APPLICATION NUMBER:

212862Orig1s000

OTHER REVIEW(S)
Clinical Review of Request for Priority Review of NDA 212-862

Introduction

The applicant, Global Alliance for TB Drug Development, Inc., requests a priority review for the NDA 212-862, submitted on December 14, 2018 for pretomanid as part of a combination regimen with bedaquiline and linezolid (BPaL) for the treatment of adults with pulmonary extensively drug resistant (XDR), or treatment-intolerant (TI) or nonresponsive (NR) multidrug resistant (MDR) tuberculosis (TB).

MDR-TB is caused by Mycobacterium tuberculosis (MTB) that is resistant to at least isoniazid and rifampin, the two most effective of the four first-line anti-TB drugs, isoniazid, rifampicin, pyrazinamide, and ethambutol (HRZE). XDR-TB is a less common form of MDR-TB, that is resistant to isoniazid and rifampin plus any fluoroquinolone and at least one of the three injectable second-line drugs (i.e. amikacin, kanamycin, or capreomycin). Patients who have XDR-TB or TI/NR MDR-TB, the intended patient population in this NDA, have limited treatment options.

In August 2018, the WHO reclassified the drugs for the prolonged treatment of MDR-TB in three priority groups:

- **Group A**: levofloxacin OR moxifloxacin, bedaquiline, and linezolid
- **Group B**: clofazimine and either cycloserine or terizidone
- **Group C**: any add-on drug from among ethambutol, delamanid, pyrazinamide, imipenem-cilastatin or meropenem, amikacin (or streptomycin), ethionamide or prothionamide, and p-aminosalicylic acid.

The current recommended treatment regimen for the treatment of XDR and TI/NR MDR-TB is a multi-drug combination of second- and third-line oral drugs with an injectable antimycobacterial drug. The regimen is individually tailored based on the susceptibility pattern of the M. tuberculosis isolate, and patients are usually treated with five to eight drugs for up to two years or longer. Poor efficacy, adverse reactions, intolerance, and drug-drug interactions with antiretroviral drugs and other concomitant medications are among the many challenges with antimycobacterial multidrug regimens administered for prolonged periods. Compliance is difficult, and patients endure long hospital stays as treatment has usually been administered in an inpatient setting or more recently in outpatient directly observed therapy (DOT) programs to assure adherence.

Regulatory History


CLINICAL REVIEW

The Qualifying criteria for priority review designation are outlined in the guidance on Expedited Programs for Serious Conditions – Drugs and Biologics.²

The qualifying criteria are as follows:
1. Serious Condition

Tuberculosis is potentially fatal unless it is diagnosed early and treated with an appropriate regimen of antimycobacterial drugs. *Mycobacterium tuberculosis* primarily causes pulmonary disease, but it can also disseminate to other organs such as bone, liver, central nervous system, and adrenal glands. If a patient’s tuberculosis is left untreated, or if a person is infected with MDR-TB, mortality can be as high as 50% for those with active disease.

Surveys of worldwide drug resistance indicate that drug-resistant tuberculosis (DR-TB) is an increasing problem.\(^1\) In 2018, the WHO estimated that there were approximately 558,000 cases of MDR-TB worldwide; of these, it is estimated that 230,000 deaths from MDR-TB occurred in 2017. China, India, Russia, and the countries of the former Soviet Union have the highest number of MDR-TB cases in the world.\(^2\) Several African and South East Asian nations also have a high burden of MDR-TB disease. The prevalence of DR-TB in the United States decreased between 1991 and 2006 (3.5 to 1.1 percent) and remained stable between 2005 and 2006 (1.2 percent), even as drug-resistant tuberculosis increased worldwide.\(^3,4\) MDR-TB disproportionately affects foreign-born individuals and this group accounted for 85% of cases of MDR-TB in the US in 2015.\(^4\)

Patients infected with XDR-TB or TI/NR MDR-TB have a high mortality rate and limited treatment options. Treatment success across South African studies averaged at 14%, with a range of 2% to 22%; outside South Africa, rates of treatment success are more variable, ranging from 15% to 60%, with only two studies reporting treatment success rates above 50%.\(^5,6\) There is an unmet need for efficacious, safe, and shorter regimens for treatment of MDR-TB and XDR-TB.

2. Demonstrating the potential to be a significant improvement in safety or effectiveness

On a case-by-case basis, FDA determines at the time of NDA, BLA, or efficacy supplement filing whether the proposed drug would be a significant improvement in the safety or effectiveness of the treatment, prevention, or diagnosis of a serious condition. Significant improvement may be illustrated by the following examples:

- **Evidence of increased effectiveness in treatment, prevention, or diagnosis of a condition:**

The applicant has provided substantial evidence of effectiveness of the BPaL regimen in patients with XDR- and TI/NR MDR-TB. The efficacy assessment of the 6-months BPaL regimen for the treatment of XDR-TB and TI/NR MDR-TB was based on the Nix-TB trial. Based on an interim data cutoff of January

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Pretomanid in combination with bedaquiline and linezolid for the treatment of XDR- and TI/NR MDR-TB

18, 2019, the rate of favorable outcomes for the primary endpoint of bacteriologic failure, relapse, or clinical failure was 89%, with a 95% confidence interval from 81% to 94%. The lower confidence limit for the success greatly exceeded the prespecified historical control rate of 50%. At this interim data cutoff timepoint, a total of 32/38 (84%) patients had favorable outcomes at 24 months following the end of treatment. The efficacy findings were also consistent in the pre-specified population of 45 patients. Results were robust to the handling of screening failures in the analysis or interim analyses.

The 50% historical control threshold rate was evaluated based on a literature review of existing treatment outcomes for XDR-TB. A random effects meta-analysis of published treatment success rates had an upper confidence limit of 34%. In addition, the high success rates in Nix-TB was observed in South Africa in a patient population with a high rate of HIV infection, where previous studies have reported poor outcomes. This literature review was supplemented by a comparison of Nix-TB outcomes to a matched historical control group from patients at one of the study centers who had been treated for XDR-TB without bedaquiline, linezolid, or pretomanid. The two groups were similar on measured baseline factors such as age, sex, HIV status, and weight, but the patients in Nix-TB treated with BPaL had much greater rates of treatment success and lower mortality rates.

Although there remains the possibility that non-randomized comparisons could be confounded, historical controls can provide convincing evidence of efficacy when the outcomes with currently available treatment options are poor and the treatment effect is too large to be easily explained by confounding factors, and this is the most straightforward interpretation of Nix-TB results.

- **Elimination or substantial reduction of a treatment-limiting adverse reaction:**

The applicant has not provided data to support an elimination of substantial reduction of a treatment-limiting adverse reaction(s) with use of BPaL relative to the available individualized treatment regimens for XDR- TI/NR MDR-TB.

Across the clinical development program, 1507 subjects in 19 completed or ongoing studies of pretomanid: three Phase 3 studies, six Phase 2 studies, and ten Phase 1 studies. Among the 1507 subjects, 1168 (77.5%) were exposed to pretomanid either alone (411 [27.3%] subjects) or in combination with other antimycobacterial drugs (757 [50.2%] subjects). The remaining subjects were in control groups not including pretomanid.

Eight patients died in the Nix-TB study. Adverse events such as peripheral neuropathy, optic neuropathy, hematopoietic cytopenias, acute pancreatitis, seizures, and elevations of hepatic transaminases, total bilirubin, lipase, amylase, and lactic acid were reported during BPaL treatment. Peripheral and optic neuropathies and myelosuppression are known adverse effects of linezolid. In most patients, adverse events were managed by dosing interruptions followed by dose reductions of linezolid or a dosing interruption of the entire BPaL regimen. The subjects who discontinued the BPaL regimen were the 6 (5.5%) subjects who died during the treatment period. All patients who survived were able to resume antimycobacterial therapy to complete study treatment.

In the pooled Phase 1 and Phase 2 trials, there were no deaths or SAEs associated with pretomanid and common TEAEs included headache, nausea, diarrhea, and skin rash. Increases in hepatic transaminases and decreases in hemoglobin were also reported. Overall, pretomanid was generally well tolerated in
NDA 212-862
Pretomanid in combination with bedaquiline and linezolid for the treatment of XDR- and TI/NR MDR-TB
the pooled Phase 1/2 studies; however, the duration of treatment with pretomanid was short (1 to 43
days) as compared to 6 to 9 months in the Nix-TB trial.

- **Documented enhancement of patient compliance that is expected to lead to an improvement in serious outcomes**

  The applicant has not provided data to support an improvement in patient compliance with the BPaL regimen relative to the available individualized treatment regimens for XDR-TB or TI/NR MDR-TB. In the Nix-TB trial, linezolid was permanently discontinued due to treatment emergent adverse events (TEAEs) in 28 (26%) subjects. BPaL was permanently discontinued in the 6 (5.5%) patients who died on treatment.

  Dosing of BPaL or linezolid alone was interrupted due to a TEAE in 20 (18%) and in 48 (44%) patients, respectively. The dose of linezolid was reduced in 43 (39.4%) patients during the treatment period. The doses of pretomanid and bedaquiline were not changed during the trial. Peripheral sensory neuropathy was the most common TEAE leading to discontinuation, dose reduction, or a dosing interruption of linezolid. Increased hepatic transaminases or drug-induced liver injury (DILI) caused interruption of BPaL in 6 (5.5%) and 2 (1.8%) patients, respectively.

- **Evidence of safety and effectiveness in a new subpopulation**

  The FDA guidance on Expedited Programs for Serious Conditions also states that, “Although such evidence [to support a priority review] can come from clinical trials comparing a marketed product with the investigative drug, a priority review designation can be based on other scientifically valid information. Generally, if there is an available therapy, sponsors should compare their investigational drug to the available therapy in clinical testing with an attempt to show superiority relating to either safety or effectiveness. Alternatively, sponsors could show the drug’s ability to effectively treat patients who are unable to tolerate, or whose disease failed to respond to, available therapy or show that the drug can be used effectively with other critical agents that cannot be combined with available therapy. Although such showings would usually be based on randomized trials, other types of controls could also be persuasive, for example, historical controls.”

  *The NDA does not contain sufficient safety or effectiveness data for pretomanid in a subpopulation other than XDR-TB and TI/NR MDR-TB.*

**Summary and Recommendation**

The available evidence from the Nix-TB trial of pretomanid as part of a regimen containing bedaquiline and linezolid administered for six months support an efficacy advantage over historical controls receiving available multi-drug regimens for XDR-TB. In this single phase 3 clinical trial in 109 patients with XDR-TB or TI/NR MDR-TB, superiority of the BPaL regimen on clinical outcomes was reported as compared to historical control data.

This clinical reviewer recommends a priority review for NDA 212-862 for pretomanid as part of a combination with bedaquiline and linezolid for the treatment of adults with pulmonary XDR-TB, or TI/NR MDR-TB, a serious condition and showed a significant improvement in effectiveness relative to the historical control (literature and matched historical control cohort comparison) and an acceptable safety profile. Additionally, the NDA will receive a priority review as the product has qualified infectious disease product (QIDP) designation.
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/s/

ELIZABETH M OSHAUGHNESSY
08/09/2019 04:21:04 PM

SUMATHI NAMBIAR
08/09/2019 04:49:55 PM
1 PURPOSE OF MEMORANDUM

In response to the Agency’s request, the Applicant submitted final copies of their previously submitted pretomanid bottle (30 count) and blister foil (2x14) container labels and carton labeling. These container labels and carton labeling were previously found acceptable from a medication error perspective in previous label and labeling reviews.a,b The Division of Anti-Infective Products (DAIP) requested that we review the proposed final container labels and carton labeling for Pretomanid (Appendix A) to confirm that no changes have been made and determine if they are acceptable from a medication error perspective.

2 FINDINGS AND CONCLUSION

We note that the strength statement on the blister label has been relocated to the same line as the established name and dosage form (i.e., Pretomanid Tablet, 200 mg), the statement [REDACTED] has been relocated to the same line, and the “Rx only” statement has been relocated from the top to the bottom of the blister (see images below):

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However, we confirm that we have no concerns with these changes from a medication error perspective and we have no additional recommendations at this time.
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/s/

DEBORAH E MYERS
08/09/2019 01:31:16 PM

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08/09/2019 04:45:01 PM
Division of /Anti-Infective Products

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: NDA 212862

Name of Drug: Pretomanid 200 mg Tablet

Applicant: TB Alliance

Labeling Reviewed

Submission Date: 12-14-18

Receipt Date: 12-14-18

Background and Summary Description:
Pretomanid (PA-824) is a nitroimidazo-oxazine, currently in clinical development for the treatment of drug-sensitive tuberculosis (DS-TB), MDR-TB, and XDR-TB. Pretomanid is a new molecular entity and is not currently marketed in the US or anywhere in the world. A pre-IND meeting with FDA and TB Alliance was held on October 1, 2004 to discuss the adequacy of the completed and planned non-clinical studies to support an IND and the design of phase I clinical studies for the treatment of DS-TB and MDR-TB.

On April 28, 2005, IND 69,580 was opened for pretomanid, known as PA-824, for the treatment of DS-TB and MDR-TB. Clinical trials of pretomanid (> 14 days) in various anti-mycobacterial drug regimens are summarized in Table 1.


On December 14, 2018, the applicant submitted an NDA for pretomanid as part of regimen with bedaquiline and linezolid for the treatment of XDR-TB and TI/ NR MDR-TB. The NDA has fulfilled the criteria for Priority Review as outlined in the FDA guidance on Expedited Programs for Serious Conditions – Drugs and Biologics and was granted a Priority Review.
Review
This review is based on the applicant’s submitted Word format of the prescribing information (PI). The applicant’s proposed PI was reviewed in accordance with the labeling format requirements listed in the “Selected Requirements of Prescribing Information (SRPI)” checklist (see Section 4 of this review).

Recommendations
The applicant will be asked to submit a waiver request to increase the length of HL to more than half a page. No other SRPI format deficiencies were identified in the review of this PI.

Fariba Izadi 7-10-19
Regulatory Project Manager Date

Carmen DeBellas 7-10-19
Chief, Project Management Staff Date
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/s/

FARIBA IZADI  
07/11/2019 01:16:09 PM

CARMEN L DEBELLAS  
07/11/2019 01:21:58 PM
PATIENT LABELING REVIEW

Date: July 8, 2019

To: Sumathi Nambiar, MD, MPH
Director
Division of Anti-Infective Products (DAIP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Marcia Williams, PhD
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Karen Dowdy, RN, BSN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

David Foss, Pharm. D., MPH, BCPS
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): pretomanid

Dosage Form and Route: tablets, for oral use

Application Type/Number: NDA 212862

1 INTRODUCTION

On December 14, 2018, The Global Alliance for TB Drug Development, Inc. submitted for the Agency’s review an Original New Drug Application (NDA) 212862 for pretomanid tablets. Pretomanid tablets is a New Molecular Entity (NME) with a proposed indication, as part of a combination regimen with bedaquiline and linezolid, in adults for the treatment of pulmonary extensively drug resistant (XDR) or treatment-intolerant or nonresponsive multidrug-resistant (MDR) tuberculosis (TB).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to requests by the Division of Anti-Infective Products (DAIP) on January 10, 2019 and January 4, 2019, respectively, for DMPP and OPDP to review the Applicant’s proposed Medication Guide (MG) for pretomanid tablets.

2 MATERIAL REVIEWED

• Draft pretomanid tablets MG received on December 14, 2018 and received by DMPP and OPDP on June 24, 2019.

• Draft pretomanid tablets Prescribing Information (PI) received on December 14, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 24, 2019.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG we:

• simplified wording and clarified concepts where possible
• ensured that the MG is consistent with the Prescribing Information (PI)
• removed unnecessary or redundant information
• ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
• ensured that the MG meets the Regulations as specified in 21 CFR 208.20
ensured that the MG meets the criteria as specified in FDA’s Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS
The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS
- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.
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/s/

KAREN M DOWDY  
07/08/2019 05:31:01 PM

DAVID F FOSS  
07/08/2019 05:40:17 PM

MARcia B WILLIAMS  
07/08/2019 07:08:24 PM

LASHAWN M GRIFFITHS  
07/09/2019 08:18:14 AM
**Pre-decisional Agency Information**

**Memorandum**

**Date:** July 3, 2019

**To:**
Elizabeth O’ Shaughnessy, M.D.
Division of Anti-Infective Products (DAIP)

Fariba Izadi, Regulatory Project Manager, DAIP

Abimbola Adebawale, Associate Director for Labeling, DAIP

**From:**
David Foss, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

**CC:**
Jim Dvorsky, Team Leader, OPDP

**Subject:** OPDP Labeling Comments for PRETOMANID tablets, for oral use

**NDA:** 212862

In response to DAIP’s consult request date January 4, 2019, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for the original NDA submission for Pretomanid.

**PI:** OPDP’s comments on the proposed labeling are based on the draft PI received by electronic mail from DAIP on June 24, 2019, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed Medication Guide will be sent under separate cover.

**Carton and Container Labeling:** OPDP has reviewed the attached proposed carton and container labeling received by electronic mail from DAIP on June 24, 2019, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact David Foss at (240) 402-7112 or david.foss@fda.hhs.gov.

Reference ID: 4458077
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/s/

DAVID F FOSS
07/03/2019 06:09:01 PM
1 PURPOSE OF MEMORANDUM
The Applicant submitted revised container labels and carton labeling received on June 12, 2019 for Pretomanid. The Division of Anti-Infective Products (DAIP) requested that we review the revised container labels and carton labeling for Pretomanid (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.¹

2 CONCLUSION
The revised container label is unacceptable from a medication error perspective (i.e., the revised container label (30 count bottle) does not include the "Limited Population" statement on the principal display panel (PDP)). Below, we have provided our recommendation in Table 1 for the Applicant. We ask that DAIP convey Table 1 in its entirety to Global Alliance for TB Drug Development, Inc., so that our recommendation is implemented prior to approval of this NDA.

3 RECOMMENDATIONS FOR GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT, INC.

We recommend the following be implemented prior to approval of this NDA:

Table 1. Identified Issues and Recommendations for Global Alliance for TB Drug Development, Inc. (entire table to be conveyed to Applicant)

<table>
<thead>
<tr>
<th>IDENTIFIED ISSUE</th>
<th>RATIONALE FOR CONCERN</th>
<th>RECOMMENDATION</th>
</tr>
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<tbody>
<tr>
<td>Container Label (30 count bottle)</td>
<td>As currently presented, the revised container label (30 count bottle) does not include the “Limited Population” statement on the principal display panel (PDP).</td>
<td>“The statement “Limited Population” should be included on the principal display panel of the product carton(s) and, if space permits, immediate containers, adjacent to the proprietary name or nonproprietary name...” and “...To provide clarity, FDA recommends including an asterisk next to the “Limited Population” statement with a footnote at the bottom of the PDP stating “See the full prescribing information for [drug name] for information about the limited population.””</td>
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</table>

Add the “Limited Population” statement, adjacent to the nonproprietary name (i.e., Pretomanid Tablets) on the PDP of the 30 count container label. To provide clarity, include an asterisk next to the “Limited Population” statement with a footnote at the bottom of the PDP stating “See the full prescribing information for [drug name] for information about the limited population.”

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b See 21 CFR 210.10(i) for additional information about packaging that is too small for the additional statements.
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/s/

DEBORAH E MYERS  
06/24/2019 04:21:27 PM

OTTO L TOWNSEND  
06/24/2019 04:46:11 PM
Medical Officer’s Review of NDA 212862
Consult Request from
Division of Anti-Infective Products

NDA 212862
Submission Date: 12/14/2018
Consult Receipt Date: 1/29/19
Review Date: 6/1/2019

40 Wall Street, 24th floor
New York, NY 10005

Drug: Pretomanid (PA-824)
Pharmacologic Category: nitroimidazooxazine antimycobacterial

Comments/Special Instructions:

In NDA 212862, pretomanid, a nitroimidazooxazine antimycobacterial drug is indicated, as part of a combination regimen with bedaquiline and linezolid, in adults for the treatment of pulmonary extensively drug resistant (XDR) or treatment-intolerant or nonresponsive multidrug resistant (MDR) tuberculosis. The pivotal study in this NDA is NixTB trial (n=109 patients).

Clinical Summary of Safety, Section 6.9 in module M2 in the NDA presents by-study results for AREDS2 slit-lamp assessments in DS-TB subjects in Studies NC-002, NC-005, and NC-006. The results for the 200 mg PaMZ and 6-month 200 mg PaMZ treatment groups in Studies NC-002 and NC-006, respectively, reflect both DS-TB and MDR-TB subjects. Links are provided to the study reports within the sections 6.9.

Since July 2009, based on DTOP recommendations, clinical studies with pretomanid exposure longer than 14 days have included slit-lamp examinations with AREDS2 scoring of lens opacities; these studies report no association of concern between pretomanid exposure and cataracts in humans (Section 3.9, Section 5.9, and Section 6.9). Results of SMQ explorations for TEAEs potentially indicative of cataract formation are presented in Section 3.4.7.1 (Study Nix-TB), Section 4.4.5 (Study ZeNix), Section 5.4.7.1 (MDR-TB pooling group), Section 6.4.7.1 (DS-TB pooling group), Section 7.4.7.1 (phase 2 pretomanid-alone pooling group), Section 8.4.7 (phase 1 pooling group), and Section 11.4 (Discussion). Close ocular monitoring is continuing during the ongoing clinical development program.

Study NC-002: A Phase 2 Open-Label Partially Randomized Trial to Evaluate the Efficacy, Safety, and Tolerability of the Combination of Moxifloxacin plus PA-824 plus Pyrazinamide after 8 weeks of Treatment in Adult Patients with Newly Diagnosed Drug-Sensitive or Multidrug-Resistant, Smear-Positive Pulmonary Tuberculosis.
Study NC-005: A Phase 2 Open-Label Partially Randomized Trial to Evaluate the Efficacy, Safety and Tolerability of Combinations of Bedaquiline, Moxifloxacin, PA-824 and Pyrazinamide During 8 Weeks of Treatment in Adult Subjects with Newly Diagnosed Drug-Sensitive or Multi Drug-Resistant, Smear-Positive Pulmonary Tuberculosis

Study NC-006: A Phase 3 Open-Label Partially Randomized Trial to Evaluate the Efficacy, Safety and Tolerability of the Combination of Moxifloxacin plus PA-824 plus Pyrazinamide after 4 and 6 months of Treatment in Adult Subjects with Drug-Sensitive Smear-Positive Pulmonary Tuberculosis and after 6 months of Treatment in Adult Subjects with Multi-Drug Resistant, Smear-Positive Pulmonary Tuberculosis.

