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December 13, 2019

Dear Sharonann and Vivian,

Thank you for your interest in the BPaL regimen and the Nix-TB trial. Your continued advocacy for access and innovation in the field of tuberculosis is critical to ensuring the global health community's progress in beating this terrible disease.

To maximize transparency and to address the questions raised in your letter to us on October 25th, we have systematically gone through each question and provided a response. This represents our best effort in sharing data that is available or is currently being collected. In the instance that novel data can be generated to further advance the science of pretomanid, we would welcome the opportunity to discuss.

Please note that these responses are purely intended for the purpose of scientific exchange and should in no way be viewed as promotional. Further, our responses may include references to information outside of the approved US FDA label but that has already been put into the public domain through previous publications and/or presentations. None of this information should be construed as applying to pretomanid sales in the United States, which has a distinct set of FDA regulations governing product marketing and communications. Rather, these responses are only intended for those working in global public health.

Your letter specifically raised the concern of hepatotoxicity. With respect to this, we would like to provide some clarifying details at the outset of this reply. As presented in the US Product Label for pretomanid, hepatic enzyme elevations may have been caused by factors other than pretomanid and bedaquiline. In fact, in the Nix-TB Trial, all 9 patients whose treatment was interrupted for elevated liver enzymes were rechallenged with pretomanid and bedaquiline and were able to complete their full course of treatment. Thus, no surviving patients were withdrawn from completing the full therapeutic course for hepatic adverse events, and no patients died from hepatic adverse events.

We also take note of your interest in data on the use of pretomanid in pregnant or lactating women or children. At this point we do not yet have data on these important populations, which is the case for nearly all drugs receiving their first marketing approval.

Below are our responses to the specific questions that you have raised. If additional details are sought, please advise and we will be sure to supply that information to the best of our ability.

While waiting for clinical trial results, there remain a number of questions regarding the potential future role of pretomanid, both within the BPaL regimen and as an individual drug:

- *How effective is pretomanid outside of the BPaL regimen – what are pretomanid's independent contributions to the safety and efficacy of the BPaL regimen for XDR-TB or resistance/intolerance to MDR-TB;*

  Robust preclinical models clearly demonstrate the critical contribution of pretomanid in the BPaL and other combination regimens. Please see Figure 1 and the discussion on pages 14 and 15 of the Sponsor Briefing Document for the FDA Antimicrobial Drugs Advisory Committee meeting, June 6, 2019 (Hereafter "Briefing Document"): https://www.fda.gov/media/127593/download

  In addition, pretomanid monotherapy has demonstrated clinical anti-TB activity in two studies of Early Bactericidal Activity in patients with newly diagnosed TB. Details of this monotherapy EBA activity are published in references *Diacon 2010 and Diacon 2012a*. In addition, pretomanid has demonstrated activity in various combinations in other studies of 2 weeks to 6 months of therapy in patients with both DS and MDR TB. A table of 16 studies of pretomanid and key results are in Appendix 10, Table 45 of the Briefing Document, and key publications are in references *Diacon 2012b, Dawson 2012, Diacon 2015,* and in *Tweed 2019*. The FDA approval of pretomanid as part of BPaL is indicative of the fact that the totality of data met the requirements for U.S. regulatory approval.

- *How does pretomanid compare to other available second line TB drugs, especially with delamanid, which is from the same class of drugs;*

  We have not conducted clinical trials comparing pretomanid to delamanid. There are many publications on the use of each of these drugs in clinical trials, although there are no direct comparisons within the same trial. Our focus at TB Alliance has been and continues to be on developing pretomanid in novel regimens that are optimized for efficacy and safety. Of note, pretomanid is only approved for use in the United States, and that is only in the regimen combined with bedaquiline and linezolid for the treatment of people with XDR-TB or treatment-failed/intolerant MDR-TB. While there are no trials underway that we are aware of that are comparing pretomanid and delamanid, we would be very receptive to the possibility of clinical trial networks undertaking such studies.

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- *How does the BPaL regimen compare to other regimens containing Group A and B drugs with or without delamanid – BPaL was compared to historical data from patients with XDR-TB treated between 2008–2012 and who did not receive bedaquiline, linezolid, or delamanid, all of which are part of the standard of care for XDR-TB patients today;*

  Patients with XDR-TB treated in Cape Town, South Africa at one of the sites of the Nix-TB trial have reported cure rates that were below 20% prior to the use of bedaquiline or linezolid. That has more recently improved to a rate of approximately 66% when bedaquiline and linezolid (81% of the 68 patients) were components of their regimens (Olayanju 2018). These patients received a median of 8 drugs for a 24-month treatment.

  Drawing from the database of patients used in the Olayanju 2018 publication, a matched cohort comparison of patients from the Nix-TB study relative to patients treated during the same time period with bedaquiline, and the majority with linezolid, in Cape Town, South Africa has been completed. These results will be submitted soon for publication. Publication timelines will obviously depend on speed of review and acceptance of the manuscript.

