations from the historical data to that proposed to be enrolled in the trial and should clearly discuss the comparability of the endpoints used.

Additionally, you will need to include plans to control the type I error due to the four test arms in the trial. Please comment on whether you have considered simplifying the study to evaluate two rather than the four treatment regimens in the current design of Study NC-007.

**TB Alliance Response:**

Registration phase 3 study proposal
- 6 months treatment, 25 subjects per arm
- Definitive outcome study
- Study arms:
  - JPaL(1200mg)
  - JPaL(1200mg x 2 mos)
  - JPaL(600mg)
  - JPaL(600mg x 2 mos)

**Status of Participants in NiX-TB Trial as of 19 May 2016**

- 38 Enrolled and assigned to treatment
  - 47% are HIV infected
  - 30 with XDR-TB
  - 7 with MDR treatment non-responsive
  - 1 with MDR treatment intolerant

- 24 Completed 6 Months of Treatment (None required longer), and are in Follow-up – No relapses to date
  - 5 in 6-7 months follow-up
  - 9 in 4-5 months follow-up
  - 10 in 0-2 months follow-up
  - 10 Ongoing Treatment

Reference ID: 3950329
Meeting Discussion:
TB Alliance considers the JPaL regimen a breakthrough because of its potential to significantly improve management of drug resistant TB. TB Alliance stated that patients with XDR-TB and MDR-TB are usually treated with up to 8 anti-mycobacterial drugs (oral and injection) and many of these drugs are toxic. TB Alliance’s goal is to reduce the number of drugs in the regimen and to shorten the treatment course from what is presently used.

The Division asked if any subjects discontinued therapy due to linezolid toxicity in the NiX-TB study. TB Alliance responded that none of the subjects had to discontinue linezolid but the dose had to be reduced in some. In response to the Division’s question regarding the signs and symptoms of optic neuropathy, TB Alliance stated that there were no reports of optic neuropathy. Peripheral neuropathy was reported; but the symptoms resolved after the patients discontinued linezolid for 1-3 weeks. TB Alliance explained that the treatment duration was not extended to make up for any missed linezolid doses while symptoms of peripheral neuropathy resolved. TB Alliance confirmed that neurological exams were required during the trials.

The Division asked whether TB Alliance has considered simplifying the study to evaluate two rather than the four treatment regimens, as currently proposed, in Study NC-007. TB Alliance responded that this could be done; however, they thought it was critical to answer all the questions regarding dosing regimens and duration of treatment earlier rather than later.

TB Alliance will submit a justification for the chosen target of 50% based on upper end of the historical control for treatment of XDR-TB. TB Alliance stated that having a control group is not feasible because it would be difficult to compare the 24-month control group regimen with the proposed 6-month study regimen. TB Alliance stated it is unethical to use placebo control in this patient population. Also, patients might choose not to enroll in the study if they were to be randomized to longer, more toxic, and potentially less efficacious treatment. It is also likely that availability of bedaquiline and linezolid around the world might undermine use of current standard of care and enrollment in the study altogether.

The Division stated that because historically controlled trials are the weakest type of controlled trial, it is important to consider whether a concurrently controlled trial might be feasible. The Division noted that if a longer treatment regimen was compared to the shorter JPaL regimen, it would not be necessary to define the primary endpoint at the
end of the longer regimen. Superiority could possibly be shown at a much earlier time point.

If it is determined that a concurrently controlled trial is not possible, it will be important to provide a data-driven justification, similar to information provided for a noninferiority margin justification, for the historical control. TB Alliance asked if the historical control would be an estimate of the response rate of the current standard of care for XDR-TB. The Division stated that the historical control could be based on an untreated population or a population with ineffective treatment and would not need to be based on the current standard of care for XDR-TB. In determining the relevant target for efficacy, the clinically relevant rate that should be excluded should also be considered. A mortality endpoint should be considered as well, especially given the Boxed warning regarding mortality in the bedaquiline label.

The Division stated that as this trial will need to be considered an adequate and well-controlled trial, it will be important to have statistically valid results with control of the type I error. TB Alliance should determine how best to address multiplicity.

The Division agreed to review and provide feedback on the protocol synopsis for the proposed study design.

**CMC**

9. Does the agency have any concerns about using the proposed linezolid product in the Phase 3 trial?

**FDA Response:**

In general, we recommend that the US approved drug products are used in clinical studies conducted under INDs. If you have to use a non-US approved drug product in your clinical study, we recommend that you submit the following information:

1. In order for FDA to evaluate your request of using a non-US approved drug product, the following information is required to be submitted to the IND before the non-US approved drug product can be used:

   a) The quantitative composition of the drug product with any compendial quality standards listed for the inactive ingredients

   **TB Alliance Response:** Available

   b) The name and location of the manufacturing site(s) for the drug product and drug substance

   **TB Alliance Response:** Available
c) A Certificate of Analysis for each batch of the drug product to be used in the clinical study

**TB Alliance Response:** Available

d) Statement of comparability to the US approved drug product

**TB Alliance Response:** Can be made Available

e) Statement that the non-US approved drug product is approved for marketing in an ICH region.