EDR Location: \CDSESUB1\evsprod\NDA212862\0001

Questions/Requests:
1. Does the DTOP have additional comments that were not included in the prior consultations about pretomanid?
2. Please provide any labeling recommendations that you think are warranted.
3. We would like to request your presence at the Advisory Committee for NDA 212862 scheduled for June 5-6, 2019.

Background:

From the DTOP consultative ophthalmology review dated 7/13/2011 for IND 69,580:

An initial IND Safety Report submitted to the IND (SN0027, submitted 19 December 2007) described the detection of cataracts in two 3-month toxicology studies in monkey and rat. To enhance understanding, assure patient safety, and follow the ORB’s recommendation as outlined in the 01 December 2008 ORB meeting minutes (SN0038, submitted 22 December 2008), the TB Alliance proposed incorporating ocular monitoring (with slit-lamp examinations) using an appropriate standardized lens evaluation system into future clinical studies pre- and post-treatment.

Dr. Alan Laties, an expert clinical ophthalmologist, recommended for studies less than 12 weeks in duration that ocular assessments (with slit-lamp examinations) should be performed at baseline and 3 to 6 months after the end of dosing, and for studies 12 or more weeks in duration, this evaluation should be conducted at baseline, end of dosing and 3 to 6 months after the end of dosing (SN0039, submitted 11 June 2009). Based on the evidence submitted and the proposed ocular monitoring plan, three additional clinical studies (PA-824-CL-006, PA-824-CL-009, and PA-824-CL-010) have been completed.

Ophthalmology exams were completed post-study in 76 participants in Studies CL-005 (n=30) and CL-007 (n=46) and prospectively at pre-treatment and post treatment time points in 111 participants from Studies CL-006 (n=14), CL-009 (n=32) and CL-010 (n=65). For all studies combined, the incidence of lens opacities observed is displayed in Table 1.
Only 187 subjects have completed ophthalmic examinations: 76 underwent examination post-study and 111 prospectively.

The ocular assessment was to consist of an ophthalmologic medical history, visual acuity test, and slit lamp examination. Slit lamp examination was to be used to determine lens opacity occurrence using the AREDS 2 lens grading system.

- For studies less than 12 weeks in duration, the ocular examination was to be performed at baseline and 3 to 6 months after end of dosing.

- For studies of 12 or more weeks in duration, this evaluation was to be conducted at baseline, end of dosing, and 3 to 6 months after end of dosing.

**Ophthalmologic Examinations - DS-TB Pooling Group:**

Presented within *NDA 212862 Module 2.74. Summary of Clinical Safety, Section 6.9*, are by-study results for AREDS2 slit-lamp assessments in DS-TB (i.e., drug susceptible) subjects in Studies NC-002, NC-005, and NC-006. The results for the 200 mg PaMZ and and 6-month 200 mg PaMZ treatment groups in Studies NC-002 and NC-006, respectively, reflect both DS-TB and MDR-TB (i.e. multi-drug resistant) subjects.

**NC-002**

Data were available for 111 eyes in 56 subjects treated with 100 mg PaMZ, 160 eyes in 80 subjects treated with 200 mg pretomanid-moxifloxacin-pyrazinamide (PaMZ) including both DS-TB and MDR-TB subjects, and 108 eyes in 54 subjects treated with isoniazid, rifampicin, pyrazinamide, and ethambutol (HRZE) as control. A score increase (indicating worsening of opacity) of $\geq 1$ from baseline in cortical opacity was observed in 1 eye (0.6%) in the 200 mg PaMZ group and no eyes (0%) in the other treatment groups. An increase of $\geq 1$ from baseline in nuclear opacity was observed in 1 eye (0.9%) in the 100 mg PaMZ group and no eyes in the other treatment groups. No subject showed an increase of $\geq 1$ from baseline in posterior subcapsular opacity, or a score decrease (indicating improvement) of $\geq 1$ for any category of lens opacity. No subject in Study NC-002 had an increase or decrease of $\geq 2$ in any AREDS2 score.

**Reviewer’s Comments:**

The data submitted show no clinically meaningful effect of pretonamid on the potential for cataract formation at the doses and durations studied.
Data were available for 104 eyes in 52 subjects treated with BPaZ, 104 eyes in 52 subjects treated with bedaquiline, pretomanid, and pyrazinamide (BPaZ) using a bedaquiline loading dose, and 116 eyes in 58 subjects treated with HRZE as control. The BPaZ group was composed of only MDR-TB subjects. A score increase (worsening) of \( \geq 1 \) from baseline was observed in 1 eye (1%) in the BPaZ group (with no bedaquiline loading dose); this was an increase in cortical opacity. No other DS-TB treatment group had a score increase of \( \geq 1 \) from baseline. Two eyes (2%) in the BPaZ group (with no bedaquiline loading dose) showed a score decrease (improvement) of \( \geq 1 \) from baseline, which was a decrease in nuclear opacity. No other DS-TB treatment group had a score decrease of \( \geq 1 \) from baseline. No subject in Study NC-005 had an increase or decrease of \( \geq 2 \) in any AREDS2 score.

**Reviewer’s Comments:**

*The data submitted show no clinically meaningful effect of pretonamid on the potential for cataract formation at the doses and durations studied.*

NC-006

Data were available for 123 eyes in 62 subjects treated with 100 mg PaMZ for 4 months, 132 eyes in 66 subjects treated with 200 mg PaMZ for 4 months, 147 eyes in 74 subjects treated with 200 mg PaMZ for 6 months (includes both DS-TB and MDR-TB subjects), and 126 eyes in 63 subjects treated with HRZE as control. A score increase (worsening) of \( \geq 1 \) from baseline in cortical opacity was observed in 2 eyes (1.6%) in the 100 mg PaMZ group and 1 eye (0.8%) in the 4-month 200 mg PaMZ group. Three eyes (2.3%) in the 4-month 200 mg PaMZ group and 4 eyes (2.7%) in the 6-month 200 mg PaMZ showed increases of \( \geq 1 \) from baseline in nuclear opacity scores. Increases of \( \geq 1 \) from baseline in posterior subcapsular scores were observed in all treatment groups: 3 eyes (2.4%), 2 eyes (1.5%), 1 eye (0.7%), and 1 eye (0.8%) for 100 mg PaMZ, 4-month 200 mg PaMZ, 6-month 200 mg PaMZ, and HRZE control, respectively.

Decreases (improvements) of \( \geq 1 \) from baseline in cortical opacity scores were observed in 2 eyes (1.6%) in the 100 mg PaMZ group and 3 eyes (2.0%) in the 6-month 200 mg PaMZ group. Nuclear opacity scores showed score decreases of \( \geq 1 \) from baseline in 2 eyes (1.6%) in the 100 mg PaMZ group, 1 eye (0.7%) in the 6-month 200 mg PaMZ group, and 2 eyes (1.6%) in the HRZE control group. All treatment groups showed decreases of \( \geq 1 \) from baseline in posterior subcapsular opacity scores: 2 eyes (1.6%), 2 eyes (1.5%), 3 eyes (2.0%), and 1 eye (0.8%) for 100 mg PaMZ, 4-month 200 mg PaMZ, 6-month 200 mg PaMZ, and HRZE control, respectively.

**Reviewer’s Comments:**

*The Age-Related Eye Disease Study (AREDS) Clinical Lens Grading System (ARLNS) employs 3 standard photographs of increasing severity for classifying each of the 3 major types of opacity (nuclear, cortical, posterior subcapsular). The system was designed to require minimal examiner training for persons already proficient in the use of the slit lamp. AREDS2 is an adaptation of the ARLNS.*
Currently there is no mechanism, short of surgery, to treat cataracts. A change of ≥2 in AREDS2 is notable because changes of ≥1 are frequently seen with inter-rater variability.

Three subjects in Study NC-006 had an increase of ≥2 in AREDS2 score:
- Subject , a 24-year-old female in the HRZE control group, had baseline cortical, nuclear, and posterior subcapsular scores of 0 in both eyes. At Week 22, the subject had a right posterior subcapsular score of 2, with all other scores being 0. At the Month 9 visit, the right posterior subcapsular score was 0.5, with the right cortical and nuclear scores remaining 0. Near and distance visual acuities were normal at all time points.

Reviewer's Comments: Subject , with lens scores of 0 at baseline, was noted at Week 22 to have a right posterior subcapsular score of 2. By Month 9, the right posterior subcapsular score was 0.5. This change in lens score appears attributable to rater variability; there is no physiologic mechanism to explain a decrease in the cataract.

- Subject , a 54-year-old male in the 4-month 200 mg PaMZ group, had baseline cortical, nuclear, and posterior subcapsular scores of 0, 0.5, and 0, respectively, in both eyes. At Week 22, the scores were 0, 1, and 1, respectively, in the right eye and 0, 1, and 0 in the left eye. At the Month 9 visit, right posterior subcapsular score was 4, with corresponding cortical and nuclear scores of 0 and 2, respectively. The left eye scores remained unchanged from Week 22. Distance vision in the right eye was impaired at screening at , improved at Week 22 at , but then could not be documented at Month 9. Of note, the subject had an invasive aspergillosis infection in his nasal cavity during the study.
Reviewer's Comments: Subject , had baseline posterior subcapsular scores of 0 in both eyes. At Week 22, the posterior subcapsular score was 1. At the Month 9 visit, right posterior subcapsular score was 4.

The subject had an invasive aspergillosis infection in his nasal cavity, biopsy confirmed, during the study which was treated with IV amphotericin. His past medical history per the SAE reporting form included “nuclear sclerotic cataracts” for which he received topical tropicamide and phenylephrine. Distance vision in the right eye was reduced at screening but improved at Week 22 but then could not be documented at Month 9. It appears likely that this subject entered the study with a significant cataract OD, probably posterior subcapsular and not nuclear.

- Subject , a 47-year-old male in the 4-month 200 mg PaMZ group, had baseline cortical, nuclear, and posterior subcapsular scores of 0, 0, and 1, respectively, in the right eye and 0, 0.5, and 0, respectively, in the left. At Week 22, the scores were 0, 0, 1, respectively, for the right eye and 0, 0, 2, respectively for the left eye. All scores in both eyes were 0 at the Month 9 visit. Distance visual acuity in each eye was the same at Month 9 compared with screening.

Reviewer's Comments: Subject , with lens scores of 0 or 1 at baseline, was noted at Week 22 to have a left posterior subcapsular score of 2. All scores in both eyes were 0 at the Month 9 visit. This change in lens score appears attributable to rater variability; there is no physiologic mechanism to explain a decrease in the cataract.

Conversely, 1 subject had a decrease of ≥2 in AREDS2:

- Subject , a 53-year-old male in the HRZE group, had a nuclear score of 2.5 in the left eye and nuclear score of 2 in the right eye at screening, which were then 0 at Week 22 and Month 9. The cortical and posterior subcapsular scores were 0, and both near and distance visual acuities were normal at all time points.

Reviewer's Comments: Subject had a nuclear score of 2.5 in the left eye and nuclear score of 2 in the right eye at screening, which were then 0 at Week 22 and Month 9. This change in lens score appears attributable to rater variability; there is no physiologic mechanism to explain a decrease in the cataract.

Reviewer Summary Comments DS-TB Pooling Group:
Clinical studies with pretomanid exposure longer than 14 days have included visual acuity assessments, slip-lamp examinations, and AREDS-2 lens opacity scoring since July 2009. The data submitted show no clinically meaningful effect of pretomanid on the potential for cataract formation at the doses and durations studied. Ocular monitoring continues in the ongoing clinical development program.
Optic Neuropathy:
Study Nix-TB was a Phase 3, open-label trial assessing the safety and efficacy of bedaquiline plus pretomanid plus linezolid in subjects with pulmonary infection of either extensively drug-resistant tuberculosis (XDR-TB) or treatment intolerant/non-responsive multi-drug resistant tuberculosis (MDR-TB). See Module 5.3.5.2.

Optic neuropathy is a known adverse effect of long-term use of linezolid. Trial procedures required repeated evaluations of visual acuity and color vision. If the Investigators detected a 2 or greater decrease in the lines read on the vision charts from baseline or a loss of 1 or more plates read accurately in color vision, they were to refer the patient to the trial center trial ophthalmologist for further evaluation.

Two optic neuropathy events in Study Nix-TB were considered serious, were confirmed on retinal examination as optic neuropathy/neuritis and resulted in discontinuation of linezolid; both events resolved. No subject was withdrawn from treatment in Study Nix-TB because of an event of optic neuropathy.

Reviewer’s Comments:
Optic neuropathy is a known adverse effect of long-term use of linezolid. The data submitted show no clinically meaningful effect of pretonamid on the potential for optic neuropathy at the doses and durations studied.

Questions/Requests:
1. Does the DTOP have additional comments that were not included in the prior consultations about pretomanid?

The data submitted show no clinically meaningful effect of pretonamid on the potential for cataract formation at the doses and durations studied. Ocular monitoring continues in the ongoing clinical development program.

2. Please provide any labeling recommendations that you think are warranted.

No recommended revisions to the labeling based on the currently available dataset.

3. We would like to request your presence at the Advisory Committee for NDA 212862 scheduled for June 5-6, 2019.

William Boyd, M.D., and Wiley Chambers, M.D. will attend the Advisory Committee meeting.
Summary/Recommendations:

1. Clinical studies with pretomanid exposure longer than 14 days have included visual acuity assessments, slip-lamp examinations, and AREDS-2 lens opacity scoring since July 2009. The data submitted show no clinically meaningful effect of pretonamid on the potential for cataract formation at the doses and durations studied. Ocular monitoring continues in the ongoing clinical development program.

2. Optic neuropathy is a known adverse effect of long-term use of linezolid. The data submitted show no clinically meaningful effect of pretonamid on the potential for optic neuropathy at the doses and durations studied.

William M. Boyd, M.D.
Clinical Team Leader
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/

WILLIAM M BOYD
06/05/2019 02:48:27 PM

WILEY A CHAMBERS
06/05/2019 03:50:18 PM
Date: 5 April 2019
To: Elizabeth O’Shaughnessy, MD, Medical Officer
Yuliya Yasinskaya, MD, Team Leader
Division of Anti-infective Products (DAIP), Office of New Drugs (OND)

Copy: Sumathi Nambiar, Director, DAIP
Gerald Dal Pan, Director, OSE
Robert Ball, MD, Deputy Director. OSE
Mark Avigan, MD, OSE

From: John R. Senior, MD, Office of Pharmacoepidemiology, (OPE)/OSE

Drug Name: Pretomanid, also referred to as PA-824
Dose/Formulation: Oral tablets, in combination with bedaquiline and linezolid
NDA Number: 212862
IND Number: 069580
Applicant/sponsor: TB Alliance (Global Alliance for TB Drug Development)

Issue: Reports of hepatotoxicity and hepatic deaths in patients treated with anti-tuberculosis regimen of pretomanid/moxifloxacin/pyrazinamide for pulmonary extensive drug-resistant tuberculosis

INTRODUCTION

A request for consultation was sent to Dr. Mark Avigan on 31 December 2018, shortly after receipt on 14 December by DAIP of a new drug application (NDA) 212862 for use of pretomanid to treat drug-resistant tuberculosis. Dr. Avigan had been consulting to DAIP since 2015 on PT-824 (pretomanid) under IND 69580, and he had written a review on 3 March 2016, in which he pointed out some of the hepatotoxicity problems in using combinations of pretomanid with moxifloxacin and pyrazinamide. On 10 January 2019 he asked me also to look at that consultation. My supervisor, Dr Robert Ball, asked me on that same afternoon to work on the pretomanid consultation, but to send acceptance immediately in order to join a conference call with DAIP scheduled for the next day, 11 January. I accepted and notified DAIP that I would do so and follow-up as quickly as possible. Although NDA 212862 was recent but of high importance, the IND (investigational new drug) 69580 application dates back to 2004 when correspondence began with Dr. Ted Murphy of Research Triangle International on 4 June, and Dr. Elizabeth O’Shaughnessy on 18 June began work for a pre-IND meeting scheduled for 5 August 2004 that led to subsequent submission of new IND 69580 on 27 April 2005. PA-824, had been first described in 2000 in Nature by a Seattle research group working at Pathogenesis Corporation, acquired later that year by Chiron, and later by TB Alliance, the sponsor of NDA 212862. The Seattle group described promising effectiveness in vitro against multi-drug-resistant Mycobacterium tuberculosis (MDR-TB). The IND submitter, TB Alliance, is a small, not-for-profit public-private partnership aimed at finding treatment for drug-resistant tuberculosis started in February 2000 in Cape Town, South Africa.

The consultation request of 31 December 2018 seeks expert opinion by 5 April 2019 about the hepatotoxic potential of pretomanid shown by submitted data, and on labeling recommendations. It also requests attendance at internal preparatory meetings and an Advisory Committee meeting 5-6 June 2019. Reports of liver toxicity and hepatic deaths with regimens including pretomanid, moxifloxacin, and pyrazinamide had led to clinical hold during the IND phase, removed when additional hepatic safety monitoring was implemented in ongoing clinical trials. Draft labeling is proposed, for dosing with oral pretomanid 200 mg tablets daily, bedaquiline 400 mg daily for two weeks then 200 mg three times/week, and linezolid 1200 mg daily, for a total of 26 weeks. The PDUFA goal date is 14 August 2019.

SPECIFIC ISSUES FOR THE CONSULTATION REQUEST

After initial intensive back-and-forth about what specifically was wanted to be reviewed, Dr. O’Shaughnessy on 26 February sent linkages to where the key data can be found and upon what to focus. They included:

1. Module 5, 5.3.5.2, sectio 8.3.3.4.4 Hepatic Disorders. Narratives are included for two patients, 02-9004-004 and 02-9020-018.  

Reference ID: 4433080
2. She also wrote “The IR went out on Feb 6th. We will ask the Applicant if they are on track to submit the the HEAC report in the first week of April.”

To me on 8 February, Dr. O’Shaughnessy wrote that to her the 3 main questions were:

- What is the hepatotoxic potential of the bedaquiline/pretomanid /linezolid regimen in the pivotal Nix-TB trial? (Your comment below on the safety of the regimen is noted).
- What is your opinion on the hepatotoxic potential of pretomanid based on the hepatic data the applicant submitted, i.e., their analysis of hepatic safety in section 2.7.4.11.3; eDISH/Hy’s law narratives in section 5.3.5.3, and the Nix-TB CSR Addendum in section 5.3.5.2.? [for example, the eDISH analysis identified 9 subjects in the integrated clinical database as meeting laboratory criteria for potential Hy’s law cases – your opinion on these cases would be greatly appreciated].
- Your recommendations on changes, if any, to the draft label that the applicant submitted?

With regard to the smaller studies, two phase 2 studies, CL-007 and CL-010, are relevant because they have data on pretomanid alone in patients. In these two studies, pretomanid was administered once daily for 2 weeks at doses ranging from 50 to 1200 mg. In both studies, a combination tablet containing isoniazid 75 mg, rifampicin 150 mg, pyrazinamide 400 mg, and ethambutol 275 mg (HRZE, trade name Rifafour e-275), dosed by weight) was used as a comparator. These two studies provide some evidence regarding the safety of pretomanid when used alone although the length of treatment was only 2 weeks.

She also wrote that the NC-006 trial (STAND trial), i.e., the study with the 3 hepatic deaths, provides background, but as we know the regimen was different in this trial – pretomanid/moxifloxacin/pyrazinamide (PZA). Which drug (PZA? or moxifloxacin? or both?), or pretomanid? or a combination of drugs caused the dramatic rise in hepatic transaminases around Week 3 that led to the deaths of three patients is still a question. [Your prior comments about about PZA as a probable culprit are noted].

She said she would discuss this further with Yuliya and send any further questions they have.

Note: I had replied by email earlier that afteroon of 8 February that I was impressed with the greater safety and efficacy of substituting linezolid for moxicfloxacin and pyrazinamide, and the possible effects of better absorption and delivery to the lungs, bypassing liver initially.

On 26 February, Dr. Yuliya Yasinskaya wrote to me, saying:

We wanted to check with you whether you have everything you need to complete your review on the potential for hepatotoxicity with pretomanid alone and in combination with bedaquiline and linezolid. It would be very helpful to have a bulleted summary review update from you prior to our midcycle meeting scheduled for March 18, 2019, so it is available to the review team at the meeting. Thank you very much! Yuliya Yasinskaya’

BACKGROUND

Pretomanid was developed and reported\(^1\) by 2000 by investigators at the Pathogenesis Corporation in Seattle WA, with contributions from several academic investigators. The story goes even farther back to about 1993 when William Baker and Ken Stover first saw the structure of CGI 17341, a lead antitubercular compound from Ciba-Geigy. Their aim was to find new drugs that were active against replicating M. tuberculosis, for which they investigated a series of compounds originally developed as cancer chemotherapeutic agents. Out of a class of bicyclic nitro-imidazo-furans, a lead anti-tubercular compound was mutagenic, but Baker from the National Institutes of Health (NIH) found that out of 328 3-substituted nitro-imidazo-pyrans (NAPs) there were 100 with antitubercular activity with as more or greater effect that the lead nitro-imidazo-furan had but without the mutagenicity. Among these NAPs, one compound they called PA-824 showed inhibitory effects at sub-micromolar concentrations against multidrug-resistant M. tuberculosis and promising activity when given orally in animal infection models. Shortly after publication of the Nature article\(^1\), Chiron Corporation acquired PA-824 and then licensed its development to the Global Alliance for TB Drug Development (TB Alliance). Baker said, “This is the first drug that can kill both replicating and dormant phase TB, and now it’s about to be tested in humans It’s gone down a long road from our work in the early 1990s.”