- *Is BPaL effective against TB that might be resistant to bedaquiline, linezolid, or delamanid;*

  The BPaL regimen is intended to be used in patients who have TB susceptible to the three drugs in the regimen. There is minimal to no data on BPaL effectiveness against TB that is resistant to bedaquiline, linezolid or delamanid.

- *How should patients that develop early toxicity to one or more of the drugs in BPaL be managed;*

  Please see the attached US Product Label (also available at this link) for recommendations on monitoring and managing adverse events.

- *Should bedaquiline, linezolid, or delamanid resistance testing be available and performed prior to starting the BPaL regimen;*

  The US Product Label does not require resistance testing before the BPaL regimen is used. Additional countries that approve pretomanid in the regimen will make their own assessments regarding the need for resistance testing based on the epidemiology of TB in their region and the treatment history of the patient. Please note that in the Nix-TB trial, results of bedaquiline, linezolid and pretomanid resistance testing were only available after patients were entered on study and none were removed based on the baseline results. However, the protocol excluded patients who had received more than 14 days of bedaquiline or linezolid.

- *Is there cross-resistance between pretomanid and delamanid, since they are in the same drug class;*

  As noted in the US Product Label, “Cross resistance of pretomanid with other compounds in the same class has been observed.”

- *What is the effectiveness and safety of pretomanid in children and what is the correct dosage for pediatric use – there is no pharmacokinetic data in children;*

  There are no data yet on the use of pretomanid in children. TB Alliance has a Pediatric Investigational Plan that has been approved by the European Medicines Agency. A 10 and 50mg dispersible formulation for use in children has been developed with our global commercialization partner, Mylan, and will begin evaluation in humans in 2020.

- *What are the results of studies that show pretomanid is safe after male fertility concerns from animal studies;*

  Studies relevant to testicular safety have been presented in briefing documents for the FDA Advisory Committee meeting (see Section 7.6.2 of the Briefing Document). Testicular toxicity was noted in non-clinical toxicology studies in rodents. In multiple toxicology studies in non-human primates up to nine months of duration, no histopathologic changes in the male genital organs have been identified. The potential for testicular toxicity was examined in Studies NC-002, NC-005, and NC-006 (also known as the STAND trial). These studies provided an assessment of serum hormone levels relevant to male reproductive health, including follicle stimulating hormone (NC-002, NC-005, NC-006), luteinizing hormone (NC-002, NC-006), inhibin B (NC-006), and testosterone (NC-002, NC-006). As a whole, these hormone assessments demonstrated an improvement in the underlying hypogonadism that is generally associated with illness (tuberculosis), as reflected by increases in the testosterone and inhibin B levels in all treatment arms, which is consistent with improvements in the underlying disease state. In addition, the study comparing two different dose levels of pretomanid (NC-006; 100 mg versus 200 mg) showed no adverse serum hormone effects resulting from doubling the exposure. In conclusion, none of the changes observed thus far in

pretomanid clinical trials suggested testicular damage. A study to rule out any effects of pretomanid on the semen of human males will begin in 2020.

- *How will the BPaL regimen perform in HIV infected patients with low CD4 counts or receiving an antiretroviral treatment regimen containing dolutegravir;*

  HIV-infected patients with CD4 counts as low as 50 were eligible to enroll in Nix-TB, and there were patients who had CD4's below 100 that participated. HIV-infected patients, most of whom were receiving ARV's, had the same efficacy as non-HIV-infected patients in Nix-TB. There is no anticipated drug interaction with dolutegravir, as neither drug has a significant effect on hepatic enzymes or transporters that would affect the clearance of either drug.

- *Is the BPaL regimen safe to use in patients with underlying liver disease, and what is the recommended clinical monitoring plan for hepatotoxicity in such patients taking BPaL;*

  The US Product Label does not exclude patients with underlying liver disease although it notes to monitor symptoms, signs, and laboratory tests for liver disease while a patient takes the regimen. The US Prescribing Information recommends to monitor symptoms and signs (such as fatigue, anorexia, nausea, jaundice, dark urine, liver tenderness, and hepatomegaly) and laboratory tests (ALT, AST, alkaline phosphatase, and bilirubin) at a minimum at baseline, at two weeks, and then monthly while on treatment and as needed..

  The US Product Label provides guidelines and information regarding the potential for liver adverse effects, and publications of Phase 2 studies have presented information on hepatic effects. A manuscript presenting data from the STAND trial is being finalized and will be submitted for publication shortly. The Nix-TB trial excluded patients with transaminase levels greater than three times the upper limit of normal.

- *What is the functional impact of peripheral neuropathy for people who received BPaL and developed this adverse event;*

  The functional impact of peripheral neuropathy is highly variable across individual patients and depends on many factors. Initial experience is presented in the Briefing Document in Section 7.6.8, beginning on page 96, and will be submitted to a peer reviewed publication. As more patients have completed follow up to the endpoint 24 months after completion of therapy, further detailed analyses will be made and published to characterize the incidence and time course of peripheral neuropathy associated with the use of linezolid in the trial.