**TB Alliance Response:** WHO approved

2. To support the bridging between the proposed US and non-US drug products, you should provide the following supportive information/data;

a) A head to head comparison table demonstrating that the qualitative and quantitative compositions of the formulations for the non-US and US-drug products, as well as the manufacturing equipment/processes/etc. for these products are essentially the same.

**TB Alliance Response:** Can provide

b) In vitro drug release profile comparison and the results from an appropriate statistical test (e.g., f2 test) demonstrating that the non-US and US-drug products have similar in vitro drug release rate characteristics using the US-approved in vitro drug release method (n=12 units/test).

**TB Alliance Response:** Dissolution data and BE data are available (Macleods)

If we determine that the provided information/data is not supportive, a bioequivalence study bridging the non-US and US approved drug products will be needed.

**TB Alliance Response:** BE data is available (Macleods)

**Meeting Discussion:**
The Division asked TB Alliance to formally submit the information requested above to the IND.

The Division asked TB Alliance how they intend to dose and label a 300 mg linezolid tablet if a 600 mg scored tablet is not available in US. TB Alliance stated that they will need additional time to research and finalize their decision on how to provide the lower dose.
Additional Comments/Questions:

Clinical Pharmacology:

Since bedaquiline is a CYP3A substrate, we recommend that you evaluate the drug-drug interaction potential of pretomanid and bedaquiline in vitro and determine the I/Ki ratio(s) for this interaction. Based on the results of this in vitro evaluation, an in vivo drug-drug interaction study between pretomanid and bedaquiline may be needed.

TB Alliance response:

- **Clinical DDI study of pretomanid at 400 mg did not show inhibition of midazolam pharmacokinetics** (CYP3A4 catalyzed clearance of midazolam). *(Ref: Study CL-006 and IB).*
  - Dosing with PA-824 at 400 mg/day for 14 days (to steady state) had minimal effect on the PK of midazolam at 2 mg (co-administered with pretomanid on the last day) and its 1-hydroxy metabolite as assessed by comparing to the Cmax, AUC0-t, and AUC0-inf of midazolam and 1-OH midazolam PK in the absence of pretomanid. The Cmax and AUC values for midazolam after coadministration with PA-824 were approximately 85% those observed after treatment with midazolam alone. (Note: pretomanid at 200 mg, Cmax,ss = ~4 ug/mL, AUC0-24h = ~80 ug*h/mL, from NC-002.)

- In vitro (HLM), **IC50s of pretomanid inhibition of CYP3A4: 50 uM (testosterone) and >100 uM (midazolam)**, suggesting that pretomanid is a weak CYP3A4 inhibitor. *(ref. IB)*

- **In a clinical DDI study, bedaquiline exposure was not significantly increased by a potent CYP3A4 inhibitor ketoconazole.**
  - Following co-administration of bedaquiline with ketoconazole at 400 mg (CYP3A4 IC50 <0.1 uM), the mean AUC24 of bedaquiline increased 22% while the mean Cmax was unaffected compared with bedaquiline administered alone. *(JAC, V69(9), pp2310, 2014)*

Therefore, we conclude that co-administration of pretomanid and bedaquiline will not cause bedaquiline PK changes due to CYP3A4 inhibition.

Meeting Discussion

The Division stated that the Sponsor’s response was acceptable and confirmed that no additional in vitro studies are required at this point.

The Division asked if the bedaquiline PK data from NC-007 can be compared to the available data in the literature and be submitted for review. TB Alliance agreed.

The Division stated that their main concern is the possibility of additional toxicity when bedaquiline is taken together with pretomanid. TB Alliance stated that they will provide...
the Division with the PK data from Study NC-005 in July, including both PK and safety data for the bedaquiline and pretomanid regimen.

The Division asked if TB Alliance is

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

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

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans at:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to:

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. Beginning May 5, 2017, the following submission types: NDA, ANDA, BLA and Master Files must be submitted in eCTD format. Commercial IND 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.

**Office of Scientific Investigations (OSI) Requests**

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

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

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

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

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
a. Site number
b. Principal investigator
c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator’s site address or contact information since the time of the clinical investigator’s participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, by site, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).

5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

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

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:

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

/s/

SUMATHI NAMBIAR
06/23/2016