The TB Alliance is a not-for-profit partnership dedicated to discovery and development of new, faster-acting, and affordable medicines for treating tuberculosis, founded in South Africa in 2000. Tuberculosis was said to infect almost a quarter of the world population, kills approximately 1,600,000 people annually, costing the world economy over $16 billion each year. The Alliance states that the TB drug market lacks sufficient financial incentives for a single private pharmaceutical company to invest in the research needed, because TB is prevalent mainly in poor people in developing countries in Asia, Africa, and South America. The TB Alliance was designed to operate as a virtual biotechnology firm, sharing risks and incentives with many research institutions and pharmaceutical companies. It was agreed at Cape Town, South Africa that new treatments found would have to be affordable and accessible in the developing world, and that they be adopted as soon as they became available. Tuberculosis has become resistant to many drugs serially, to various combinations of drugs, and now infects millions of patients resistant to all drugs and combinations available. Since discovery of isoniazid (INH) and other agents against tuberculosis in the past half-century or so, drug after drug has become resistant, and more and more combinations are being tried.

As a result of this experience, the finding of pretomanid may be of particular interest, as indicated by the submission of this NDA 212862, based upon a modest number of patients treated in clinical trials. There seems to be little value in repeating what Dr. Avigan...
has already pointed out in his previous response to request for consultation to IND 69580 of 23 October 2015 that was submitted to DARRTS on 3 March 2016 by Karen Townsend. He reviewed findings of clinical trials NC-005 and NC-006 using the combination of moxifloxacin (Moxi) and pyrazinamide (PZA) with or without pretomanid in NC-005 and Moxi, PZA, and PA-824 (pretomanid) in NC-006. In similar groups of patients in Africa. The results were evaluated by academic consultant Paul Watkins, who is very well known to both Dr. Avigan and me, who suspected that the most likely culprit for the hepatotoxicity of the regimens was pyrazinamide, which was common to all regimens that were injurious to the livers of patients. Dr. Avigan concluded with a list of challenges for the sponsor, to be sure that patients had timely access to hospital care if needed, the removal of delays in obtaining serum samples for liver tests, need for on-site assessments by physicians with hepatology experience, and follow-up of patients.

Drs. O’Shaughnessy and Yasinskaya, working closely together, have offered several key suggestions to the sponsor recently, after partial clinical hold was imposed following the alarming results of the STAND trial NC-006 in which three patients died because of probable drug-induced liver failure after a regimen with pretomanid, moxifloxacin, and pyrazinamide. They helped the sponsor with design of the pivotal Nix-TB clinical trial in which bedaquiline and linezolid were substituted for moxifloxacin – pyrazinamide, and the ZeNix trial to optimize linezolid exposure in a series of communications 21 August 2016, 9 May 2017, and 19 December 2019 toward the decision by the sponsor to submit NDA 212862 on 14 December 2018. As emphasized to me by Dr. O’Shaughnessy (see above under Specific Issues for this consultation request, let us look at the two cases of possible drug-regimen-induced liver injury that were considered potentially serious, and the ten other cases that showed only serum transaminase elevations, using the eDISH program.

The TB Alliance submitted this application on 14 December 2018, requesting priority review, as agreed to in the pre-NDA meeting minutes, a request for exclusivity for 7 years based on orphan drug status, and a 5-year extension based on a qualified infectious disease product (QIDP), with exemption from the user fee based on orphan status. Based also on the orphan status, no pediatric assessment was included, and no proprietary name assigned, intending sale of the product under its established name, pretomanid. TB Alliance authorized contract research organization, Rho Inc., to interact with FDA on their behalf through David Shoemaker, PhD, Senior Vice-President, Research and Development at 919-595-6340 or david_shoemaker@rhoworld.com.

**Pivotal Study Nix-TB** Study Nix-TB, termed the pivotal study for NDA 212862, is a phase 3, open-label clinical trial to assess safety and efficacy of oral pretomanid, bedaquiline, and linezolid for treating patients with pulmonary extensively drug-resistant tuberculosis (XDR-TB) or treatment-intolerant, multidrug-resistant tuberculosis (MDR-TB). The dosing was bedaquiline 400 mg daily for two weeks, then 200 mg three times/week on alternate days for 26 to 39 weeks; pretomanid 200 mg daily for 26 to 39 weeks, and linezolid 600 mg twice daily, for 26-39 weeks in South African patients aged 14 and older. The study of BPaL had been planned in 2015 to lift the clinical hold imposed after the alarming results of study NC-006 (STAND, as mentioned above, to enroll up to 200 patients, but that was cut to 109 who could complete 9 months by 15 November 2017. Sites for the Nix-TB Rescue Study in South Africa were Durban, Sizwe, and Brooklyn Chest. It may be seen in the eDISH graph below that two subjects had peak values of serum ALT >3 ULN and TBL >2x ULN, and 10 more had elevated ALT peak values only, during their treatment courses.

![Graph showing peak ALT and TBL values](image-url)
Dr Guo separated subjects into two groups, -182 and -274, based on the length of treatment (days), and indicated by different symbols, red triangles of -182 and green circles for -274, approximately ly 6 or 9 months. Two subjects in the right upper quadrant were of special interest, because they showed serum total bilirubin indicating possible reduction in overall liver function (clearance of bilirubin from the circulation and excreting it in the bile).

The eDISH program consists of three steps, the first an overall look at all the subjects in a given trial or set of trials to find any of special interest with respect to liver injury that might have been caused by the drug in question, here pretomanid. There may of course have been many other possible causes for increased serum ALT and TBL that would have to be considered. The second step of the eDISH program is aimed at clarifying the tim-course of the events that might have caused the effects, and third step a summary of the history, physical findings and laboratory data to establish the likelihood of causality, using the medical differential diagnostic process (not a frequentist statistical process). It is intended to gather and use information the way a medical doctor does, to make the most accurate diagnosis of cause so that appropriate treatment can be prescribed. Statisticians are not empowered by society or law to make such decisions, and the process of medical differential diagnosis is learned in medical school and subsequently improved in medical practice for a lifetime. The eDISH program was developed in 2002-3 and aimed at providing the medical reviewers of FDA/CDER, particularly OND, to avoid approving new drugs that might cause serious, disabling or life-threatening liver injury in some patients to whom it was given. For drugs given in combination, such as the regimen of pretomanid, bedaquiline, and linezolid, there are of course eight possibilities:

- any one of the three drugs alone, (Pa, B, or L) might be causal;
- any of the three possible pairs (Pa-B, Pa-L, or B-L),
- all three together: (Pa-B-L),
- or none of them and some other cause, such as viral, alcoholic, or ischemic hepatitis, or other possible causes.

This is very difficult or impossible to do in a relatively small study of only 109 subjects. Let us see what information we do have by looking at all of the 12 subjects individually who showed at some time during their exposure to the BPaL regimen elevation of their serum transaminases above three times the upper limit of normal (>3xULN). There were 12 such subjects, 2 in the right upper quadrant who also showed increases in serum total bilirubin above 2xULN and 10 who didn’t in the lower right quadrant. The two major laboratory measures are taken as the most sensitive known indicators of hepatocellular injury serum activity of alanine aminotransferase (ALT), and the specific measure of overall liver function of clearing bilirubin from the circulation, serum concentration of total bilirubin. The liver is the only organ in the body that can remove bilirubin from blood and excrete it into the bile and thence to elimination in stools. The eDISH program, first step, therefore is a screening measure of both sensitivity and specificity for consideration of all the subjects treated in a given clinical trial. It does not diagnose why the measures are elevated in any particular subject. That is a matter for careful consideration of the individual persons whose values are being considered, and it requires a great deal more information that includes past medical history, symptoms and clinical findings, other medications or substances to which they have been exposed. Infections, circulatory disturbances --- as obtained by a trained and experienced physician when evaluating the case. This requires a developed clinical narrative. Such narratives were provided for initial eDISH analysis only for the two subjects in the right upper quadrant, but they have been sought subsequently for the ten in the right lower quadrant.

The first subject,
This 25-year-old black male participant was participating in a Phase 3 open-label trial assessing the safety and efficacy of bedaquiline plus PA-824 plus linezolid in participants with pulmonary infection of extensively drug resistant tuberculosis (XDR-TB) or treatment-intolerant non-responsive multi-drug resistant tuberculosis (MDR-TB) and developed elevations of ALT or AST > 3 X ULN and Bili > 2 X ULN. Medical history: This participant was initially diagnosed with drug sensitive TB on an unknown date in [b] (6) . Later cultures confirmed MDR-TB on [b] (6) and he was changed to an MDR regimen. His sputum results showed Pre-XDR on (amikacin resistant, ofloxacin sensitive). He failed to maintain culture conversion and was labelled a treatment failure. On [b] (6) , he was diagnosed with XDR-TB. He was admitted to the local TB hospital and started XDR treatment. He later absconded from hospital on an unknown date in [b] (6) . He returned a year later [b] (6) and was readmitted with ongoing XDR TB (based on a sputum result from [b] (6) ). Spontaneous pneumothorax occurred [b] (6) and resolved. Referred to [b] (4) for screening for the Nix-TB trial on an unknown date in [b] (6) He was consented on the NIX trial on [b] (6) while an inpatient at the local TB hospital. He started treatment including bedaquiline, linezolid and pretomanid on [b] (6) H e culture converted on [b] (6) on sputum (week 4) and completed trial drug regimen on [b] (6) . While on NIX treatment he developed some mild adverse events including nausea, vomiting, swelling and itching of the right eye, bilateral optic disc swelling and multiple respiratory tract infections all of which resolved uneventfully. Elevated Liver Enzymes: The participant experienced one Grade 3 (severe) adverse event (AE) of elevated liver enzymes termed by the Investigator “drug induced liver injury” which started on [b] (6) , his week 8 visit on trial. The abnormal aspartate aminotransferase (AST) and alanine aminotransferase (ALT) results flagged on [b] (6) and the Investigator requested repeat LFT’s. Participant noted to be asymptomatic with normal abdominal exam on this day; however, had intermittent complaints of nausea. On [b] (6) , Sponsor contacted the site regarding an abnormal bilirubin result, these were not flagged in the alerts and had not been received on site due to a delay in the reporting of the results from the trial lab. The participant was reviewed at site. After discussion with the Investigator, urgent blood and urine tests were sent via [b] (4) including a hepatitis screen, INR and urine drug screen. The results were negative for hepatitis B and C, the INR was mildly elevated from baseline 1.28 (0.8-1.2) at a value of 1.5 (0.9-1.3) and the u rine drug screen was negative for cannabinoids, opiates, bendodiazepines, barbiturates, amphemamines, cocaine, methadone and mandrax. The participant had a history of alcohol use prior to enrolling to the trial. The amount used was not quantified in source. No alcohol or herbal medicine use was reported while on trial. Concomitant medications used within 1 month prior to the onset of the AE included pyridoxine and metoclopramide. Pyridoxine was started on [b] (6) for the prevention of peripheral neuropathy and stopped on [b] (6) . Metoclopramide was started on [b] (6) for the indication of nausea, just prior to the onset of the drug induced liver injury and stopped unknown day in [b] (6) . Trial drug regimen was stopped on [b] (6) due to the event of drug induced liver injury and treatment was restarted on [b] (6) as per Investigator’s decision. At the participants next visit at week 9 [b] (6) , he reported nausea (first episode, from [b] (6) to unknown date in [b] (6) ) and second episode from [b] (6) to [b] (6) . He had developed a moderate anaemia on bloods drawn at this visit with an Hb of 8.6 g/dL (13-7.5 g/dL). After his week 11 visit on [b] (6) , and on review of his blood results, his trial drug was restarted on [b] (6) with a reduced dose of linezolid of 600 mg once daily due to anaemia. At his week 12 visit [b] (6) the AE of “drug induced liver injury” had resolved. By week 13 his haemoglobin had improved and linezolid dose was increased to 600 mg twice daily. The total bilirubin returned to normal at week 12 [b] (6) and remained within normal ranges until the end of treatment visit on [b] (6) . The ALT result was normal at the week 20 visit [b] (6) and remained normal until the end of treatment visit on [b] (6) . The AST result was normal at the week 26 visit [b] (6) and remained normal until the end of treatment visit on [b] (6) . He completed the final trial visit (month 24) on [b] (6) , all AEs resolved. The results of the ALT, AST and Total Bilirubin over time are graphically displayed in the full narrative, which also provides tabular listings of liver function test results and key demographic data for the participant. Sponsor’s Differential Diagnosis: This participant had a progressive increase in ALT, AST, Bilirubin and Alkaline Phosphatase from week 6 through week 10 after beginning trial medication. Screens for Hepatitis B and C were negative and a screen for drugs of abuse were negative. Alcohol use may have contributed to the hepatic laboratory abnormalities, given the prior history of alcohol use and the elevated GGT. A contribution from local remedies or unknown toxins as causes cannot be ruled out. The picture of hepatic enzyme rises with bilirubin, but also with alkaline phosphatase, along with a very rapid resolution of these abnormalities, suggests an obstructive picture, such as possibly by biliary stones that passed. The decrease in abnormalities coincides with the interruption of trial drug regimen. However, there was no further abnormality after trial drug was resumed and continued for the remaining 4 months of dosing, and thus it is unlikely that the trial drug caused the hepatic laboratory abnormalities.[END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] [END / [971 words] This reduction in length of the narrative, without loss of essential diagnostic information, indicates that all narratives are not the same, and that it requires special skills to write an informative but concise description of the patient. That is taught and learned gradually by
It must be emphasized that the DISH program has never been made public nor provided to be used by anyone outside the FDA. The initial screening graph has been widely copied and used incorrectly to “diagnose” DILI, which it does not do. The diagnosis of causality by the drug requires a different and non-frequentist approach more like that which physicians use when making diagnoses and acting upon them. Efforts to revise the program and allow it to be used by industry and others in general will require resolution of possible security issues involving access to confidential data.

Subject

Patient Narrative

This 36 year-old mixed race female participant participated in a Phase 3 open-label trial assessing the safety and efficacy of Bedaquiline plus PA-824 plus linezolid in participants with pulmonary infection of either extensively drug-resistant tuberculosis (XDR-TB) or treatment intolerant/non-responsive multi-drug resistant tuberculosis (MDR-TB) and the participant experienced worsening epigastric pain and was also diagnosed with pneumonia. The participant’s medical history provided by the Investigator included an original diagnosis of MDR-TB on and then XDR-TB diagnosed on , uncoded intermittent anxiety since an unknown date in insomnia since an unknown date in chronic obstructive airways disease since and dyspepsia since . The participant is human immunodeficiency virus (HIV) negative. Concomitant medications for the treatment of tuberculosis prior to enrollment included moxifloxacin, terizidone, pyrazinamide, isoniazid, ethambutol, para-aminosalicylic acid, clofazimine, amoxicillin + clavulanic acid, kanamycin, and ethionamide. Other concomitant medications included: tropicamide, salbutamol, ibuprofen, paracetamol, oxyzometoline, lansoprazole, cyclizine, metoclopramide, boric acid, myroxylon balsamum + pereira balsam, hyoscine butyl bromide, pholcodine, antazoline + tetryzoline, lansoprazole, zolpidem, calamine, glycerol, ipratropium bromide, tramadol, triamcinolone acetonide, theophylline, pyridoxine, amoxicillin + clavulanate, and bromhexine oriprenaline sulfate. On , at Screening visit, participant’s smear tested positive for rifampicin resistance and for acid-fast bacteria (AFB) using Ziehl-Neelsen stain. On the same day, laboratory test results showed white blood cell count (WBC) 9.4 x 10^9/L (<33 x 10^9/L). On , the participant received her first dose of the trial drug regimen for MDR-TB in this trial. Sputum Mycobacteria Growth Indicator Tube liquid culture was positive, and AFB showed negative result. ZiehlNeelsen stain test was repeated which showed AFB negative result. The laboratory test results showed: WBC 9.7 x 10^9/L, alanine aminotransferase (ALT) 9 U/L (<33 U/L), and aspartate aminotransferase (AST) 20 U/L (<31 U/L). On (Day 27), the participant presented at her week 4 visit complaining of Grade 1 mild vomiting and Grade 2 moderate abdominal pain upper since . This was the first time she had reported these symptoms. The
the participant reported that the pain was associated with meals, and she had decreased her oral intake because of it. The participant described the pain as severe, with no diarrhea noted. Examination of the participant revealed epigastric tenderness, with mild guarding and no rebound. She did not have bruising or back pain and was not jaundiced or pale. The participant had a mild tachycardia of 105 beats/minute (bpm), but other vitals were within range of her baseline visit. The laboratory test results showed: WBC 7.8 x 10^9/L, ALT 14 U/L and AST 21 U/L. The Investigator suspected severe gastritis, but sought to exclude other organ involvement, particularly pancreatitis. On (Day 31), the participant started treatment with lansoprazole 30 mg orally, paracetamol 1 g orally, and cyclizine 50 mg orally. Clinically, the pain had improved, and she tolerated oral fluid intake. She returned to the ward to continue her symptomatic treatment. On (29) the Investigator reported that an examination showed decreased pain and tenderness in the epigastrium, and treatment was continued. On (29) in the morning, the participant reported that she was too weak to attend her follow-up visit. The Investigator went to the ward to see her and noted she had no further vomiting, but that with oral intake her epigastic pain recurred and had worsened from the previous day. She also appeared pale, with dry mucous membranes compared with the previous day and no jaundice was noted. The participant’s vitals showed blood pressure 119/81 mmHg, pulse rate 100 bpm, respiration rate 34 breaths/minute, and temperature 35.9 degrees C. An abdominal examination revealed no distention, markedly more epigastric tenderness with localized guarding in the epigastrium. The rest of the abdomen was soft, no diarrhea, melena stool or rectal blood was reported. She was started on intravenous infusion (IVI) rehydration and repeat blood samples were taken. Considering her worsening symptoms, the event of worsening epigastric pain was considered severe in severity and reported to Sponsor as a serious adverse event (SAE), the trial drug regimen was interrupted. According to local laboratory result, her potassium was concerning, at 5.9 mmol/L (3.5-5.1 mmol/L). Her continued treatment in the ward was nil per mouth, IVI saline (1 L, every 8 hours) and symptomatic treatment with lansoprazole and paracetamol. The participant had no oral intake except for clear fluids to moisten mucous membranes and oral medication. The participant was moved closer to the nursing station for closer monitoring by the nurses. On (30), the participant showed improvement over the previous day. She did have some vomiting overnight but tolerated her IVI fluid well. On examination, the participant’s vitals were stable, her respiratory rate improved from 34 bpm to 26 bpm. Her abdomen was still tender in the epigastrium; however, repeat electrolytes showed her potassium was no longer elevated. On (31), the participant showed a continued improvement in epigastric pain; however, still had some nausea. Treatment with IV fluid was stopped and oral fluid intake was encouraged, and diet introduced to monitor for recurrence of symptoms. On (34), a visit at week 5 revealed residual but improving epigastric tenderness still associated with pain. The participant’s WBC count was 9.0 x 10^9/L. The SAE was considered resolved in retrospective review of symptoms on the same day. On (30), a review visit revealed much improved epigastric pain, tolerating bland oral intake, and symptom relief due to treatment with lansoprazole 30 mg. The blood test results were normal or near baseline values. The trial drug regimen was reintroduced, with linezolid reduced to 600 mg once daily (QD) (preventing another a diverse event of progressive peripheral neuropathy symptoms) and no dosage adjustment of Pa-824 nor bedaquiline. The Investigator confirmed that an endoscopy had not been carried out for the assessment of the SAE. Note: The SAE of epigastric pain was resolved on (31). The following information were added into the case by the Sponsor as the site reported a non-serious adverse event of abdominal pain shortly after the resolution of abdominal pain upper. The Sponsor also noticed the liver enzymes were elevated later into the treatment course, with ALP and gamma glutamyl transferase (GGT) significantly elevated. The elevations of the liver enzyme were not correlated with the administration of the trial drug. As epigastric pain is quite non-specific, the Sponsor added the following information with the intention of providing more clinical information as to better understand the case. On (6), laboratory test results showed WBC count 9.4 x 10^9/L, ALT 46 U/L, and AST 78 U/L. On (43), another event of Grade 1 abdominal pain was reported. The participant was treated with lansoprazole, scopolamine butylbromide (Buscopan), and magnesium trisilicate/magnesium carbonate (Magasil). On (43), the trial drug regimen was stopped again due to the abdominal pain. Over the weekend of the participant admitted she had consumed alcohol in the form of one a half beers. No further information is available regarding the participant’s alcohol consumption history. On (6), an abdominal ultrasound showed no features of TB, no biliary duct dilation or focal liver lesion. Abdominal CT scan was deferred in view of normalizing liver function tests and a normal abdominal ultrasound. On (6), the trial drug regimen was reintroduced. On (6), the trial drug regimen was stopped again due to liver enzymes increase. On (6), the trial drug regimen was reintroduced. A table of key liver function test results is provided in the full narrative. On an unknown date in (6), the abdominal pain resolved. On (6), linezolid dose reduced to 300 mg QD due to peripheral neuropathy, bedaquiline and PA-824 were not impacted. On (6), linezolid was stopped due to the worsening sensory peripheral neuropathy, bedaquiline and PA-824 were not impacted. On the same day, ALT was 26 U/L and AST was 27 U/L. A graph of the participant’s hepatic laboratory test results over time is presented in the full narrative. On (81), Sputum Mycobacteria Growth Indicator Tube liquid culture was negative. On (Day-241), the participant completed her treatment. On the same day, WBC was 9.9 x 10^9/L. The Investigator reported that the participant was fully compliant with trial treatment and visit attendance, except one missed appointment when the participant was away from hospital over a weekend (absconded without permission). The participant came to the site for a visit immediately upon return. Liver function tests were normal on (81) and CT scan was not performed. On (512), the participant developed productive cough (yellow). A non-serious event of lower respiratory tract infection (Grade 1) was reported as resolved. On (512), the participant developed a non-serious pleuritic chest pain (Grade 1). On (512) the participant changed medication to...
triamicinolone acetonide (Flutex) and theophylline syrup (Adco-alcophyllin) for lower respiratory tract infection and coughing, respectively. On (Day 515), the participant went to the day hospital. According to the participant, she was given oxymetazoline hydrochloride (Allergex) and hyoscine butyl-bromide (Buscopan) for abdominal cramps due to heartburn; non-serious adverse event of gastritis (Grade 1) was reported which started on an unknown date in (b) (6). On (Day 517), the participant presented for her month 9 follow up visit and was unwell, appearing pale and lethargic. On examination, she was tachycardic and had a temperature of 38.4 degrees C. The participant had a mild to moderate respiratory distress and new crepitations in the right mid and lower zones anteriorly on auscultation of the chest. Mild epigastric tenderness on palpation of the abdomen was present. A chest X-ray showed old cavities in the right lung and new patchy opacification in the right mid lobe zone. The Investigator’s assessment was that of pneumonia (Grade 2) with mild to moderate respiratory distress with a background history of chronic obstructive lung disease due to TB and mild gastritis. The Investigator referred the participant to her local hospital for further assessment and management of pneumonia. On at 17:33, an electrocardiogram (ECG) was abnormal showing sinus tachycardia, a left axis deviation, QRS 84 ms, QT/QTcBaz 296/411 ms, PR 118 ms, P 88 ms, RR/PP 518/517 ms and P/QRS/T 22/30/39 degrees. Blood results (at 18 :10) showed hemoglobin 10.8 g/dL (12.0-15.0 g/dL), red blood cell count 3.70 x 10^12/L (3.80-4.80 x 10^12/L), platelet count 547 x 10^9/L (186-454 x 10^9/L), WBC count of 22.74 x 10^9/L (3.90-12.60 x 10^9/L), C-reactive protein 364 mg/L (<10 mg/L), hematocrit 0.316 L/L, mean cell volume 85.4 fl., mean cell hemoglobin 29.2 pg, mean cell hemoglobin concentration 34.2 g/dL, red cell distribution width 12.3%, sodium 132 mmol/L, potassium 4.5 mmol/L and urea 1.7 mmol/L, which suggested an infective process. Other laboratory tests showed creatinine 39 umol/L and estimated glomerular filtration rate (Modification of Diet in Renal Disease formula) greater than 60 mL/min/1.73 m². Additional laboratory results at 18:27 showed sodium 134.8 mmol/L, potassium 3.32 mmol/L, chloride 87.9 mmol/L. Blood arterial gas showed PCO2 (T) (partial pressure of carbon dioxide) 5.17 KPa, PO2 (T) (partial pressure of oxygen) 9.0 KPa, HCO3 (bicarbonate) 25.9 mmol/L and SBC (standard bicarbonate concentration) 25.9 mmol/L, FIO2 (fraction of inspired oxygen) 21%, pH was 7.432. On the Investigator contacted the hospital and was informed that the participant was admitted to the female medical ward. Blood cultures showed no growth. The participant responded significantly to oral amoxicillin/clavulanic acid (Augmentin). On , the participant was discharged and was referred to the Investigator for follow-up. Discharge medication included paracetamol 1 g orally every 4 hours for 1 week and amoxicillin + clavulanic acid (Co-amoxiclav) 1 g orally twice a day for 3 days. No further follow-up was scheduled. The event community acquired pneumonia was reported as resolved on . The abdominal pain upper event occurred 26 days after the first dose of the trial drug regimen. The event improved and then gradually resolved with trial drug interruption and symptomatic treatment. Linezolid is known to cause abdominal pain/distention. Another non-serious abdominal pain event occurred after the trial drug regimen was reintroduced. With symptomatic treatment, abdominal pain seemed to be resolved while linezolid dose was reduced to 300 mg QD and other trial drugs (bedaquiline and PA-824) were ongoing. Abdominal ultrasound did not reveal abnormal finding. In summary, based on the available information, the contributory role of trial drug regimen (with a focus on linezolid) could not be excluded. The event of abdominal pain upper was considered unexpected for all drugs in the trial drug regimen. The event of pneumonia occurred about 9 months after completion of trial treatment. The participant’s underlying chronic obstructive lung disease due to TB increased her risk for pulmonary infection and the concurrent infection could be the possible cause of the reported event. There was no convincing evidence identified in supporting potential trial drugs induced effects. Tabular listings of key demographic characteristics, adverse events, and relevant clinical chemistry test results for the participant are presented in the full narrative. Investigator Judgment on Relatedness Event#1: Abdominal pain upper: The Investigator considered the event of abdominal pain upper as possibly related to the investigational trial drug regimen. Sponsor Judgment on Relatedness Event#1: Abdominal pain upper: The Sponsor considered the event of abdominal pain upper as possibly related to the trial drug regimen and considered unexpected for all drugs in the trial drug regimen. Sponsor’s Differential Diagnosis of Hepatic Laboratory Abnormalities: This participant had initial symptoms of abdominal pain which resolved on Day 34, prior to an elevation in hepatic enzymes and bilirubin which peaked at approximately week 10. When ALT/AST/total bilirubin were elevated, GGT and ALP were also elevated. This suggests a potential picture of cholestasis or potential hepatic obstruction rather than a primary drug induced liver injury. The participant admitted alcohol use while out of the hospital on pass and the elevated GGT suggest that the toxic effects of alcohol may have contributed to the abnormalities. Furthermore, the elevated enzymes and total bilirubin came back to normal or near normal while the participant was still on trial drug treatment, making it unlikely that the investigational drug regimen was the cause of the hepatic laboratory abnormalities. Investigator Judgment on Relatedness Event#2: Pneumonia: The Investigator reported that the event of pneumonia was unrelated to the trial drug regimen. Sponsor Judgment on Relatedness Event#2: Pneumonia: The Sponsor also assessed the event of pneumonia as unrelated to the trial drug regimen. The causal relationship between trial drug regimen and the reported event cannot be established. The event of pneumonia was unexpected for the trial drug regimen.[END]