  Peripheral neuropathy was closely monitored during treatment and continues to be closely monitored during the two-year follow-up post completion of treatment. Monitoring is done with both a standardized questionnaire as well as physical exam. Thus far, reversibility has been observed in the large majority of patients who experienced peripheral neuropathy and in both of the patients who experienced optic neuritis.

- *Could other regimens (some being tested currently in clinical trials such as ZeNix, TB PRACETAL, or endTB) with a lower dose of linezolid or longer durations have similar favorable outcomes with fewer and less severe adverse events;*

  Ongoing trials like TB PRACTECAL trial (run by MSF) and TB Alliance's ZeNix trial are evaluating pretomanid in combination with linezolid, with linezolid used at lower doses and/or for shorter durations of administration than those of the current BPaL regimen. However, the only clinical trial we are aware of that randomizes patients to different durations and dosages is the ZeNix trial, which is scheduled to have top line results available mid-2021.

- *What are the critical concentrations of pretomanid to inform drug susceptibility testing;*

  Setting critical concentrations for TB drugs is the mandate of FDA, CLSI, EUCAST, and WHO, not the Sponsor. The TB Alliance has collected and tested mycobacterial isolates from clinical trials as well as strain collections, and will be working with these organizations to facilitate recommendations. The TB Alliance is also involved in providing a standardized and validated protocol for pretomanid susceptibility testing.

- *Can the mechanisms of resistance to pretomanid be well described and have the predictive mutations been discovered;*

  In general, characterization of resistance is considered an integral part of the development of anti-infective agents. The knowledge base around resistance to any drug builds over time, as clinical usage increases. We are working to identify mechanisms of resistance, and we are working with diagnostic laboratories to standardize testing methodologies and reagents for phenotypic resistance testing. As

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knowledge develops of molecular mechanisms we will work with partners to develop a rapid test of resistance. Section 12.4 (Microbiology/Resistance) of the US product label notes:

> "Mutations in five *M. tuberculosis* genes (*ddn*, *fgd1*, *fbiA*, *fbiB*, and *fbiC*) have been associated with pretomanid resistance. The products of these genes are involved in bioreductive activation of pretomanid within the bacterial cell. Not all isolates with increased minimum inhibitory concentrations (MICs) have mutations in these genes, suggesting the existence of at least one other mechanism of resistance. The *in vitro* frequency of resistance development to pretomanid ranged from 10^{-7} to 10^{-5} at 2 to 6 times the pretomanid MICs. Cross resistance of pretomanid with other compounds in the same class has been observed."

- *Can the use of the BPaL regimen be safely expanded beyond its FDA approved indication (XDR-TB or TI/NR MDR-TB) to include patients with MDR-TB;*

  Currently the BPaL regimen is only approved by the US FDA to be used in patients with XDR-TB or TI/NR MDR-TB; this was the population in the pivotal Nix-TB trial which provided the information for approval. The ongoing TB PRACTECAL trial includes patients with MDR-TB, and the ZeNix trial includes patients with pre-XDR-TB in addition to the population studied in Nix-TB.

- *What is the optimal dose and duration of linezolid (in part being answered in ongoing clinical trials);*

  The optimal dose and duration of linezolid in the BPaL regimen is not yet known. The US Product Label approves pretomanid to be used with bedaquiline and linezolid, with linezolid to be administered at 1200 mg total daily dose for up to 6 months. The label provides information about reducing or interrupting the dose or discontinuing linezolid as required to manage adverse events related to this drug. Whether there is a more optimal dose and duration is being studied. The ongoing ZeNix trial evaluates the regimen with arms randomizing patients to receive linezolid either for 2 or 6 months and at daily doses of either 1200 mg or 600 mg. We expect results of this trial to be available mid-2021.

- *Can the effectiveness of the BPaL regimen be improved by adding one or more additional second line TB drugs to the BPaL regimen.*

  Pretomanid has been developed in the context of a specific regimen. It is approved to be used only in combination with bedaquiline and linezolid, and without any additional drugs. The ongoing TB-PRACTECAL Trial is evaluating pretomanid in regimens with bedaquiline and linezolid alone, and in this regimen with the addition of either clofazimine or moxifloxacin; results are not yet available. We do not have any data which would answer the question of whether the effectiveness of the BPaL regimen can be improved or the safety profile would be adversely impacted with the addition of other second line TB drugs. We would be receptive to the possibility of clinical trial networks undertaking such trials.

We greatly appreciate your interest in TB treatment and hope that these answers are helpful in addressing your important questions. As mentioned above, please do not hesitate to reach out for further clarification as needed. We look forward to a sustained and fruitful dialogue with civil society as we pursue our mission of discovering, developing, and delivering new TB drug regimens that are impactful and accessible to the people who need them.

Sincerely,

Mel

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