This even more lengthy narrative (2445 words) can be condensed to:

A mixed-race female aged 36 had a history of intermittent anxiety, obstructive lung disease, and HIV that was treated with tropicamide, salbutamol, ibuprofen, paracetamol, oxymetazoline, lansoprazole, cyclizine, metoclopramide, boric acid, myroxylon and coughing, respectively. On (Day 515), she was started on BPaL on (Day 1). On (Day 29) she...
complained of vomiting and anorexia after three days of moderate to severe epigastric pain, associated with meals. She showed tachycardia 105/min and epigastric tenderness, and was started on lansoprazole, paracetamol, and cuelzine, the BPaL interrupted. She improved by_dat [35] and BPaL restarted, but pain recurred [35] (Dat 43), and BPaL again was stopped for what was termed gastritis. The patient later admitted she had been drinking beer on the weekend of [35] (Day 58) but stopped again on [35] (Day 73) because of serum ALT increase that subsided and she restarted BPaL on [35] (Day 86). Because of peripheral neuropathy, linezolid dose was reduced to 300 mg daily on [35] (Day 141), then stopped on [35] (Day 181), when it was noted her sputum culture for TB was negative. She completed treatment [35] (Day 251) and entered follow-up. She developed pneumonia [35] (Day 517), successfully treated in hospital with amoxicillin. [274 words]

Comment: In this case, the narrative provided was repetitious and lengthy, and the necessary information could be extracted with far fewer words. The narratives provided were apparently not written by a physician experienced in making medical differential diagnoses. Critical elements in narratives should include medical history of illnesses and drugs to which the patient was exposed and why. It is important to know whether the sputum culture was made negative and when, and if patient improved as a result. Even a follow-up weight at the end of treatment would be of interest.

Other cases: Elevated serum transaminases without significant bilirubin increase on treatment

The ten patients who did not have elevated TBL had no narratives provided for eDISH analyses. Search of the submission shows that at least brief narratives were submitted elsewhere for five of them, including [35] and [35]. The other five were requested from the sponsor on 18 March and received on 26 March. Let us look at what the sponsor has and will report, and again see if the narratives are helpful in making a diagnosis of what most likely caused to liver test elevations. In this section, I shall not print out the lengthy “narratives” submitted that in several cases included many pages of numbers for dates and tests done, which are more concisely presented in the eDISH time-course graphs, but links to the full submitted narratives will be available as links for persons at the FDA or TB Alliance who have allowed access to that confidential information.

The patient below [35] was a male aged 23 with body mass index of 24.8, XDR TB since [35] started on BPaL on [35] (Day 1) but negative sputum culture. His medical history included gynecomastia, increased transaminases, hematemesis, seizures, unilateral cavities on chest x-ray, mild chest pain and excessive sweating. He had previous spuera positive for TB but had been treated with terizidone, pyrazinamide, levofloxacin, par-aminosalicylate, clofazimine, ethambutol, amoxicillin/clavulanate, and azithromycin before the BPaL regimen was begun. Sputum cultures were consistently negative during this trial until completed on [35] (Day 187).

The patient below [35] was a 38-year-old Black female, HIV-positive, with XDR TB since [35] started on BPaL on [35] (Day 1) but negative sputum culture. Her medical history included gynecomastia, increased transaminases, hematemesis, seizures, unilateral cavities on chest x-ray, mild chest pain and excessive sweating. He had previous spuera positive for TB but had been treated with terizidone, pyrazinamide, levofloxacin, para-aminosalicylate, clofazimine, ethambutol, amoxicillin/clavulanate, and azithromycin before the BPaL regimen was begun. Sputum cultures were consistently negative during this trial until completed on [35] (Day 187).

![Time Course of Liver Tests](image)

The patient below [35] was a 38-year-old Black female, HIV-positive, with XDR TB since [35], hepatitis B-positive, complaining of hearing loss, constipation, hot feet, found to have anemia and lymphopenia, but denied alcohol use. She had been treated for resistant TB with kanamycin, ethionamide, terizidone, moxifloxacin, and pyrazinamide before being started on BPaL on [35]. On [35] (Day 19 of BPaL treatment) L was interrupted because of peripheral neuropathy. On [35] (Day 41) she was found to have elevated serum amylase values that persisted and abdominal ultrasound on [35] (Day 65), confirmed and suggestive of pancreatitis. Concurrent elevation of ALT and TBL occurred, subsided. Linezolid was restarted at 600mg daily on [35] (Day 98) but serum amylase and ALT again rose and all trial drugs were stopped [35] (then Days 100-106). She completed her 6-month trial of BPaL on [35] (Day 206). During the follow-up period she had a seizure while at home on [35] Day 2090 another on [35] (Day 278), investigation of which by magnetic resonance imaging revealed a right
temporal lobe tuberculoma that was biopsied and excised (Day 380). Sputum cultures for TB converted from positive initially to negative from (Day 24) to (Day 456).

The patient below, , was a Black female aged 20, body mass index 22.5, who started BPaL on , completed   She had been diagnosed with drug-sensitive TB in , the XDR  after failure of kanamycin, moxifloxacin, ethionamide, teridizone, pyrazinamide, ethambutol, capreomycin, linezolid, amoxicillin/clavulanate, azithromycin, levofoxacin, para-aminosalicylate, and clofazimine. Sputum culture had been positive on , resistant to isoniazid, rifampin, kanamycin, and ofloxacin but negative just before starting BPaL on  Her history also included right-sided lung cavities by x-ray, deafness, oral condyloma latum, anogenital warts, intermitteny mild parathesia, hypothyroidism, astigmatism. At start of BPaL she reported tiredness and weakness.
Subject was a Black male, 35, body mass index 21.5, started BPaL on . His medical history included constipation, skin hyperpigmentation, unilateral deafness, cerebrovascular accident, vomiting, pleuritic pain and hemoptysis from . Medications taken within 30 days before the trial regime included codeine, clofazimine, cyclomydril, Dumiva, Aluvia, Truvada, Tazocin, Maxolon, lactulose, nevirapine, normal saline, Panadol, isoniazid, ethambutol, ethionamide, levofloxacin bedaquiline, pyrazinamide. He was noted to have elevated serum gamma-glutamyl-transferase when starting treatment, thought to be unrelated to the study regime. On treatment, serum transaminases increased on , with rise in bilirubin within the normal range. The BPaL treatment was interrupted , and again because of the transaminases increase. He completed the treatment on , and he gained 8 kg of weight.
This subject, a thin (BMI 18.1) Black woman aged 31, was started on BPaL on . Her medical history included bilateral deafness since , osteoarthritis since  and peripheral neuropathy since . She tested negative for HIV. MDR TB was diagnosed  and XDR TB on . Medication taken within 30 days before starting the study regimen included pyridoxine, isoniazid, para-aminosalicylic acid, clofazimine, mydriacyl, petogen, spersallerg, ethambutol, moxifloxacin, teridizone, and pyrazinamide. She showed a peak ALT of 112 (3.4 times the ULN of 33) about 8 weeks after starting the regimen, but the elevated values fell back to normal despite continuing drug treatment, . No serum bilirubin increase was noted. and she completed the treatment on (Day 183), and outcome was judged favorable
and on her Hb was 9.7, the acidosis was decreasing, and she felt better. She was restarted on B and Pa, with reduced L, given paracetamol and tramadol for peripheral neuropathy. She continued to improve, and by had Hb10.6 g/dL, then up to 11.7 on . She was re-started on tramadol and paracetamol, and on (Day 111) her Hb was 12.4 g/dL. The investigator concluded that the gastritis, pancreatitis, and neuropathy were probably due to linezolid, and she completed the treatment course on (Day 195).

This patient was a Black male aged 21 of about normal body mass index (22.8 kg/m²) whose medical history included negative testing for HIV, treatment before starting BPaL only by pholcodine, and previous finding of drug-sensitive TB in MDR Tb since . He was started on BPaL on . At screening and start, he had slightly elevated transaminases (not shown in the eDISH graph) that peaked at 3.05xULN on (Day 40), then subsided to normal despite continuing the drug regimen. His treatment outcome was assessed as favorable.
Subject

This subject was not included in the eDISH analysis because his peak ALT reached only 2.95xULN, but a short narrative was provided by the sponsor nevertheless on 26 March 2019. He was a slightly overweight Black male aged 44 who was started on BPaL. His medical history included diabetes mellitus, hypertension and retroviral infection since an He was found to have tuberculous meningitis, skin hyperpigmentation, gastroesophageal reflux disease since , and increased serum amylase since . He was diagnosed with XDR TB on previous medications within a month of starting BPaL included enalapril, metformin, amlodipine, clofazimine, pyridoxine, Humulin, mydriacil, nevirapine, abacavir, lamivudine, paracetamol, isoniazid, para-aminosalicylic acid, ethambutol, etionamide, pyrazinamide, moxifloxacin. When examined on (87 Days prior to Screening), his sputum culture was positive, and four days later was reported as resistant to isoniazid, rifampin, ofloxacin, pyrazinamide, ethambutol, and kanamycin. His chest x-ray showed unilateral cavities consistent with TB, and he was mildly short of breath, had moderate chest pain, and felt tired and weak.

At screening and initiation of BPaL, his gamma-glutamyl-transferase was modestly elevated and rose further to peak at 6.9xULN on (Day 42) and 6.9xULN on (Day 137), never having normalized nor explained. His ALT rose slightly and peaked at 121 (2.93xULN) on (Day 42). BPaL treatment was interrupted through , then was resumed and continued without recurrence of transaminase rise for the treatment ending . The gamma-glutamyl-transferase activity resolved on (Day 391). Treatment outcome at one year was considered favorable, but TB reactivated on (Day 656).

Comment: The last sentence of this narrative should raise a warning flag! Reactivation of TB more than a year after completing a full course of the new BPaL regimen calls for inquiry and explanation. Was it a new reinfection or emergence of TB resistance? Will retreatment again “cure” his reinfection or not? Is this a first occurrence of TB resistance to pretomanid? The narrative submitted previous and found in section 16.5.1. did not mention the reactivation. The unexplained and persistent elevation of the gamma-glutamyl-transferase activity in this patient deserves investigation also, and immediately. Although the enzyme is present in many tissues, it is especially rich in the liver, but it is very unspecific. It has been well-established as a serum marker for alcoholic hepatitis, which should be considered. Was this man a secretive alcoholic, not admitting it when asked?

DEATHS

There were 8 deaths among the 109 subjects entered into Study Nix-TB. They are, listed in Table 14 of the NDA, with links to narratives and case report forms. In order of entry into the study, they were:

1) . A Black male aged 34, , who died (Day 35) of severe pulmonary and disseminated
TB;

2) A mixed race female 20, who died (Day 51) of upper gastrointestinal bleeding;

3) A Black female 31, who died (Day 35) of acute, severe worsening of pulmonary TB;

4) A Black male 35, who died (Day 53) of acute hemorrhagic pancreatitis and multi-organ failure;

5) A Black male aged 55, who died much later on (Day 486) of sepsis secondary to gangrene from peripheral vascular disease;

6) A Black male 34, who completed the study on (Day 369) of what was determined to be “natural causes”;

7) A mixed-race female 29, was treated for 11 weeks (to Day 76), and died (Day 93) of worsening pneumonia;

8) A mixed -race female 26, who died (Day 76) of septic shock secondary to pneumonia.

Comment: It is notable that none of these patients were diagnosed as having died of acute liver failure, or even with severe liver injury. Those who died early, within the first three months or so of treatment, may have been started too late for recovery to be possible, even if sputum conversion was achieved. This is perhaps inevitable in a study such as this when desperate measures are taken for desperate disease states. The two patients who died more than a year after treatment was started, (Day 486), and (Day 369), had other problems.

Consider the Drugs Administered in the Nix TB Study

- It was well established by Hyman J. Zimmerman in his two textbooks of 1978 and 1999. It has become clear that hat and numerous papers that drug-induced hepatotoxicity is a matter both of the drug administered and the susceptibility to the drug of the patient being treated. It has become clear that both factors must be considered, and each varies greatly. Some drugs are more likely to be toxic the more people than are other drugs, and some patient are more likely to be susceptible than are other people. When more than one drug is given in combination, the difficulty of determining which is probably causing the toxicity is much increased, by a power of 2 for each different drug. Thus, one drug alone can be compared to placebo, $2^1 = 2$. Two drugs can be given as both together, each of the two separately, or neither, $2^2=4$. For three drugs, they can be given together, each separately, or any of three pairs eliminating one of the three, or none, $2^3=8$. The worrisome STAND trial (NC006) done under IND 69580 but considered in this NDA 212862, had 3 deaths out of 284 patients studied on the three drugs pretomanid, moxifloxacin, and pyrazinamide. The chance of finding statistically significant differences in such small studies divided into 8 subgroups each is very re It is somewhat of a leap of faith to base an NDA using two new drugs replacing two others on such small numbers, but the striking difference in efficacy of the BPaL regimen compared to that of PaMZ, without obvious toxicity, justified the action by the sponsor.

Isoniazid

When isoniazid (INH) was found in 1952 to be the first drug in history to have powerful and specific antibacterial activity in vitro and in vivo against M. tuberculosis, it was world news. This was immediately confirmed by others (Domagk and Bayer), but the first reports of hepatotoxicity followed within a year, and many other reports soon followed, including fatal reactions. The history of isoniazid hepatotoxicity is well summarized in the excellent series called LiverTox, developed at NIH, freely available using any browser to access the web, and now including over 1100 drugs. Of even greater concern, resistance to isoniazid also followed, and although isoniazid (INH) is still a first-line treatment option, it is now administered in combination with other anti-TB agents. Nearly all the subjects among the 109 nported in the Nix-TB study had previously been treated with INH in combination with other agents.

Pyrazinamide

This drug is a synthetic pyrazine analog of nicotinamide introduced in 1955 but not widely used until 972. Common adverse effects include precipitation of gout attacks, photosensitivity anorexia and nausea, muscle pain, and skin rash, in addition to
liver toxicity used in combination with other drugs such as isoniazid or rifampin. It has been found to be a well-known cause of serious liver toxicity that may be fatal. As described in LiverTox, combination anti-TB therapy with pyrazinamide is associated with frequent transient moderate elevations of serum transaminases. Onset of hepatotoxicity is generally apparent only after 4 to 8 weeks of exposure, and sometimes may worsen after its administration is stopped. The pattern of injury is hepatocellular, but the mechanism is unknown. Because it is given with other agents, its contribution to hepatotoxicity is not entirely clear.

**Moxifloxacin**

Among the more recently developed antibacterial agents, moxifloxacin was approved in the United States in 1999 for treatment of a variety of infections causing respiratory tract infections such as pneumonia, bronchitis, sinusitis. It is a fluoroquinolone derivative that acts by blocking ability to replicate DNA by many bacterial species, such as Staphylococci, Klebsiella, Enterobacter, Bacillus anthracis, and Mycobacterium species. It does however cause adverse effects in some patients, including tendon rupture and tendonitis, peripheral neuropathy, hepatitis, *torsades des pointes*, psychiatric depression and hallucinations, uveitis, and other problems.

**Linezolid**

This relatively new antibiotic was discovered in the early 1990s at Upjohn (Now Pharmacia) as U-100592, an oxazolidinone agent effective against resistant Staphylococcus aureus and Enterococcus faecalis, approved for clinical use in 2000. It works by blocking initiation of protein production in Gram-positive bacteria such as streptococci, resistant enterococci, methicillin-resistant Staph. aureus and MDR-TB. It is thought to cause nerve damage, sometimes irreversible optic neuritis, bone marrow suppression, high blood lactate, headache, nausea, diarrhea, and rash. Its main use is for treating severe infections by aerobic bacteria that are resistant to other antibiotics, a sort of reserve antibiotic-of-drug-of-last-resort. It is also listed in LiverTox.

**Bedaquiline**

This drug was first described in 2004 at Janssen (part of Johnson & Johnson since 1961), after being in development for seven years, intentionally to be effective against M tuberculosis. It was approved recently for use in 2012 but only with other anti-TB agents. It is listed in LiverTox because of liver test abnormalities occurring on 8 to 10% of patients treated with drug combinations including bedaquiline. Its main use is for treating infections by aerobic bacteria. Johnson & Johnson sought accelerated approval of bedaquiline for treatment of *neglected disease* Common side effects include nausea, arthralgias, headache, chest pain, rash and QT interval prolongation but without sudden death. The liver test abnormalities are usually mild-to-moderate, asymptomatic, and reversible despite continued administration.

**Pretomanid**

This is the newest of the drugs and the focus for NDA 212862. It is the only drug for treating M tuberculosis that is not (yet?) listed in LiverTox. As noted by the Freston committee, no Hy’s Law case or serious liver injury has ever been seen or reported from pretomanid alone, but it is not to be given alone, which makes the question difficult to resolve. There were no cases of positive rechallenge, the strongest evidence supporting causality of hepatotoxicity by a drug, even though it is in disfavor because of published reports of danger when done carelessly.

**Strategy to Induce Patients to Accept and Use the BPaL Regimen**

As important as is finding a new effective and safe regimen of drugs, the problem of finding reliable methods or procedures to get the patients to use it. Experience has shown that many participate only for short periods, interrupt treatment, fail to finish the prescribed course. This idea needs considerable thought and discussion, and may be an unusual response to the specific questions posed about the hepatotoxicity of pretomanid. I offer the lipophilicity effect as a topic worthy of such discussion, consideration, and perhaps part of a plan for post-marketing study if DAIP decides to approve the NDA now.

**LIPOHILIC EFFECT**

The tubercle bacillus, M. tuberculosis, is characterized by its high water-insolubility, its cell wall composed of an unusual waxy coating mainly due to presence of mycolic acids. That is responsible for visualizing them using the Ziehl-Nielsen stain and making them acid-fast. M. tuberculosis is highly aerobic and requires oxygen to grow. The infection is spread by inhalation of microdroplets into the lungs where oxygen is highly available. Isoniazid interrupts mycolic acid synthesis, necessary for the special cell wall of M. Tuberculosis. synthesis of which is essential for its viability. So, why are pretomanid, bedaquiline, and linezolid so effective in killing M. tuberculosis? The physical chemistry of each may provide a clue that needs much further investigation. They are all very lipophilic, meaning that they partition preferentially into octanol rather than into water when shaken with a mixture of those.
twosolvents, and then centrifuged to create two distinct layers, octanol above water.

It was also observed that the BPaL administered orally was better absorbed when given after a meal, especially a fatty meal. Not only that, but it is also known that when fats, such as triglycerides, are absorbed from the proximal intestine, they do not go directly to the liver via the portal vein but are transported as intestinal lymph chylomicrons via the thoracic duct to the right heart and to the lungs via the pulmonary arteries. While at Harvard in 1960-2, I studied the mechanism of fat absorption by the intestine, and found that ingested triglycerides are initially hydrolyzed by lipases that remove the fatty acids in the 1 and 3 positions, and that the intestinal cells can activate the fatty acids to re-esterify the monoglycerides. They then can be shown by double radioactive tracer labeling to enter the thoracic duct lymph preferentially, and thence to the right heart and out to the pulmonary arteries. Other lipid substances are co-transported in the lymph directly to the lungs and bypassing the liver initial. Their lipophilicity makes them able to insert into the lipid walls of the tubercle bacilli. Only after return from the lungs to the left heart are the lipid components then sent to the liver via the aorta and hepatic artery. The lungs are where the tubercle bacilli are, and therefore the treating drugs are first delivered and in highest concentration to where the disease is primarily located, and only after dilution and delay to the liver. This may be an important reason why this particular combination is more effective and less hepatotoxic than alternative regimens with different physical chemical properties. It is not just speculation but a possible way to optimize the use of the new lipophilic BPaL regimen for clinical effectiveness in a convenient, low-cost way. It will take work and thought to determine if this is so, but the concept is offered for consideration and comment by the sponsor and other reviewers at the FDA.

CONCLUSIONS

These conclusions are offered for rapid review, correction, and comment by other reviewers at the FDA, slightly ahead of the requested schedule on 31 March, requesting rapid turn-around by 3 April and in time for an updated version by 5 April as scheduled. I have tried to answer the questions posed in the opening paragraphs of this document, and I have added some new thoughts for consideration. Starting with the specific questions, please see where my thinking has been going in these recently past almost 12 weeks:

- **What is the hepatotoxic potential of the bedaquiline/pretomanid /linezolid regimen in the pivotal Nix-TB trial?**

Briefly, very little from the reported results of this trial with safety data for 109 subjects but it was a small study indeed that could scarcely allow any confident conclusions to the question. As stated above, with three drugs there are 2^3 or 8 possible combinations that need to be compared: 3 for: each drug alone: pretomanid, bedaquiline, and linezolid; 3 more for pairs of them: BPa, BL, and PaL; 1 for all three together, BPaL; and 1 for none of them but some other cause for the liver abnormalities observed.

There is no existing standard with which to compare the drug-induced hepatotoxicity potential with any of the possibilities, no biomarker, no algorithm, no method. Controversy has raged for three decades about how this could or should be done, from the Roussel-UCLF Causality Assessment Method (RUCAM of 1989-93), the EDISH program of 2002-4, and the Drug-Induced-Liver-Injury-Network (DILIN) sponsored by the National Institutes of Health (NIH) 2004-19, taking on almost religious fervor in some advocates.

- **What is your opinion on the hepatotoxic potential of pretomanid based on the hepatic data the applicant submitted, i.e., their analysis of hepatic safety in section 2.7.4.11.3; eDISH/Hy’s law narratives in section 5.3.5.3, and the Nix-TB CSR Addendum in section 5.3.5.2.**

Opinions aside, the data received were sent to Dr. Ted Guo, with laboratory values of serum enzymes and bilirubin for all dates for each subject of the 109 in the safety set. Results are shown in the first graphic on page 4 above, in which it can be seen at a glance that most of the subjects (97/109 = 89%) showed no abnormalities at any time after the BPAL regimen was given. For the 12 who showed elevated serum aminotransferases, of whom 2 also showed slight elevations of serum total bilirubin that resolved despite continuing or being re-challenged with the drug regimen, and none had clinically significant consequences. All 12 have been reviewed, case-by-case individually, in the time-course graphs shown above on pages 5-19, including an extra subject # on page 20 who had peak serum bilirubin of 2.95 xULN but who showed delayed reactivation of TB after a full treatment course.

Special efforts were made to obtain narratives for all of the 10 subjects with transaminase elevations, the last few just received a few days ago on 26 March. It is evident that the narratives did not seem to be consistent and perhaps were written by different staff members or consultants. It is also unclear whether Dr. Guo received all of the laboratory data, and more appears to have been added in later-written narratives as lists of dates and values.

In this study there were 8 deaths, 6 during the planned treatment course and two delayed until after treatment was completed. None were due to liver failure but were attributed to other causes. Many of the subjects enrolled were patients with far advanced
TB and its complications. For some patients, treatment may have been started too late, but that was perhaps inevitable in a study designed as was Nix-TB.

New information of great pertinence was submitted by the sponsor just in the past week, in submissions 0015 and 0016 sent on 26 and 28 March, respectively. It is noted that narratives sent to Dr. Guo for eDISH analyses: differed substantially from those about the same patients now submitted. Dr James Freston is listed as the respondent for the ad hoc hepatotoxicity committee (He is very well known to me and will serve with me as a co-moderator of a Session on 8 May for the 2019 Drug-Induced-Liver-Injury Conference in College Park MD.)

Your recommendations on changes, if any, to the draft label that the applicant submitted?

In the labeling for pretomanid, it would be prudent to state that pretomanid when administered with other drugs such as moxifloxacin and pyrazinamide, has been associated with severe hepatotoxicity and death. It will be important to observe patients treated with the new regimen and check serum markers for liver injury periodically to enlarge the experience with this apparently efficacious regimen.

REFERENCES


_______________ John R. Senior, MD _____________ as corrected 13 May 2019
Appendix I: Narratives for eDISH Subjects

There were subjects for whom narratives could be found in the attached document entitled "16.5.1 Narratives for Patients with Negative Baseline Cultures," Five subjects with negative baseline cultures who also were found to have serum transaminase elevations in eDISH, including:

<table>
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<th>patient number</th>
<th>pages in the document (of 199)</th>
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<td>4</td>
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<td></td>
<td>5</td>
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<td></td>
<td>48-51---54 and 55-57---60</td>
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<td>186-188---199</td>
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</table>

The narratives for these patients have been summarized from the material submitted, to shorten it.

In addition, there were fourteen others in this document who did not show transaminase elevations, including:

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<td></td>
<td>6 and 83-84</td>
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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/

SARAH J HARRIS
05/14/2019 11:24:07 AM

JOHN R SENIOR
05/14/2019 11:33:06 AM
Clinical Inspection Summary
NDA 212271, Fosfomycin for Injection (CONTEPO)

Clinical Inspection Summary

<table>
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<tr>
<th>Date</th>
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<tr>
<td>From</td>
<td>Aisha Johnson, MD, MPH, MBA, Medical Officer Min Lu, MD, Acting Team Leader Kassa Ayalew, MD, MPH, Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)</td>
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<td>To</td>
<td>Elizabeth O’Shaughnessy, MD, Medical Officer Yuliya Yasinkaya, MD, Clinical Team Leader Fariba Izadi, PharmD, Regulatory Project Manager</td>
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<td>NDA/BLA #</td>
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<td>Drug</td>
<td>Pretomanid</td>
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<td>Treatment of pulmonary extensively drug resistant (XDR) or treatment-intolerant or nonresponsive (TI/NR) multidrug resistant (MDR) tuberculosis (TB) in adult patients in combination with bedaquiline (B) and linezolid (L).</td>
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| Consultation Request Date | 15 January 2019 |
| Action Goal Date         | 14 August 2019 |
| PDUFA Date               | 14 August 2019 |

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from a single Phase 3 study (Protocol NIX-TB) were submitted as the primary efficacy and safety study in support of this 505(b)(1) NDA for pretomanid, an NME. All three study sites participating in Study NIX-TB were selected for clinical inspection as part of PDUFA pre-approval clinical investigation and data validation.

The study data derived from these clinical sites, based on the inspections, are considered reliable in support of the proposed indication. The final classification for Dr. Andreas Diacon and Dr. Nosipho Ngubane’s sites is no action indicated (NAI).

The preliminary classification for Dr. Pauline Howell’s site is No Action Indicated (NAI). A clinical inspection summary addendum will be generated if conclusions change upon receipt and review of the final Establishment Inspection Report (EIR) of Dr. Pauline Howell. Preliminary classification is based on communications with the ORA investigator. Inspection classification becomes final when the Establishment Inspection Report is received from the field, has been reviewed, and a letter is issued to the inspected entity.
II. BACKGROUND

Pretomanid (Pa) is a nitroimidazooxazine antibacterial drug. NDA 212862 is a 505(b)(1) application and pretomanid is a new molecular entity (NME). The proposed product has been granted Qualified Infectious Disease Product (QIDP) and Fast Track designations for the proposed indication along with orphan drug status and a Tropic Disease Priority Review Voucher.

Study NIX-TB
A Phase 3 Open-label Trial Assessing the Safety and Efficacy of Bedaquiline Plus Pretomanid Plus Linezolid in Subjects with Pulmonary Infection of Either Extensively Drug-resistant Tuberculosis (XDR-TB) or Treatment Intolerant/Non-responsive Multi-Drug Resistant Tuberculosis (MDR-TB)

All patients receive the following treatments as this is an open-label trial:
- Bedaquiline (Days 1 to 14): 400 mg once daily (4 × bedaquiline 100 mg tablets),
- Bedaquiline (Weeks 3 to 26/39*): 200 mg 3 times a week (TIW) (2 × bedaquiline 100 mg tablets); plus
- Pretomanid 200 mg once daily, Day 1 through Weeks 26/39* (1 × pretomanid 200 mg tablet); plus

* Note: Patients received a minimum of 6 months (i.e., until Week 26) of trial treatment. If patients were culture positive or reverted to being culture positive between Month 4 and Month 6 and their clinical condition suggests they may have ongoing TB infection, the trial treatment could have been extended to 9 months (i.e., Week 39) or the patient could have been withdrawn from the trial.

The primary objective of the trial is to evaluate the efficacy, safety, tolerability, and pharmacokinetics (PK) of bedaquiline plus pretomanid plus linezolid (B-L-Pa) after 6 months of treatment (with an option to treat for 9 months in patients who were culture positive or reverted to being culture positive between Month 4 and Month 6) in patients with either pulmonary XDR-TB, treatment-intolerant MDR-TB, or non-responsive MDR-TB.

Bedaquiline (B), linezolid (L), and pretomanid (Pa) have not been used in combination in humans and thus their combined toxicity profile is not known. Safety adverse events of concern include adverse events of myelosuppression and peripheral and optic neuropathy, as linezolid use is known to be associated with these events. Subjects in the study are also to be under close surveillance for hepatotoxicity, as that risk for pretomanid and bedaquiline is not yet well characterized. Other adverse events of special concern are seizures or other neurologic events. Seizures have been reported in patients taking linezolid, seizures have been noted in animal toxicology studies of pretomanid at higher doses. In addition, the review division is interested in adverse events of pancreatitis.

The primary endpoint of the trial was the incidence of clinical failure, bacteriologic relapse, or bacteriologic failure through follow-up until 6 months after the End of Treatment.
Relevant definitions:

- Clinical failure (Treatment failure) is defined as being declared an unfavorable status at or before the End of Treatment, or failing to attain a culture negative status, or the patient was withdrawn at or before the End of Treatment for clinical (TB) reasons including being retreated (or changing from trial treatment) for TB;

- Bacteriologic relapse (Relapse) is defined as failing to maintain a culture negative status or being declared an unfavorable outcome after the End of Treatment in patients who attained culture negative status by the End of Treatment, and had culture conversion to a positive status with the same MTB strain or after the End of Treatment in patients who attained culture negative status by the End of Treatment and were withdrawn for clinical (TB) reasons including being retreated (or changing from trial treatment) for TB;

- Bacteriologic failure (Reinfection) is defined as failing to maintain culture negative status or being declared an unfavorable outcome (including being withdrawn for clinical [TB] reasons including being retreated or changing from trial treatment for TB) after the End of Treatment in patients who attained culture negative status by the End of Treatment and had culture conversion to positive status with a MTB strain that was different from the infecting strain at baseline. If reinfection could not be distinguished from relapse, the patient was to be assumed as having relapsed.

At the time of NDA submission, 45 subjects had completed the study (i.e., Subjects were assessed for the primary endpoint, died, or relapsed during the first 12-month period of the study). The initial NDA submission included the efficacy data of these 45 subjects along with the safety data of 109 subjects.

This study is being conducted at three centers in South Africa.

The first subject enrolled in the study on 16 April 2015. The study is ongoing. The last subject is scheduled to complete the study on 30 May 2020.

**Rationale for Site Selection**

The review division requested that all three sites participating in the NIX-TB study be inspected. This decision to inspect all three sites was based on the fact that the pivotal study is ongoing, and the efficacy results submitted with the NDA are from the first 45 patients who either were assessed for the primary endpoint, died, or relapsed during the first 12-month period of the study along with the safety results of 109 patients were included in the initial NDA submission.
III. RESULTS (by site):

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<th>Inspection Date</th>
<th>Classification</th>
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<td>Dr. Pauline Howell</td>
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<td>March 18-21, 2019</td>
<td>NAI*</td>
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<td>Clinical HIV Research Unit (CHRU)</td>
<td>Site #2 NIX-TB 57 subjects</td>
<td>April 1-5, 2019</td>
<td>NAI</td>
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<td>Sizwe Tropical Diseases Hospital 2 Modderfontein Road Sandringham, Johannesburg, South Africa</td>
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</table>

Key to Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
*Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

1. Dr. Pauline Howell/ Site # 1 /Protocol NIX-TB

At this site, there were 59 subjects screened and 40 subjects enrolled. Of these, 22 subjects completed 24 months of the study. There were 16 subjects continuing in follow-up at the time of the NDA submission. Two subjects discontinued from the study. Subject withdrew consent. Subject was withdrawn after end-of-treatment (but before 24 months) due to recurrent disease. Records of 14 subjects were reviewed during the inspection.
The records reviewed included: informed consent forms, international ethics committee study approvals and correspondence, site monitoring records, subject diaries, source documentation of study visits, case report forms, adverse events, and laboratory reports.

The records were generally complete and in good order.

The primary efficacy endpoint data was verifiable. There was no evidence of under-reporting of adverse events. The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

2. Dr. Andreas Diacon/ Site # 2 / Protocol NIX-TB

At this site, there were 69 subjects screened and 57 subjects enrolled. Eleven subjects were not enrolled because they met at least one exclusion criterion. An additional subject withdrew consent prior to randomization. A total of 18 subjects completed 24 months and 30 subjects continued to be in follow-up at the time of the NDA submission. Nine subjects discontinued from the study. Subjects (b) (6) and (b) (6) were lost to follow-up after completing the treatment period. Seven subjects died during the study. The inspection reviewed 19 of 23 subjects identified as being part of the 45 subjects submitted as part of the primary interim efficacy analysis. Safety data of an additional seven subjects was also reviewed. All reported deaths were reviewed.

The inspection found the records to be reasonably organized. During the inspection source records were thoroughly reviewed for 3 subjects. In addition, source records for nine more subjects were reviewed focusing on inclusion and exclusion criteria, primary efficacy results, and all adverse events including liver and pancreas toxicity.

During the inspection, the following under-reporting of adverse events was noted:

1. Subject (b) (6) had persistent Grade 4 elevations in GGT and Grade 1 elevation of AST. The AE was reported as Grade 1 “Raised Liver Function Tests (Ductal Enzymes)” rather than Grade 4 GGT.
2. Subject (b) (6) reported bilateral hand tremors at Week 9 on (b) (6) with an unknown start date. There was no documented follow up to this complaint and no AE was reported.
3. Subject (b) (6) reported foot cramps at the Month 24 visit on (b) (6). No AE was reported.

OSI Reviewer Comment: Adverse events of special interest for pretomanid include those related to the liver and/or pancreas. Misrepresentation of these events has the potential to provide an inaccurate safety profile of the drug. However, it is unlikely that a single misrepresentation will affect the safety profile of pretomanid.

In addition, the following findings were discussed with clinical investigator:
a. Site should maintain legible copies of all source documents. Several subjects had missing chest x-rays used for eligibility. In addition, certified copies must be exact copies of the original including all data and color copy (if needed). Certified copies had information cut-off in some subject files.

b. There were repeat protocol deviations regarding enrollment, sputum collection times and vision assessments were not corrected in a timely manner.
   i. Subjects were enrolled and dosed without the protocol-required three-day washout from prior TB medications. These were reported as major protocol deviations.
   ii. Site repeatedly failed to perform the visual acuity test at the required visits.
   iii. For 21 subjects enrolled, sputum collected hours after the subjects woke in the morning were marked as early morning sputum (EMS). The study monitor communicated in a letter (8/8/2016) that only sputum collected at first waking should be labeled EMS. Some sputum samples were also collected at less than one-hour intervals. The protocol specifies that sputum should be collected in at least one-hour intervals.

OSI Reviewer Comment: The repeat protocol deviations described above (b) were reported to the NDA as major protocol violations.

The primary efficacy endpoint data was verifiable. There was no evidence of underreporting of SAEs. Although some protocol deviations were noted (as described above), they are unlikely to significantly impact primary safety and efficacy analyses. There were no objectionable conditions noted other than those described above and no Form FDA-483, Inspectional Observations, issued.

3. Dr. Nosipho Ngubane/ Site # 4 / Protocol NIX-TB

At this site, there were 15 subjects screened and 12 subjects enrolled. All 12 subjects completed the first dosing interval (14 days) without any dropouts or loss to follow-up. The subject records of all 12 subjects screened were reviewed.

The records reviewed included: informed consent forms, international ethics committee study approvals and correspondence, site monitoring records, subject diaries, source documentation of study visits, case report forms, adverse events, and laboratory reports.

The records were generally complete and in good order. At the end of this inspection, the following findings were discussed with the investigator:
   a. Site should have retained actual subject compliance records which were documented directly on the investigation product kits. Study staff plan to retrieve the used kits from the central depot and make copies of the compliance records for site files.
b. Week 8 spot sputum samples were collected five minutes apart in Subjects (b)(6). The protocol specifies that these samples should be collected at least one hour apart.

c. Certified copies must be exact copies of the original including all data and color copy (if needed).

d. Site should assure that manually completed sputum laboratory reports are complete and accurate when received from the laboratory.

e. Investigational products were temporarily held in an unsecure area with other supplies used by the hospital.

The primary efficacy endpoint data was verifiable. There was no evidence of under-reporting of adverse events. The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

{See appended electronic signature page}

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Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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Kassa Ayalew, M.D., M.P.H
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Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

Reference ID: 4422422
CC:

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NDA 212,862

Division of Bone, Reproductive and Urologic Products (DBRUP)

Memorandum of Consultation

To: Sumathi Nambiar, MD, MPH  
Director,  
Division of Anti-Infective Products (DAIP)  
Office of Antimicrobial Products (OAP)  
Center for Drug Evaluation and Research (CDER)

From: Jordan Dimitrakoff, MD, PhD  
Medical Officer,  
Division of Bone, Reproductive and Urologic Products (DBRUP)  
Office of Drug Evaluation III (ODEIII)

Suresh Kaul, MD, MPH  
Medical Team Leader, DBRUP

Through: Audrey Gassman, MD  
Deputy Division Director, DBRUP

Date of Consult Request: January 27, 2019

Date of Consult Completion: April 11, 2019

Drug: Pretomanid (PA-824)

Doses: 200 mg tablet

Indication: Treatment of Tuberculosis

Re: Response to January 2019 Consult Request from the Division of Anti-Infective Products (DAIP). DBRUP was asked to provide expert opinion on a previously identified non-clinical testicular toxicity signal in a novel anti-tuberculosis drug (Pretomanid) and provide labeling recommendations

Materials reviewed:
- NDA 212,862 submission from the Global Alliance for TB Drug Development (TB Alliance);
- Medical Officer Consultation Memoranda for IND 69,580, dated April 24, 2013; consult review dated September 14, 2017; DBRUP final written response on October 5, 2017.
1. Executive Summary
The present memorandum outlines DBRUP’s evaluation of testicular toxicity findings related to pretomanid (PA-824). A signal of testicular toxicity with pretomanid was identified during a review of previously submitted nonclinical studies (QTC00003 –QTC00007) in rats. The Sponsor was asked to obtain clinical data to further evaluate this testicular toxicity signal and incorporate safety evaluations into their clinical development program. Clinical safety data (male reproductive hormone levels) were submitted from three clinical trials (NC-002, NC-005, and NC-006). The DBRUP reviewer evaluated the safety data from these three trials related to the testicular toxicity signal and identified significant methodologic limitations in the Sponsor’s safety data collection. Although the submitted reproductive hormonal data from study NC-006 is reassuring and suggests that the product does not have an effect on the hypothalamic-pituitary axis, there is insufficient overall evidence to definitively rule out a direct pretomanid-associated testicular toxicity.

A dedicated semen study is necessary to evaluate this testicular toxicity safety signal.

A detailed review of our evaluation of this safety signal and responses to your specific questions are provided below. We will provide further assistance and guidance for the requested dedicated semen study.

2. Background

2.1. Regulatory Background for This Consult
On December 14, 2018, the Global Alliance for TB Drug Development (TB Alliance) submitted a New Drug Application (NDA) under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Pretomanid (PA-824) 200 mg tablets.

On January 27, 2019, DAIP requested a consult from DBRUP stating: “Testicular toxicity has been observed with pretomanid in animal studies. There is a safety concern that pretomanid (previously known as PA-824) is possibly associated with testicular toxicity in men. This safety concern was reviewed by DBRUP, in a consult review dated 9/14/2017, in DARRTS and the DBRUP provided input as a final written response on October 5, 2017. The applicant, as agreed in consultation with DBRUP, is planning to conduct a semen analysis study in male subjects with tuberculosis receiving pretomanid-containing regimen. In their Clinical Summary of Safety (Section 6.6.3) located in Module 2 of the NDA, the applicant states that evaluations of male reproductive hormones in studies NC-002, NC-005, and NC-006 showed no evidence that pretomanid is a testicular toxicant in humans. This section discusses study analyses of male reproductive hormones in three clinical studies NC-002, NC-005, and NC-006.”

Pretomanid (PA-824) has been previously evaluated under the four commercial and one research INDs, as outlined in Table 1 below.
Table 1. Regulatory History of Pretomanid*

<table>
<thead>
<tr>
<th>Application Number</th>
<th>Application Type</th>
<th>Application Status</th>
<th>Product Name(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IND-069580</td>
<td>Commercial</td>
<td>Active</td>
<td>Pretomanid (PA-824)</td>
</tr>
</tbody>
</table>

*Source: Applicant’s submission in DARRTs

3. Overview of Nonclinical Testicular Toxicity Findings

The nonclinical testicular toxicity findings that identified the original safety signal are summarized in Dr. Martin Kaufman’s Memorandum of Consultation. For additional details, the reader is referred to the full-text memorandum in DARRTS (Reference ID: 3300698, dated April 24, 2013). No new nonclinical studies have been submitted for review since Dr. Kaufman’s 2013 memorandum.

4. Overview of Data from Clinical Trials Evaluating Testicular Toxicity

The Sponsor evaluated serum reproductive hormones in all three studies. Results from these hormonal evaluations and DBRUP’s interpretations are presented for each individual trial below.

4.1. Clinical Trial NC-002 – Key Safety Results

Title: “A Phase 2 Open-Label Partially Randomized Trial to Evaluate the Efficacy, Safety, and Tolerability of the Combination of Moxifloxacin plus PA-824 plus Pyrazinamide after 8 weeks of Treatment in Adult Patients with Newly Diagnosed Drug-Sensitive or Multidrug-Resistant, Smear-Positive Pulmonary Tuberculosis”

This clinical trial included 181 subjects with DS-TB (60 subjects received pretomanid 100 mg combination, 62 subjects received pretomanid 200 mg combination, and 59 subjects got HRZE) and 26 with MDR-TB who completed 8 weeks of treatment with either a DS-TB or MDR-TB regimen, as outlined below.

Key inclusion criteria:
- Drug-sensitive Tuberculosis (DS-TB) Arm
  - Adult patients (including male and female patients) who met the inclusion criteria and none of the exclusion criteria, age between 18 and 65 years (inclusive), with newly diagnosed, smear-positive DS-TB were randomized to one of three treatment groups:
- Moxifloxacin 400 mg plus PA-824 100 mg plus pyrazinamide 1500 mg
- Moxifloxacin 400 mg plus PA-824 200 mg plus pyrazinamide 1500 mg
- Rifafour group was included as a control for the DS-TB arm. Additionally, it was included as a control for the quantitative mycobacteriology.

- Multidrug-resistant Tuberculosis (MDR-TB) Arm
  - Adult patients (including male and female patients) who met all the inclusion criteria and none of the exclusion criteria, aged between 18 and 65 years (inclusive), with newly diagnosed, smear-positive MDR-TB were assigned to the following treatment group:
    - Moxifloxacin 400 mg plus PA-824 200 mg plus pyrazinamide 1500 mg.

### Table 2 - Median Serum Reproductive Hormones*

<table>
<thead>
<tr>
<th>Dose/Group</th>
<th>FSH (U/L) [median]</th>
<th>LH (U/L) [median]</th>
<th>Free Testosterone (nmol/L) [median]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>EOT Day 57</td>
<td>Baseline</td>
</tr>
<tr>
<td>Drug-Sensitive TB 100 mg PaMZ N=60</td>
<td>6.100</td>
<td>6.800</td>
<td>6.200</td>
</tr>
<tr>
<td>200 mg PaMz N=62</td>
<td>4.950</td>
<td>4.300</td>
<td>5.575</td>
</tr>
<tr>
<td>MDR-TB HRZE N=59</td>
<td>6.000</td>
<td>5.600</td>
<td>6.800</td>
</tr>
<tr>
<td>200 mg PaMZ N=26</td>
<td>6.600</td>
<td>6.600</td>
<td>6.000</td>
</tr>
</tbody>
</table>

*Data obtained from Sponsor Table 55, page 258, Module 2.7.4, NDA submission

**DBRUP Comments:**

In this NDA submission, the Sponsor provided serum FSH, LH, and free testosterone values from study NC-002. DBRUP reviewed the reproductive serum hormone data and concluded that it is not interpretable. While the median values at 8 weeks (57 days) are not above the generally accepted FSH value threshold of 8 IU/L and therefore, appear to be somewhat reassuring, however, the duration of these observations is shorter than the 26-week evaluation recommended in our Agency guidance on testicular toxicity testing.1

In addition to the data being of shorter duration, we have the following comments on interpreting the Sponsor’s serum reproductive values:

- Serum reproductive hormones (testosterone, FSH and LH) can fluctuate within a range over time, making clinical interpretation difficult. Small changes and trends in serum reproductive hormones are not always interpretable and do not necessarily correlate with testicular toxicity. Because the Sponsor’s data was not collected over a sufficient duration of time, the DBRUP reviewer cannot use this data as supportive to rule out testicular toxicity. Even if all serum reproductive hormone values are obtained and reported as normal over a 26-week period, semen analyses data will still be necessary.

- Free testosterone levels have not been shown to provide useful evaluation of testicular toxicity. The Sponsor used analog testing to obtain their free testosterone levels and presented this data as supportive. Analog tests can provide misleading information and, per the Endocrine Society Guidelines, should not be ordered. Based on DBRUP’s review of the analog data, the free testosterone levels provided are uninterpretable.

In conclusion, the results from study NC-002 are not sufficient to definitively rule out pretomanid-associated testicular toxicity.

4.2. Clinical Trial NC-005

Title: “A Phase 2 Open-Label Partially Randomized Trial to Evaluate the Efficacy, Safety and Tolerability of Combinations of Bedaquiline, Moxifloxacin, PA-824 and Pyrazinamide During 8 Weeks of Treatment in Adult Subjects with Newly Diagnosed Drug-Sensitive or Multi Drug-Resistant, Smear-Positive Pulmonary Tuberculosis”

In Study NC-005, 179 subjects were screened and baseline serum FSH levels were obtained after 4 and 8 weeks. Additionally, 2-weeks post treatment serum FSH levels were also obtained.

Groups:
All three groups received PA-824 (Pa; 200 mg/kg/d) plus pyrazinamide (Z) and bedaquiline (J) per the following paradigm:

- **Group One**: Higher dose loading paradigm for bedaquiline [J (loading dose/t.i.w.) PaZ];
- **Group Two**: 200 mg/kg/d bedaquiline [J (200 mg) PaZ], and
- **Group Three**: Moxifloxacin added to the 3 other drugs [J (200 mg) MPaZMDR] for multidrug-resistant TB (MDT).

The fourth group received a standard Rifafour (HRZE) treatment regimen.

The median FSH values in each group at the different time points are shown in Table 3 below.

**Table 3. Median FSH Values Over Time in Study NC-005**
### DBRUP Comment:

From a clinical perspective as stated above, it is not appropriate to interpret isolated serum FSH values over time without concomitant information regarding inhibin, total serum testosterone and LH values from the same sample collected at the same time point. Additionally, the Sponsor has not described the methodology/specific testing method, timing of the hormonal measurements relative to drug intake and normal reference values for the test kit they employed to measure FSH. It is difficult to assess Pretomanid’s actual effect on serum FSH. In addition, it is difficult to interpret the effect of small changes of FSH on spermatogenesis.

Therefore, the results from study NC-005 are not sufficient to definitively rule out pretomanid-associated testicular toxicity.

### 4.3. Clinical Trial NC-006

**Title:** “A Phase 3 Open-Label Partially Randomized Trial to Evaluate the Efficacy, Safety and Tolerability of the Combination of Moxifloxacin plus PA-824 plus Pyrazinamide after 4 and 6 months of Treatment in Adult Subjects with Drug-Sensitive Smear-Positive Pulmonary Tuberculosis and after 6 months of Treatment in Adult Subjects with Multi-Drug Resistant, Smear-Positive Pulmonary Tuberculosis”

This clinical trial evaluated the toxicity and efficacy of PA-824 in combination with Moxifloxacin and Pyrazinamide (Pa-M-Z) compared to the combination of Isoniazid, Rifampicin, Pyrazinamide and Ethambutol (Rifafour). PA-M-Z was administered for either 4 or 6 months. In the 4-month treatment arm, PA-824 was given at either 100 or 200 mg in the Pa-M-Z combination. Responses were compared in drug sensitive (DS) and multi-drug resistance (MDR) patients, and in HIV-positive and negative patients.

The trial design is illustrated in the following figure (reproduced from the Sponsor submission):
Hormones were evaluated at baseline (week 0), weeks 1, 2, 3, 4, 8, 12, 17, 22, 26, at the end-of-treatment (EOT) and at end-of-study (EOS) visits. The Sponsor presented aggregate data for median hormone levels for both HIV positive and HIV negative/unknown drug sensitive men receiving 4 months of treatment with moxifloxacin, pyrazinamide, and pretomanid (MPa100Z, 100 mg/kg/d; MPa200Z, 200 mg/kg/d), and 6 months of treatment with moxifloxacin, pyrazinamide, and pretomanid (MPa200Z, 200 mg/kg/d), or Rifafour (HRZE, a combination of rifampin, isoniazid, pyrazinamide and ethambutol).

**Data Analysis**

The data in the following tables is summarized from the STAND Trial Male hormonal data, table 57, pages 261-262 of Module 2.7.4 (Summary of Clinical Safety). The complete table 57 is reproduced at the end of the present review.
Table 4. Median Follicle Stimulating Hormone (FSH) Values Over Time in Trial NC-006*

<table>
<thead>
<tr>
<th>FSH (U/L) [median]</th>
<th>Baseline</th>
<th>Week 12</th>
<th>Week 26</th>
<th>EOT</th>
<th>EOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 month 100 mg PaMZ</td>
<td>5.733</td>
<td>7.100</td>
<td>5.900</td>
<td>6.900</td>
<td>6.100</td>
</tr>
<tr>
<td>4 month 200 mg PaMZ</td>
<td>6.775</td>
<td>7.500</td>
<td>6.500</td>
<td>7.100</td>
<td>7.000</td>
</tr>
<tr>
<td>6 month 200 mg PaMZ</td>
<td>6.525</td>
<td>6.800</td>
<td>6.500</td>
<td>6.800</td>
<td>6.850</td>
</tr>
<tr>
<td>HRZE</td>
<td>5.600</td>
<td>6.400</td>
<td>5.600</td>
<td>5.650</td>
<td>5.600</td>
</tr>
<tr>
<td>6 month 200 mg PaMZ</td>
<td>5.550</td>
<td>5.400</td>
<td>4.800</td>
<td>4.800</td>
<td>4.900</td>
</tr>
</tbody>
</table>

*Data obtained from Sponsor Table 57, page 261, Module 2.7.4, NDA submission

Table 5. Median Inhibin B Values Over Time in Trial NC-006*

<table>
<thead>
<tr>
<th>Inhibin B (ng/L) [median]</th>
<th>Baseline</th>
<th>Week 12</th>
<th>Week 26</th>
<th>EOT</th>
<th>EOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 month 100 mg PaMZ</td>
<td>116.630</td>
<td>137.245</td>
<td>129.165</td>
<td>127.420</td>
<td>126.850</td>
</tr>
<tr>
<td>4 month 200 mg PaMZ</td>
<td>99.025</td>
<td>118.920</td>
<td>129.155</td>
<td>129.160</td>
<td>114.910</td>
</tr>
<tr>
<td>6 month 200 mg PaMZ</td>
<td>108.125</td>
<td>142.640</td>
<td>139.965</td>
<td>124.840</td>
<td>117.815</td>
</tr>
<tr>
<td>HRZE</td>
<td>123.875</td>
<td>152.900</td>
<td>153.200</td>
<td>143.330</td>
<td>141.700</td>
</tr>
<tr>
<td>6 month 200 mg PaMZ</td>
<td>119.575</td>
<td>159.550</td>
<td>187.300</td>
<td>177.850</td>
<td>177.850</td>
</tr>
</tbody>
</table>

*Data obtained from Sponsor Table 57, page 261-2, Module 2.7.4, NDA submission
Table 6. Median Luteinizing Hormone (LH) Values Over Time in Trial NC-006*

<table>
<thead>
<tr>
<th></th>
<th>LH (U/L) [median]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
</tr>
<tr>
<td>4 month</td>
<td></td>
</tr>
<tr>
<td>100 mg PaMZ</td>
<td></td>
</tr>
<tr>
<td>4.550</td>
<td>6.900</td>
</tr>
<tr>
<td>6 month</td>
<td></td>
</tr>
<tr>
<td>200 mg PaMZ</td>
<td></td>
</tr>
<tr>
<td>5.000</td>
<td>5.500</td>
</tr>
<tr>
<td>HRZE</td>
<td></td>
</tr>
<tr>
<td>6 month</td>
<td></td>
</tr>
<tr>
<td>200 mg PaMZ</td>
<td></td>
</tr>
<tr>
<td>5.600</td>
<td>5.700</td>
</tr>
<tr>
<td>8.700</td>
<td>6.900</td>
</tr>
</tbody>
</table>

*Data obtained from Sponsor Table 57, page 261, Module 2.7.4, NDA submission

Table 7. Median Testosterone Values Over Time in Trial NC-006*

<table>
<thead>
<tr>
<th></th>
<th>Testosterone (nmol/L) [median]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
</tr>
<tr>
<td>4 month</td>
<td></td>
</tr>
<tr>
<td>100 mg PaMZ</td>
<td></td>
</tr>
<tr>
<td>9.455</td>
<td>14.475</td>
</tr>
<tr>
<td>(273) **</td>
<td>(417) **</td>
</tr>
<tr>
<td>4 month</td>
<td></td>
</tr>
<tr>
<td>200 mg PaMZ</td>
<td></td>
</tr>
<tr>
<td>(274) **</td>
<td>(382) **</td>
</tr>
<tr>
<td>6 month</td>
<td></td>
</tr>
<tr>
<td>200 mg PaMZ</td>
<td></td>
</tr>
<tr>
<td>10.705</td>
<td>17.000</td>
</tr>
<tr>
<td>(309) **</td>
<td>(490) **</td>
</tr>
<tr>
<td>HRZE</td>
<td></td>
</tr>
<tr>
<td>(329) **</td>
<td>(767) **</td>
</tr>
<tr>
<td>6 month</td>
<td></td>
</tr>
<tr>
<td>200 mg PaMZ</td>
<td></td>
</tr>
<tr>
<td>12.855</td>
<td>11.120</td>
</tr>
<tr>
<td>(371) **</td>
<td>(321) **</td>
</tr>
</tbody>
</table>

*Data obtained from Sponsor Table 57, page 261, Module 2.7.4, NDA submission

**Values converted from SI units [nmol/L] to conventional (gravimetric US) units [ng/dL].
Summary of Data from NC-006

Testosterone and LH Data Summary
Overall, testosterone levels increased with pretomanid treatment and remained within the normal range at the 26-week time point in all groups. LH remained stable throughout the study period.

Baseline testosterone values:
- Men in the 4-Month groups were hypogonadal
  - 100 mg PaMZ median testosterone level: 9.455 nmol/L (273 ng/dL);
  - 200 mg PaMZ median testosterone level: 9.518 nmol/L (274 ng/dL), resp.
- Men in the remaining three groups were eugonadal
  - DS 6-month 200 mg PaMZ group median testosterone level: 10.705 nmol/L (309 ng/dL);
  - HRZE median testosterone level: 11.408 nmol/L (329 ng/dL)
  - MDR 6-month 200 PaMZ group median testosterone level: 12.855 nmol/L (371 ng/dL)

26 Week testosterone values:
- Testosterone levels were within normal range in all four groups at 26 weeks.

Serum LH:
- Serum LH levels were within normal range at all time points in all 4 groups.

Serum FSH and Inhibin B Data Summary
FSH and inhibin B levels remained within normal limit at all time-points in all groups. The Sponsor reports one case of “a clinically significant abnormality (increased FSH) which was reported by the investigator in 1 subject (Subject treated with PaMZ; NC-006 CSR Listing 16.2.8/1.3). This subject had elevated FSH levels (considered not clinically significant) at almost all study visits, including screening. A clinically significant elevation (30.9 IU/L) was noted at the subject’s withdrawal/end-of-study visit. His FSH levels showed both an increase and a decrease compared with baseline during participation in the study”. Of note, the lack of changes in these values is not unexpected as it is not clear that there is any direct effect of pretomanid on the hypothalamic-pituitary axis.
Overall Summary of Serum Hormonal Values in Study NC-006:

1. FSH, inhibin B, and LH levels remained stable throughout the study period and at the 26-week time-point. Testosterone levels increased with pretomanid treatment and remained within the normal range at the 26-week time.

2. Study NC-006 Methodologic Issues
   a. The study design is unclear. The study is listed as “partially randomized”. Violation of randomization tends to introduce a bias towards the null hypothesis of finding no difference (even if one truly existed) that may bias the analysis towards finding no effect of pretomanid on testosterone, LH, FSH, and inhibin B levels.

   b. Stratification and Subgroup Analysis by HIV Status
   The Sponsor has presented aggregate hormonal data from both HIV-positive and HIV-negative patients. However, hypogonadism in HIV-positive men has been recognized as a unique entity with some unique clinical and lab characteristics. Consolidating and presenting the data from both HIV-positive and HIV-negative men might result in a “dilution” of the safety signal.

DBRUP concludes that the submitted reproductive hormonal data for study NC-006 is somewhat reassuring, particularly that the toxicity is not related to hypothalamic axis effects. However, in general, there is insufficient overall evidence to definitively rule out a direct pretomanid-associated testicular toxicity.

Overall summary of results from NC-002, NC-005 and NC-006:

- Results from study NC-002 are not sufficient due to short follow-up (57 days) and lack of interpretability of the free testosterone measurements that the Sponsor used.
- Results from study NC-005 are not sufficient because the Sponsor measured only FSH levels at days 57 and 70. Sponsor did not describe the methodology/specific testing method, timing of the hormonal measurements relative to drug intake and normal reference values for the test kit they employed to measure FSH.
- Results from study NC-006 are limited by the lack of clarity of the randomization and lack of stratification by HIV status which might result in “dilution” of the safety signal, although the hormonal data submitted with the NDA are reassuring.

DBRUP’s Response to DAIP Questions and Recommendations:

List of Questions from Division of Anti-Infective Products (DAIP):

1. Does the DBRUP have additional comments that were not included in prior consultations about pretomanid?

   DBRUP concludes that the Sponsor has presented insufficient clinical evidence to definitively rule out direct pretomanid-associated testicular toxicity. DBRUP believes that a dedicated semen study is necessary to evaluate the testicular toxicity safety signal from the preclinical studies.
2. Please provide any labeling recommendations that you think are warranted.

DBRUP recommends the following sentence be added at the end of section 8.3. Females and Males of Reproductive Potential, Risk Summary of the Label:

“Reduced fertility and testicular toxicity cannot be definitively ruled out in human subjects at this time.”

3. We would like to request your presence at the Advisory Committee for NDA 212862 scheduled for June 5-6, 2019.

If there are continued clinical concerns about testicular toxicity that the Division plans to discuss at the AC and if there is a specific timeframe that you would like us to attend, please let us know.
### Table 55: Median Values for Male Reproductive Hormones Over Time in Study NC-002

<table>
<thead>
<tr>
<th>Parameter Time Point</th>
<th>DS-TB Subjects</th>
<th>MDR-TB Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>100 mg PaMZ (N = 60)</td>
<td>200 mg PaMZ (N = 62)</td>
</tr>
<tr>
<td></td>
<td>Median (Min, Max)</td>
<td>Median (Min, Max)</td>
</tr>
<tr>
<td>FSH (U/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visit 1</td>
<td>6.100 (0.258, 35.400)</td>
<td>4.950 (1.080, 14.800)</td>
</tr>
<tr>
<td>Baseline</td>
<td>6.100 (0.258, 35.400)</td>
<td>4.950 (1.080, 14.800)</td>
</tr>
<tr>
<td>Visit 24 (Day 57)</td>
<td>6.800 (1.720, 27.050)</td>
<td>4.300 (1.840, 28.500)</td>
</tr>
<tr>
<td>Early Withdrawal</td>
<td>5.900 (3.780, 41.200)</td>
<td>8.330 (5.700, 13.900)</td>
</tr>
<tr>
<td>LH (U/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visit 1</td>
<td>6.200 (2.00, 24.52)</td>
<td>5.575 (2.00, 40.10)</td>
</tr>
<tr>
<td>Baseline</td>
<td>6.200 (2.00, 24.52)</td>
<td>5.575 (2.00, 40.10)</td>
</tr>
<tr>
<td>Visit 24 (Day 57)</td>
<td>5.460 (2.70, 25.58)</td>
<td>3.800 (1.90, 37.40)</td>
</tr>
<tr>
<td>Early Withdrawal</td>
<td>5.700 (3.60, 11.10)</td>
<td>6.900 (4.40, 17.80)</td>
</tr>
<tr>
<td>Free testosterone (nmol/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visit 1</td>
<td>12.700 (1.768, 25.400)</td>
<td>12.934 (3.432, 28.310)</td>
</tr>
<tr>
<td>Baseline</td>
<td>12.700 (1.768, 25.400)</td>
<td>12.934 (3.432, 28.310)</td>
</tr>
</tbody>
</table>

DS-TB = drug-susceptible tuberculosis; FSH = follicle-stimulating hormone; HRZE = isoniazid, rifampin, pyrazinamide, and ethambutol regimen; LH = luteinizing hormone; M = moxifloxacin; max = maximum; MDR-TB = multidrug-resistant tuberculosis; min = minimum; Pa = pretomanid; Z = pyrazinamide

Source: NC-002 CSR Table 14.3.4/1
Table 56: Median Values for FSH Over Time in Study NC-005

<table>
<thead>
<tr>
<th>Parameter Time Point</th>
<th>DS-TB Subjects</th>
<th>MDR-TB Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BdpPaZ (N = 45)</td>
<td>BdpPaZ (N = 48)</td>
</tr>
<tr>
<td></td>
<td>Median (Min, Max)</td>
<td>Median (Min, Max)</td>
</tr>
<tr>
<td>FSH (IU/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>4.590 (1,000, 17,100)</td>
<td>5.585 (1,200, 24,500)</td>
</tr>
<tr>
<td>Day 29</td>
<td>5.690 (1,000, 20,000)</td>
<td>6.340 (0,900, 29,350)</td>
</tr>
<tr>
<td>Day 57</td>
<td>5.770 (0,900, 24,400)</td>
<td>5.775 (1,200, 15,820)</td>
</tr>
<tr>
<td>Day 70 (follow-up)</td>
<td>5.840 (0,927, 29,700)</td>
<td>6.300 (1,400, 35,310)</td>
</tr>
<tr>
<td>EOT</td>
<td>5.855 (0,927, 29,700)</td>
<td>6.300 (1,400, 35,310)</td>
</tr>
<tr>
<td>EOS</td>
<td>5.855 (0,927, 29,700)</td>
<td>6.300 (1,400, 35,310)</td>
</tr>
</tbody>
</table>

B = bedaquiline; Bdp = bedaquiline with loading dose; DS-TB = drug-susceptible tuberculosis; EOS = end of study; EOT = end of treatment; FSH = follicle-stimulating hormone; HRZE = isoniazid, rifampin, pyrazinamide, and ethambutol regimen; M = moxifloxacin; max = maximum; MDR-TB = multidrug-resistant tuberculosis; min = minimum; Pa = pretomanid; Z = pyrazinamide.

Source: NC-005 CSR Table 14.3.4/1.2
Table 57: Median Values for Male Reproductive Hormones Over Time in Study NC-006

<table>
<thead>
<tr>
<th>Parameter Time Point</th>
<th></th>
<th>DS-TB Subjects</th>
<th></th>
<th></th>
<th>MDR-TB Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4-Month</td>
<td>4-Month</td>
<td>6-Month</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>100 mg PaMZ (N = 65)</td>
<td>200 mg PaMZ (N = 71)</td>
<td>200 mg PaMZ (N = 67)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Median (Min, Max)</td>
<td>Median (Min, Max)</td>
<td>Median (Min, Max)</td>
<td>Median (Min, Max)</td>
<td>Median (Min, Max)</td>
</tr>
<tr>
<td>FSH (IU/L)</td>
<td>5.733 (1.40, 27.20)</td>
<td>6.775 (1.60, 33.70)</td>
<td>6.525 (1.53, 52.53)</td>
<td>5.600 (0.40, 22.55)</td>
<td>5.550 (2.05, 10.75)</td>
</tr>
<tr>
<td>Week 4</td>
<td>6.400 (1.30, 30.00)</td>
<td>9.200 (2.90, 37.70)</td>
<td>9.300 (1.70, 33.50)</td>
<td>6.800 (0.40, 32.60)</td>
<td>6.200 (2.60, 9.20)</td>
</tr>
<tr>
<td>Week 8</td>
<td>6.000 (1.50, 26.90)</td>
<td>8.000 (2.50, 33.40)</td>
<td>7.200 (2.10, 38.80)</td>
<td>6.400 (0.30, 32.30)</td>
<td>6.400 (1.90, 7.10)</td>
</tr>
<tr>
<td>Week 12</td>
<td>7.100 (1.50, 28.70)</td>
<td>7.500 (2.50, 24.50)</td>
<td>6.800 (2.50, 34.80)</td>
<td>6.400 (0.30, 22.30)</td>
<td>5.400 (3.00, 7.20)</td>
</tr>
<tr>
<td>Week 17</td>
<td>7.750 (1.40, 58.70)</td>
<td>7.050 (2.70, 29.70)</td>
<td>6.850 (2.90, 30.40)</td>
<td>5.950 (1.30, 13.90)</td>
<td>5.100 (2.70, 8.00)</td>
</tr>
<tr>
<td>Week 26</td>
<td>5.900 (1.40, 31.80)</td>
<td>6.500 (2.20, 33.40)</td>
<td>6.500 (1.90, 38.20)</td>
<td>5.600 (0.70, 21.20)</td>
<td>4.800 (3.60, 7.00)</td>
</tr>
<tr>
<td>EOT</td>
<td>6.900 (1.40, 38.70)</td>
<td>7.160 (2.70, 125.70)</td>
<td>6.800 (1.70, 76.50)</td>
<td>5.650 (0.70, 32.30)</td>
<td>4.800 (3.60, 11.90)</td>
</tr>
<tr>
<td>EOS</td>
<td>6.100 (1.30, 30.90)</td>
<td>7.000 (2.20, 125.70)</td>
<td>6.850 (1.70, 76.50)</td>
<td>5.600 (0.70, 32.30)</td>
<td>4.900 (3.60, 11.90)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LH (IU/L)</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5.600 (2.05, 13.80)</td>
<td>5.950 (2.40, 18.40)</td>
<td>6.700 (2.15, 19.25)</td>
<td>6.000 (1.10, 12.85)</td>
<td>8.700 (3.10, 11.25)</td>
</tr>
<tr>
<td>Week 4</td>
<td>5.300 (1.90, 14.70)</td>
<td>6.200 (2.70, 19.00)</td>
<td>6.600 (2.20, 14.90)</td>
<td>5.650 (0.90, 18.20)</td>
<td>5.600 (3.30, 12.20)</td>
</tr>
<tr>
<td>Week 8</td>
<td>5.400 (0.90, 13.80)</td>
<td>5.500 (1.80, 16.10)</td>
<td>5.700 (2.70, 17.70)</td>
<td>4.600 (1.20, 13.30)</td>
<td>4.600 (1.70, 8.60)</td>
</tr>
<tr>
<td>Week 12</td>
<td>4.550 (1.90, 11.10)</td>
<td>5.000 (1.00, 12.50)</td>
<td>5.700 (2.90, 14.90)</td>
<td>5.600 (1.00, 11.40)</td>
<td>6.900 (6.20, 13.90)</td>
</tr>
<tr>
<td>Week 17</td>
<td>5.700 (2.00, 30.50)</td>
<td>4.950 (0.90, 11.80)</td>
<td>4.950 (2.40, 40.10)</td>
<td>4.500 (2.10, 13.10)</td>
<td>4.500 (3.00, 9.00)</td>
</tr>
<tr>
<td>Week 26</td>
<td>5.000 (2.00, 15.60)</td>
<td>5.500 (1.70, 13.60)</td>
<td>5.000 (1.80, 16.90)</td>
<td>6.000 (1.60, 15.30)</td>
<td>7.550 (4.90, 9.90)</td>
</tr>
<tr>
<td>EOT</td>
<td>5.400 (0.40, 30.50)</td>
<td>5.300 (0.90, 61.60)</td>
<td>6.000 (1.80, 39.80)</td>
<td>6.350 (1.60, 16.10)</td>
<td>5.300 (1.20, 12.20)</td>
</tr>
<tr>
<td>EOS</td>
<td>4.600 (0.40, 15.60)</td>
<td>5.400 (1.40, 61.60)</td>
<td>5.900 (1.80, 39.80)</td>
<td>6.400 (0.10, 15.30)</td>
<td>5.300 (1.20, 12.20)</td>
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</tbody>
</table>
### Inhibin B (ng/L)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Min, Max)</td>
<td>(Min, Max)</td>
<td>(Min, Max)</td>
<td>(Min, Max)</td>
</tr>
<tr>
<td><strong>Baseline</strong></td>
<td>116.630 (20.050, 225.900)</td>
<td>69.025 (17.950, 303.550)</td>
<td>108.125 (15.300, 227.350)</td>
<td>123.875 (41.170, 631.950)</td>
</tr>
<tr>
<td><strong>Week 4</strong></td>
<td>132.850 (24.400, 256.600)</td>
<td>104.150 (13.500, 240.300)</td>
<td>116.530 (13.500, 271.700)</td>
<td>120.800 (40.700, 485.470)</td>
</tr>
<tr>
<td><strong>Week 8</strong></td>
<td>138.080 (34.600, 303.450)</td>
<td>115.885 (13.500, 209.500)</td>
<td>144.100 (13.500, 315.400)</td>
<td>146.050 (23.700, 337.670)</td>
</tr>
</tbody>
</table>

### DS-TB Subjects

<table>
<thead>
<tr>
<th>Parameter Time Point</th>
<th>4-Month PaMZ (N = 65) Median (Min, Max)</th>
<th>4-Month PaMZ (N = 71) Median (Min, Max)</th>
<th>6-Month PaMZ (N = 67) Median (Min, Max)</th>
<th>HRZE (N = 68) Median (Min, Max)</th>
<th>MDR-TB Subjects (N = 13) Median (Min, Max)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Week 26</strong></td>
<td>129.155 (29.080, 278.560)</td>
<td>129.155 (13.500, 298.100)</td>
<td>139.965 (13.500, 392.970)</td>
<td>153.200 (22.100, 390.430)</td>
<td>187.300 (10.400, 191.130)</td>
</tr>
<tr>
<td><strong>EOS</strong></td>
<td>126.850 (13.500, 303.450)</td>
<td>114.910 (13.500, 298.100)</td>
<td>117.815 (13.500, 392.970)</td>
<td>141.700 (13.500, 390.430)</td>
<td>177.850 (55.700, 297.430)</td>
</tr>
</tbody>
</table>

### Testosterone (nmol/L)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(Min, Max)</td>
<td>(Min, Max)</td>
<td>(Min, Max)</td>
<td>(Min, Max)</td>
</tr>
<tr>
<td><strong>Baseline</strong></td>
<td>9.455 (2.410, 21.530)</td>
<td>9.518 (1.645, 23.770)</td>
<td>10.705 (1.735, 40.290)</td>
<td>11.140 (1.855, 29.110)</td>
</tr>
<tr>
<td><strong>Week 8</strong></td>
<td>15.790 (4.710, 33.000)</td>
<td>12.780 (5.030, 24.410)</td>
<td>15.680 (5.630, 43.720)</td>
<td>25.510 (9.710, 37.160)</td>
</tr>
<tr>
<td><strong>Week 17</strong></td>
<td>14.460 (0.350, 28.920)</td>
<td>14.900 (0.750, 27.820)</td>
<td>14.855 (1.020, 36.780)</td>
<td>23.350 (11.010, 43.750)</td>
</tr>
<tr>
<td><strong>Week 26</strong></td>
<td>17.765 (1.370, 29.460)</td>
<td>17.315 (7.080, 29.600)</td>
<td>18.920 (5.360, 32.340)</td>
<td>24.785 (10.910, 38.260)</td>
</tr>
<tr>
<td><strong>EOT</strong></td>
<td>14.120 (0.350, 28.920)</td>
<td>14.650 (0.490, 31.960)</td>
<td>17.650 (0.610, 32.020)</td>
<td>24.760 (1.300, 38.260)</td>
</tr>
<tr>
<td><strong>EOS</strong></td>
<td>16.600 (0.350, 31.980)</td>
<td>16.500 (0.490, 38.440)</td>
<td>17.650 (0.610, 32.020)</td>
<td>24.640 (0.350, 36.810)</td>
</tr>
</tbody>
</table>

**DS-TB = drug-susceptible tuberculosis, EOS = end of study, EOT = end of treatment, FSH = follicle-stimulating hormone, HRZE = isoniazid, rifampin, pyrazinamide, and ethambutol regimen; LH = luteinizing hormone; M = moxifloxacin; max = maximum; MDR-TB = multidrug-resistant tuberculosis; min = minimum; Pa = pretomanid; Z = pyrazinamide**

Source: NC-006 CSR, Table 14.3.3.1/
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/

JORDAN D DIMITRAKOFF
04/15/2019 01:11:46 PM

SURESH KAUL
04/15/2019 01:16:21 PM

AUDREY L GASSMAN
04/15/2019 01:24:12 PM
Date: April 10, 2019

From: CDER DCRP QT Interdisciplinary Review Team

Through: Christine Garnett, Pharm.D.
Clinical Analyst
Division of Cardiovascular and Renal Products /CDER

To: Fariba Izadi, RPM;
Elizabeth O’Shaughnessy, MD; and
Yuliya Yasinskaya, MD
DAIP

Subject: QT-IRT Consult to NDA # 212862 (SDN # 001)

Note: Any text in the review with a light background should be inferred as copied from the sponsor’s document.

This memo responds to your consult to us dated 2/19/2019 regarding the Division’s QT related questions and proposed USPI for pretomanid. The QT-IRT reviewed the following materials:

- Previous QT-IRT review(s) for IND dated 01/14/2019 in DARRTS (link);
- Sponsor’s concentration-QTc modeling of pretomanid (SN0001 / SDN001; link);
- Sponsor’s proposed product label (SN0001 / SDN001; link);
- Investigator’s brochure under (SN0033 / SDN034; link); and
- Highlights of clinical pharmacology and cardiac safety (SN0007 / SDN; link).

1 DAIP Question

Background: In NDA 212862, pretomanid (PA-824), a nitroimidazooxazine antimycobacterial drug, is indicated as part of a combination regimen with bedaquiline and linezolid, in adults for the treatment of pulmonary extensively drug resistant (XDR) or treatment intolerant or nonresponsive multidrug resistant (MDR) tuberculosis.

On December 6, 2013, under IND- , the Applicant submitted the study results for protocol No. 10-0058 entitled, “Phase I, Double-Blind, Randomized, Single-Center, Five-Period Crossover Study to Assess the Effects of Single Oral Doses of 400 mg and 1000 mg of PA -824 and 400 mg of PA -824 Plus 400 mg of Moxifloxacin on QTc Interval Compared to Placebo, Using Avelox.
(moxifloxacin) as a Positive Control, in Healthy Male and Female Volunteers Aged 18 to 45 Years”. Based on your review dated 1-14-19, no significant QT prolongation effect of pretomanid (400 mg and 1000 mg) was detected in TQT Study 10-0058. The pretomanid label recommends pretomanid to be administered with bedaquiline and linezolid (pretomanid should be administered with bedaquiline (400 mg once daily for 2 weeks followed by 200 mg 3 times per week [with at least 48 hours between doses] orally for a total of 26 weeks) and linezolid (1200 mg daily orally for up to 26 weeks, with dose adjustments for known linezolid toxicities).

Considering the fact that the approved labeling for bedaquiline (SIR T URO) has a boxed warning regarding QT Prolongation, (QT prolongation can occur with SIR T URO, use with drugs that prolong the QT interval may cause additive QT prolongation, monitor ECGS, discontinue SIR T URO if significant ventricular arrhythmia or QTcF > 500 ms develops), the Division is concerned that the concomitant use of pretomanid with bedaquiline could cause additional prolongation of the QT interval. In light of this information, the Applicant has submitted a Concentration-QTc modeling report of pretomanid given in combination with bedaquiline and linezolid in the NDA. We would like to request a review of this report so that the potential risk of cardiac events with this anti-tuberculosis regimen is better understood.

**Question**: Please comment on the pretomanid labeling proposed by the Applicant with regards to the QT prolongation potential of pretomanid and the bedaquiline/linezolid/pretomanid regimen as well as QT-IRT’s Response:

**Pretomanid’s effect on QTc**

Although no clinically meaningful increase in QTc was detected in the TQT study after administering single oral doses of 400 mg and 1000 mg pretomanid, there was a shallow, positive concentration-QTc relationship. This is consistent with the nonclinical data that showed pretomanid inhibits the Ik, current with an IC50 of ~6.2 μg/mL which provides a ~19-fold exposure margin over the therapeutic exposures.

Based on the concentration-QTc relationship from the data collected in the TQT study, the predicted QTc effects of pretomanid 200 mg/day given with food to males (Cmax,ss = 3.2 μg/mL) is 4 ms (90% CI: 2−5 ms) and to females is 5 ms (90% CI: 4–10 ms). Therefore, pretomanid has low risk to prolong the QTc interval at therapeutic exposures. However, clinical studies evaluating pharmacokinetics of pretomanid in subjects with renal impairment and hepatic impairment are still pending. Increases in pretomanid concentrations could further increase the QTc interval.

When pretomanid is co-administered with other QT prolonging drugs, small increases in the QTc interval are expected, which would not substantially increase the proarrhythmic risk of the combination. In the TQT study, co-administration of 400 mg pretomanid with 400 mg moxifloxacin did not significantly increase the QTc effects of the combination. As a rule of thumb, we generally expect additive effects on the QTc interval when co-administering drugs that inhibit the hERG channel; however, this is an over-simplification of the pharmacodynamic interaction and QTc effects would be influenced by other factors such as differences in the PK profile and concentrations in cardiac tissue, as well as the affinity and potency of the drugs for the hERG channel.
Labeling Recommendations for Section 12.2

The sponsor has not proposed labeling text based on the TQT study results. Our changes are highlighted (addition, deletion) below. Please note, that this is a suggestion only and that we defer final labeling decisions to the Division.

### 12.2 Pharmacodynamics

#### Cardiac Electrophysiology

**Reviewer’s comment:** Based on the available information, intrinsic and extrinsic factors that increase exposure to pretomanid are low body weight and administration with food. Clinical studies evaluating pharmacokinetics of pretomanid in subjects with renal impairment and hepatic impairment are still pending.

The categorical outliers will need to be updated when the Phase 3 trial is completed.

2 **Additional Reviewer’s Comments**

- Given that bedaquiline (including its M2 metabolite) is a known QT prolonging drug, we recommend that the clinical pharmacology review team evaluates any potential pharmacokinetic drug interactions between pretomanid and bedaquiline or linezolid and bedaquiline which could result in increased bedaquiline and/or M2 concentrations and further augmentation of the QT interval. In a TQT study for linezolid, therapeutic exposures with linezolid (1200 mg once daily) are not associated with the risk of QT prolongation to clinically relevant extent.

- The mean peak concentration of pretomanid was 1.27 μg/mL and 2.3 μg/mL for doses of 400 mg and 1000 mg, respectively in TQT study. Based on the available information and the sponsor’s population pharmacokinetics model, the peak concentrations of pretomanid at steady state with 200 mg once daily dosing in a typical drug-susceptible-TB subject under the fed condition is 3.2 μg/mL and the peak concentrations of pretomanid associated with the worst-clinical scenarios (female subjects, 35 kg weight, drug-sensitive TB subject, under fed condition) is 5.33 μg/mL. The QTc effects at these concentrations are predicted from the concentration-QTc analysis of the data obtained in the TQT study (see Table 3).
• At this stage in development, the highest clinically relevant exposures of pretomanid are not determined. Clinical studies to evaluate pharmacokinetics of pretomanid in subjects with renal impairment and hepatic impairment are still pending.

3 Background

The Global Alliance for TB Drug Development is developing an anti-mycobacterial drug, pretomanid (PA-824; MW 359), for the treatment of pulmonary extensively drug resistant, treatment-intolerant or nonresponsive multidrug-resistant (MDR) tuberculosis (TB) in adult population as part of a combination regimen with bedaquiline and linezolid. Pretomanid is a nitroimidazooxazine antimycobacterial agent and it is expected to impact Mycobacterium tuberculosis cell wall biosynthesis by inhibiting the oxidation of hydroxy-mycolate.

The proposed therapeutic dose is 200 mg once daily (oral tablet), for 26 weeks to be co-administered with bedaquiline and linezolid. The proposed doses for bedaquiline is 400 mg once daily for 2 weeks followed by 200 mg 3 times per week orally for a total of 26 weeks and for linezolid is 1200 mg daily orally for up to 26 weeks. Considering the dosing recommendation for bedaquiline, the pretomanid-bedaquiline-linezolid regimen is proposed to be taken with food.

The sponsor evaluated risk of QTc prolongation of pretomanid in a dedicated TQT study. This was a phase 1, single-center, randomized, double-blind, five period crossover study. In this study, the effects of single oral doses of 1) 400 mg and 2) 1000 mg of pretomanid and 3) 400 mg of pretomanid and 400 mg of moxifloxacin on QTc interval were compared with 4) placebo, using 5) 400 mg moxifloxacin as a positive control in healthy (male/female) subjects. The sponsor selected 400 mg pretomanid dose with the intention to achieve exposure levels similar to those expected in TB patients at steady-state with 2-fold accumulation (Study # CL-010, accumulation for Cmax 1.83-fold). Pretomanid exhibits a positive food effect with 88% increase in relative bioavailability (~1.74-fold for Cmax) under fed condition (a high-calorie, high-fat meal) compared to administration under fasted conditions (Study # CL-009). Based on the sponsor’s population pharmacokinetics model, the simulated peak concentrations of pretomanid at steady state with 200 mg once daily dosing in a typical drug-susceptible-TB subject under the fed condition is 3.2 μg/mL. Based on the available information and the sponsor’s population pharmacokinetics model, the highest exposures associated with the worst-clinical scenarios (female subjects, 35 kg weight, drug-sensitive TB subject, under fed condition, HIV negative, no concomitant anti-tuberculosis or anti-retroviral drugs, baseline albumin 35 g/L, baseline total bilirubin 5 μmol/L) is 5.33 μg/mL. The mean peak concentrations of 7.50 ±2.57 μg/mL are observed with highest dose studied (1200 mg once daily dosing under fasting condition for 14 days) in multiple dose study (Study # CL-007).

Linezolid is an oxazolidinone-class antibacterial agent indicated for the treatment of infections (NDA-021130/1/2, 2000, Zyvox® by Pharmacia and Upjohn) with 600 mg twice daily for 28 days as one of the therapeutic regimen. Although the total daily dose is similar to that of approved dosing regimen, the higher peak concentrations of linezolid are anticipated at steady-state with once daily regimen of 1200 mg. The risk QT prolongation of linezolid was studied in a randomized, positive- and placebo-controlled crossover thorough QT study (n=40). At both the 600 mg and 1200 mg doses (both administered as a 1-hour intravenous infusion), no significant effect on QTc interval was detected.
Bedaquiline is a diarylquinoline antimycobacterial agent (NDA-204384, 2012; Sirturo® by Janssen) with the therapeutic dose of 400 mg once daily for 2 weeks followed by 200 mg 3 times per week for 22 weeks with food. Bedaquiline label describes its QT prolongation risk in a box warning describing that QT prolongation can occur with bedaquiline and use with drugs that prolong the QT interval may cause additive QT prolongation. Warning and precaution section of the label describes 1) measurement and correction of serum electrolytes (potassium, calcium, and magnesium) during baseline, 2) monitoring ECGs for increase the risk for QT prolongation including combination therapy with other QT prolonging drugs, 3) criterion discontinuation of therapy including other QT prolonging drugs etc. Additionally, the product label describes the risk of QT prolongation of bedaquiline is relevant sections including over dosage, drug interaction, and clinical studies experience. The largest mean increase in QTc during the 24 weeks of bedaquiline treatment was 15.7 ms compared to 6.2 ms with placebo treatment (at Week 18) which was persisted even after the treatment was stopped. There were no documented cases of Torsade de Pointes in the safety database.

4 QT Assessment for Pretomanid

The QT-IRT reviewed the sponsor’s dedicated TQT study. No significant QT prolongation effect of pretomanid (400 mg and 1000 mg) was confirmed in this TQT Study. The largest upper bounds of the 2-sided 90% CI for the mean differences between 400 mg and placebo and between 1000 mg and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. None of the subjects had QTcF >480 ms nor ΔQTcF >60 ms. At the time of the TQT study, the highest clinically relevant exposures of pretomanid were not determined. The highest tested dose (1000 mg) provided 2-fold coverage in AUC and 1.8-fold coverage in Cmax as compared to the anticipated therapeutic dose of 200 mg once daily. The geometric mean Cmax of pretomanid was 1.27 μg/mL and 2.3 μg/mL for doses of 400 mg and 1000 mg, respectively. A shallow, positive concentration-QTc relationship was detected which is consistent with the nonclinical data that showed pretomanid inhibits the Ik, current with an IC50 of ~6.2 μg/mL which provides a ~19-fold exposure margin over the therapeutic exposures.

In addition to the TQT study, the sponsor conducted the concentration-QT analysis using time-matched data (5562 post-dose observations from 883 subjects in the 8 studies - CL-007, CL-010, NC-001, NC-002, NC-003, NC-005, NC-006 STAND, and Nix-TB) subjects with drug-susceptible TB, multi-drug-resistant TB, or extensively-drug resistant TB. Plasma concentrations of the drugs including pretomanid, bedaquiline, bedaquiline M2, moxifloxacin, pyrazinamide, and linezolid were obtained for measurement at the same time as the ECG collection.

The change from baseline in QTc based (ΔQTcF, ΔQTcB, and ΔQTcN) were studied using linear mixed-effect models for ΔQTc versus concentrations with slopes being constant across studies, visits, and timepoints, but with intercepts allowed to vary freely. For the combined regimens of two or more drugs, interaction coefficients were tested in the model to account for potential interaction between drugs. The interaction coefficients evaluated during the model development were: between pretomanid and bedaquiline M2, and between moxifloxacin and bedaquiline M2. Moxifloxacin was tested only in combination with pretomanid (plus other drug(s)). The interaction coefficients were small with 90% CI including zero, suggesting at most minor QTc interaction among pretomanid, bedaquiline, and moxifloxacin. The interaction coefficients were not included in the final model since they were not statistically significant (p value = 0.189). Subjects generally
exhibited a decrease in heart rate while on TB treatment, presumably due to the fact that subjects became healthier once the TB disease was under control.

**Figure 1: Exposure Response Relationship in Patients on Combination Regimen**

The sponsor’s analysis suggested that QTc increased with the plasma concentrations of pretomanid, bedaquiline metabolite M2, and moxifloxacin. The sponsor used population pharmacokinetics model for simulating the maximum pretomanid concentrations at steady state ($C_{\text{max, ss}}$: 3.2 μg/mL) with 200 mg once daily dosing in a typical drug-susceptible-TB subject under the fed conditions. The results of sponsor’s concentration-QT analysis are in agreement with those of the TQT (DMID 10-0058) study with the mean ΔΔQTcF and upper 90% limit (6.1 ms; Table 2) below the 10 ms threshold of regulatory concern (ICH, 2005).

**Reviewer’s comment:** The exposure response analysis cannot tease out the QT effects of pretomanid from the other drugs (e.g., bedaquiline, bedaquiline metabolite M2, linezolid, and moxifloxacin) given in the combination to various patient populations with a limited data on monotherapy. Therefore, the positive slope shown in Figure 1 may not be attributed to pretomanid concentration alone and is confounded with the administration of other drugs such as bedaquiline, its M2 metabolite, linezolid, and/or moxifloxacin.
Table 1: Summary of Concentration-QTc Slopes of Pretomanid, Bedaquiline M2 and Moxifloxacin

<table>
<thead>
<tr>
<th>Parameter</th>
<th>QTcF Estimate (90% CI)</th>
<th>QTcB Estimate (90% CI)</th>
<th>QTcN Estimate (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slope pretomanid (ms/mL/µg)</td>
<td>1.52 (1.20, 1.84)</td>
<td>1.43 (1.10, 1.77)</td>
<td>1.54 (1.22, 1.86)</td>
</tr>
<tr>
<td>Slope bedaquiline M2 (ms mL/µg)</td>
<td>17.6 (13.8, 21.4)</td>
<td>18.8 (14.8, 22.8)</td>
<td>18.4 (14.7, 22.2)</td>
</tr>
<tr>
<td>Slope moxifloxacin (ms mL/µg)</td>
<td>2.48 (1.54, 3.42)</td>
<td>2.81 (1.82, 3.8)</td>
<td>2.62 (1.69, 3.35)</td>
</tr>
</tbody>
</table>

Table 2: Comparison between results from the concentration-QTc model and the thorough QT study (Sponsor’s Analysis)

<table>
<thead>
<tr>
<th>Pretomanid Concentration (µg/mL)a</th>
<th>Source</th>
<th>ΔΔQTc b (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.27</td>
<td>Thorough QT Study</td>
<td>2.7 (≤ 4.4)</td>
</tr>
<tr>
<td>1.65</td>
<td>Concentration-QTc Model</td>
<td>2.5 (3.1)</td>
</tr>
<tr>
<td>2.33</td>
<td>Thorough QT Study</td>
<td>4.4 (≤ 6.1)</td>
</tr>
<tr>
<td>3.21</td>
<td>Concentration-QTc Model</td>
<td>4.9 (6.0)</td>
</tr>
</tbody>
</table>

*In the Thorough QT study, values are the geometric mean Cmax after a single dose. In the modeling analysis, values are median steady-state Cmax.

*For the Thorough QT study, ΔΔQTc, the placebo-adjusted change from baseline in the individual correction of QTc. For the modeling analysis, ΔΔQTc, the secular-trend-adjusted change from baseline for the data-based correction of QTc.

*For the Thorough QT study, the maximum least-squares-mean value. For the modeling analysis, the mean based on simulations of the model.

*For the Thorough QT study, based on all confidence intervals at QT observation times post dose. For the modeling analysis, the confidence limit based on simulations of the model.

Reviewer’s comment: Considering that concentration-QT analysis included 8 studies (with several confounding factors) without heterogeneity assessment, the QT-IRT recommend using the concentration-QTc analysis in the TQT study for labeling purposes. The overall results of sponsor’s concentration-QT analysis are in agreement with the FDA’s analysis with the mean ΔΔQTcF and upper 90% limit below the 10 ms threshold.

Table 3: The Point Estimates and the 90% CIs (FDA’s C-QT Analysis)

<table>
<thead>
<tr>
<th>ECG parameter</th>
<th>Treatment</th>
<th>Concentration</th>
<th>ΔΔ</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTc</td>
<td>400 mg single dose (200 mg†)</td>
<td>1.27 µg/mL</td>
<td>1.2</td>
<td>(0.6, 1.8)</td>
</tr>
<tr>
<td>QTc</td>
<td>1000 mg single dose (500 mg†)</td>
<td>2.30 µg/mL</td>
<td>2.4</td>
<td>(1.6, 3.8)</td>
</tr>
<tr>
<td>QTc</td>
<td>200 mg† (male 55 kg)</td>
<td>3.20 µg/mL</td>
<td>3.8</td>
<td>(2.2, 5.4)</td>
</tr>
<tr>
<td>QTc</td>
<td>200 mg† (female 35 kg)</td>
<td>5.33 µg/mL</td>
<td>7.8</td>
<td>(4.2, 9.8)</td>
</tr>
</tbody>
</table>

† once daily under fasting condition at steady-state; † once daily under fed condition at steady-state in a typical drug-susceptible-TB subject.

Reference ID: 4417295
Clinical Cardiac Safety

The sponsor provided integrated safety data from the currently ongoing Nix-TB study. This is a phase 3, open-label study assessing the safety and efficacy of combination of bedaquiline, pretomanid, linezolid in subjects with pulmonary infection of either extensively drug-resistant tuberculosis, or treatment intolerant/non-responsive multi-drug resistant tuberculosis. Subjects received 6 months of treatment from Day 1 to Week 26 or Day 1 to Week 39, and had follow-up visits performed at 1 and 2 months after treatment completion and then every 3 months after treatment completion for 24 months. Study involved pre-dose PK sample collection at W2, W8 and W16. PK Sub-study collected extensive samples (pre-dose, 0.5, 1, 2, 4, 8, 12, 13, 14, 16, 20, 24 h) at W16. Single 12-lead ECGs were collected at screening, Day 1, Week 1, Week 4, Week 8, Week 16, Week 26, Week 30, Week 39, and EoS/Early termination. In this ongoing study, approximately 93 (85%) subjects have received complete treatment of 26 weeks (interim data; safety 109 enrolled [15-Nov-2017], discontinued 10 (~9%), ongoing 84 (~77%), and 15 (~14%) completed study).

Seven (6.4%) subjects experienced TEAEs in the standardized MedDRA queries for QT prolongation, which consisted of the preferred terms electrocardiogram QT prolonged (6 subjects; syncope (1 subject; )). Five of the 7 events in the standardized MedDRA queries for QT prolongation were grade 1 in severity, 1 event was grade 2, and 1 event (the event of syncope) was grade 3. ECG and vital signs were not reported for the patient with grade 3 syncope.

No patients had QTcF intervals >480 ms. One subject (~1%) had a post-baseline increase of QTcF of >60 ms.

Reviewer’s comment: Given that subjects are co-administered bedaquiline in the phase 3 trial, adverse events of QTc prolongation cannot be directly attributed to pretomanid exposure.
Table 4: Categorical Outlier Analysis (Safety Population Nix-TB)

<table>
<thead>
<tr>
<th>Event Description</th>
<th>BPzL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment-emergent tachycardia</td>
<td>0/109 (0.6)</td>
</tr>
<tr>
<td>Post-baseline increase in QTcF of &gt;30 msec</td>
<td>30/109 (27.5)</td>
</tr>
<tr>
<td>Post-baseline increase in QTcF of &gt;40 msec</td>
<td>1/109 (0.9)</td>
</tr>
<tr>
<td>Post-baseline increase in QTcB of &gt;30 msec</td>
<td>12/109 (20.3)</td>
</tr>
<tr>
<td>Post-baseline increase in QTcR of &gt;60 msec</td>
<td>1/109 (0.6)</td>
</tr>
<tr>
<td>Post-baseline QTcF of &gt;450 msec</td>
<td>16/109 (14.7)</td>
</tr>
<tr>
<td>Post-baseline QTcF of &gt;480 msec</td>
<td>0/109 (0.0)</td>
</tr>
<tr>
<td>Post-baseline QTcF of &gt;500 msec</td>
<td>0/109 (0.0)</td>
</tr>
<tr>
<td>Post-baseline QTcB of &gt;450 msec</td>
<td>12/109 (20.4)</td>
</tr>
<tr>
<td>Post-baseline QTcB of &gt;480 msec</td>
<td>5/109 (4.8)</td>
</tr>
<tr>
<td>Post-baseline QTcB of &gt;500 msec</td>
<td>1/109 (0.9)</td>
</tr>
<tr>
<td>Post-baseline increase in QTcF of &gt;30 msec resulting in a post-baseline QTcF of &gt;450 msec</td>
<td>2/109 (1.4)</td>
</tr>
<tr>
<td>Post-baseline increase in QTcF of &gt;30 msec resulting in a post-baseline QTcF of &gt;480 msec</td>
<td>0/109 (0.6)</td>
</tr>
<tr>
<td>Post-baseline increase in QTcF of &gt;30 msec resulting in a post-baseline QTcF of &gt;500 msec</td>
<td>0/109 (0.0)</td>
</tr>
<tr>
<td>Post-baseline increase in QTcB of &gt;30 msec resulting in a post-baseline QTcB of &gt;450 msec</td>
<td>9/109 (7.2)</td>
</tr>
<tr>
<td>Post-baseline increase in QTcB of &gt;30 msec resulting in a post-baseline QTcB of &gt;480 msec</td>
<td>2/109 (1.8)</td>
</tr>
<tr>
<td>Post-baseline increase in QTcB of &gt;30 msec resulting in a post-baseline QTcB of &gt;500 msec</td>
<td>1/109 (0.9)</td>
</tr>
<tr>
<td>Post-baseline QRs &gt;=120 msec and a &gt;=20% increase from baseline</td>
<td>0/109 (0.0)</td>
</tr>
<tr>
<td>Post-baseline HR. :=220 msec and a :=20% decrease from baseline</td>
<td>3/109 (2.3)</td>
</tr>
<tr>
<td>Post-baseline HR. := 50 beats per minute and a :=20% decrease from baseline</td>
<td>4/109 (3.7)</td>
</tr>
</tbody>
</table>

Source: Table 24 in Summary of Clinical Safety

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqqt@fda.hhs.gov.
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/

GIRISH K BENDE
04/10/2019 12:57:26 PM

CHRISTINE E GARNETT
04/10/2019 01:00:07 PM
## LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

<table>
<thead>
<tr>
<th><strong>Date of This Review:</strong></th>
<th>March 20, 2019</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Requesting Office or Division:</strong></td>
<td>Division of Anti-Infective Products (DAIP)</td>
</tr>
<tr>
<td><strong>Application Type and Number:</strong></td>
<td>NDA 212862</td>
</tr>
<tr>
<td><strong>Product Name and Strength:</strong></td>
<td>Pretomanid tablets, 200 mg</td>
</tr>
<tr>
<td><strong>Product Type:</strong></td>
<td>Single ingredient</td>
</tr>
<tr>
<td><strong>Rx or OTC:</strong></td>
<td>Rx</td>
</tr>
<tr>
<td><strong>Applicant/Sponsor Name:</strong></td>
<td>Global Alliance for TB Drug Development, Inc.</td>
</tr>
<tr>
<td><strong>FDA Received Date:</strong></td>
<td>December 14, 2018</td>
</tr>
<tr>
<td><strong>OSE RCM #:</strong></td>
<td>2018-2703</td>
</tr>
<tr>
<td><strong>DMEPA Safety Evaluator:</strong></td>
<td>Millie Shah, PharmD, BCPS</td>
</tr>
<tr>
<td><strong>DMEPA Team Leader:</strong></td>
<td>Otto L. Townsend, PharmD</td>
</tr>
</tbody>
</table>
1 PURPOSE OF REVIEW
As part of the approval process for Pretomanid tablets, the Division of Anti-Infective Products (DAIP) requested that we review the proposed labels, labeling, and packaging for areas that may lead to medication errors.

2 MATERIALS REVIEWED

<table>
<thead>
<tr>
<th>Material Reviewed</th>
<th>Appendix Section (for Methods and Results)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product Information/Prescribing Information</td>
<td>A</td>
</tr>
<tr>
<td>Previous DMEPA Reviews</td>
<td>B</td>
</tr>
<tr>
<td>ISMP Newsletters</td>
<td>C-N/A</td>
</tr>
<tr>
<td>FDA Adverse Event Reporting System (FAERS)</td>
<td>D-N/A</td>
</tr>
<tr>
<td>Other</td>
<td>E-N/A</td>
</tr>
<tr>
<td>Labels and Labeling</td>
<td>F</td>
</tr>
</tbody>
</table>

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 FINDINGS AND RECOMMENDATIONS

Tables 2 and 3 below include the identified medication error issues with the submitted label and labeling, DMEPA’s rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Our review of the 30-tablet count bottle container label identified the statement, "Dispense only in original container" on the side panel. We contacted the Office of Pharmaceutical Quality (OPQ) to verify the intended meaning of the statement. According to OPQ, the tablets should remain in the original container and not be repackaged. Our medication error concern is that prescribed quantities that are less than 30 tablets would not be able to be dispensed outside of the original 30-tablet count bottle. Thus, the entire 30-tablet count bottle would need to be dispensed and patients may have a greater supply than needed to complete the therapy, resulting in the potential for wrong duration errors where patients continue to take the drug after it has been discontinued. We discussed our concern with DAIP and learned that patients requiring treatment with pretomanid tablets will be closely monitored by their health care provider (i.e., directly observed therapy). Therefore, in this instance, we find this mitigation strategy will likely address our medication error concern.

Table 2: Identified Issues and Recommendations for Division of Anti-Infective Products (DAIP)

<p>| Prescribing Information |</p>
<table>
<thead>
<tr>
<th>IDENTIFIED ISSUE</th>
<th>RATIONALE FOR CONCERN</th>
<th>RECOMMENDATION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.</strong> The dose of linezolid is presented as “1200 mg”</td>
<td>Readers may misinterpret numbers greater than or equal to 1,000 without a comma as hundreds “100” or ten-thousands “10000”.&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Revise the dose of linezolid from “1200 mg” to “1,200 mg”</td>
</tr>
<tr>
<td><strong>2.</strong> The dosing information for pretomanid, bedaquiline, and linezolid is presented in a paragraph</td>
<td>The presentation of the combination dosing regimen for all 3 drugs in a paragraph format may decrease readability.</td>
<td>Consider using bullets for each drug’s dosing regimen. For example:</td>
</tr>
</tbody>
</table>

---

**Full Prescribing Information**

<table>
<thead>
<tr>
<th></th>
<th>Container Labels</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>The expiration date in the human-readable portion of the product identifier is presented as MMM.YYYY</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Confusion from the presentation of the expiration date may result in deteriorated drug errors</td>
<td></td>
</tr>
<tr>
<td></td>
<td>As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate</td>
<td></td>
</tr>
</tbody>
</table>
the portions of the expiration date.\textsuperscript{b}

<table>
<thead>
<tr>
<th>Carton Labeling (28 tablet count and 30 tablet count)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.</strong> See Container Label #1</td>
</tr>
<tr>
<td><strong>2.</strong> The human-readable portion of the product identifier is missing the NDC and Serial Number as required by the Drug Supply Chain Security Act (DSCSA)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>3.</strong> See Container Label #3</td>
</tr>
</tbody>
</table>

4 CONCLUSION

Our evaluation of the proposed label and labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to the Applicant so that recommendations are implemented prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Pretomanid tablets that Global Alliance for TB Drug Development, Inc. submitted on December 14, 2018.

<table>
<thead>
<tr>
<th>Table 4. Relevant Product Information for Pretomanid</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial Approval Date</strong></td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th><strong>Active Ingredient</strong></th>
<th>pretomanid</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indication</strong></td>
<td>nitroimidazooxazine antimycobacterial drug indicated, as part of a combination regimen with bedaquiline and linezolid, in adults for the treatment of pulmonary extensively drug resistant (XDR) or treatment-intolerant or nonresponsive multidrug-resistant (MDR) tuberculosis (TB)</td>
</tr>
<tr>
<td><strong>Route of Administration</strong></td>
<td>oral</td>
</tr>
<tr>
<td><strong>Dosage Form</strong></td>
<td>tablet</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>200 mg</td>
</tr>
<tr>
<td><strong>Dose and Frequency</strong></td>
<td>200 mg once daily for 26 weeks Pretomanid should be administered with bedaquiline (400 mg once daily for 2 weeks followed by 200 mg 3 times per week [with at least 48 hours between doses] orally for a total of 26 weeks) and linezolid (starting at 1,200 mg daily orally for up to 26 weeks).</td>
</tr>
<tr>
<td><strong>How Supplied/ Container Closure</strong></td>
<td>Bottle of 30 tablets Unit dose blister pack of 28 tablets (2 strips of 14 tablets)</td>
</tr>
<tr>
<td><strong>Storage</strong></td>
<td>Store</td>
</tr>
</tbody>
</table>
APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis, along with postmarket medication error data, we reviewed the following Pretomanid tablets labels and labeling submitted by Global Alliance for TB Drug Development, Inc. on December 14, 2018.

- Container Label
- Carton Labeling
- Unit-Dose Blister Labels
- Unit-Dose Carton Labeling
- Medication Guide (Image not shown) accessible in EDR via: 
  \cdsesub1\evsprod\nda212862\0001\m1\us\114-labeling\draft\labeling\pretomanid-medication-guide.pdf
- Prescribing Information (Image not shown) accessible in EDR via: 
  \cdsesub1\evsprod\nda212862\0001\m1\us\114-labeling\draft\labeling\pretomanid-draft-labeling-text.pdf

F.2 Label and Labeling Images

Container Label

---

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/

MILLIE B SHAH
03/20/2019 12:57:10 PM

OTTO L TOWNSEND
03/20/2019 05:59:54 PM