22 May 2019

Dockets Management Staff (HFA–305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Written testimony re: docket number: FDA-2019-N-1317

Dear members of the FDA Antimicrobial Drugs Advisory Committee:

Treatment Action Group (TAG) thanks you for this opportunity to provide input into the review of pretomanid — the first tuberculosis (TB) drug candidate developed by a not-for-profit organization, and the first to be submitted for stringent regulatory review having been developed as part of a regimen. The review of pretomanid — when given with bedaquiline and linezolid in the so-called Nix-TB regimen (or BPaL) — is momentous. Simplifying treatment for some of the most difficult to treat strains of TB to just six months of three drugs would be a dramatic improvement for patients and providers alike. The review of pretomanid is also significant because approving a new drug application on the basis of a small (N=109), single-armed, non-randomized clinical trial using retrospective, non-concurrent historical controls, would mark a major deviation from the regulatory stringency the U.S. Food and Drug Administration (FDA) generally requires for new antimicrobials, particularly in diseases where randomized, controlled studies have driven medical knowledge since the very first randomized trial, which was of streptomycin for pulmonary TB back in 1948.1

Simpler, safer, and more effective new TB treatment regimens are urgently needed, particularly for the most difficult-to-treat strains of TB – such as treatment-intolerant drug-resistant TB (TI/DR-TB) and pre-extensively drug-resistant (pre-XDR-) and extensively drug-resistant TB (XDR-TB). The FDA approved the design of the Nix-TB trial when mortality rates for difficult-to-treat forms of drug-resistant TB were as high as 73 percent and even higher (98 percent) among people with comorbid conditions such as advanced HIV disease.2,3 We believe the Nix-TB trial was designed and approved in good faith.

Yet in spite of the improving prognosis for TI/DR-, pre-XDR-, and XDR-TB, the historical controls used by the sponsor and apparently accepted by the FDA for this New Drug Application (NDA) all come from a period before the widespread use of bedaquiline and (off-label) of linezolid in newer combinations to treat drug-resistant TB in programmatic settings in South Africa. Bedaquiline and

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linezolid are sometimes given with delamanid, another nitroimidazole (like pretomanid), which was granted conditional approval by the European Medicines Agency in 2014, but is not yet FDA-approved. When the Nix-TB trial was in the planning stages it was believed that bedaquiline and delamanid could not be used together due to a potential overlapping cardiac toxicity (QTc-prolongation). However in recent years, several groups have reported programmatic outcomes for treatment of drug-resistant TB using both bedaquiline and delamanid without significant reported QTc prolongation or sudden cardiac deaths. Recently-reported results from a drug-drug interaction study conducted by the AIDS Clinical Trials Group (ACTG A5343), to evaluate the safety, tolerability, and pharmacokinetics of bedaquiline and delamanid alone and in combination, which completed enrollment of 84 persons in July 2018 show that bedaquiline and delamanid can be safely used together.4

The standard of care for drug-resistant TB has changed dramatically in the years since the beginning of the uncontrolled Nix-TB study, which is the basis of this NDA. The World Health Organization (WHO) guidelines (updated in 2019) now recommend highly effective bedaquiline and linezolid as first choice agents for treating all cases of drug-resistant TB.5 This significant evolution in the standard of care for drug-resistant TB raises questions about whether the Nix-TB trial design is adequate to support full approval of pretomanid, and whether the use of historical controls from the era before the widespread use of bedaquiline in program settings to treat all forms of DR-TB is an appropriate and meaningful comparison.6 We point to the research and regulatory considerations laid out in testimony submitted by our partners in the Global TB Community Advisory Board (TB CAB) regarding pretomanid’s efficacy and safety, and the precedent its approval might set in terms of lowering the evidentiary standard for the future approval of new TB drugs and regimens.7

After TB researchers pioneered the use of randomized, controlled clinical trials in the 1940s and 1950s to validate health interventions to the benefit of medical and regulatory science across the board,8,9 the field of TB research fell into disrepair, and many historically recommended treatments

6 Ibid.
9 Fox W, Ellard GA, Mitchison DA. Studies on the treatment of tuberculosis undertaken by the British Medical Research Council tuberculosis units, 1946-1986, with relevant subsequent
have since been based on low-quality evidence, without proper characterization or validation of the safety or efficacy of agents or regimens recommended for treating TB. The FDA’s accelerated approval of bedaquiline in 2012 was a pivotal moment marking the beginning of a new era of quality evidence for TB. We urged the FDA and the Advisory Committee reviewing the NDA for bedaquiline at that time to “Be bold. Make history. But do it stringently.”

Today, we ask you to again balance boldness with stringency. To support your efforts to determine where that balance rests, we suggest exploring the following questions:

1. What evidence is there of pretomanid’s quantitative and qualitative individual, independent contribution to the efficacy of the Nix-TB regimen – bedaquiline, linezolid, and pretomanid – in humans with TI/DR-, pre-XDR-, and XDR-TB?

2. Is the lack of an active control appropriate for informing full FDA approval, when the efficacy and safety of the standard of care (and the duration of care in some settings) has dramatically improved since the design of the Nix-TB trial? In particular, is the use of a historical control from the era before the introduction of bedaquiline-based therapy for the vast majority of cases of all forms of drug-resistant TB still of continued relevance?
   a. Given the accumulating evidence on outcomes of drug-resistant TB in the bedaquiline-for-all era, would use of a historical control be appropriate in the future? Or would the new control arm in trials of regimens for the treatment of TI/DR-TB-, pre-XDR-, and XDR-TB become the Nix-TB regimen?
   b. If historical controls are used in the future for regulatory approval of new TB drugs or regimens, should a concurrent rather than retrospective cohort approach be preferred, if an active control arm is not used?

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*Schnippel K, Ndjeka N, Maartens G, et al. Effect of bedaquiline on mortality in South African patients with drug-resistant tuberculosis: a retrospective cohort study. Lancet Respir Med. 2018 Jul 9. doi: https://doi.org/10.1016/S2213-2600(18)30235-2. “A bedaquiline-containing regimen was given to 743 (4·0%) of 18 542 patients with multidrug-resistant or rifampicin-resistant tuberculosis and 273 (25·4%) of 1075 patients with extensively drug-resistant tuberculosis. Among 1016 patients who received bedaquiline, 128 deaths (12·6%) were reported, and there were 4612 deaths (24·8%) among 18 601 patients on the standard regimens. Bedaquiline was associated with a reduction in the risk of all-cause mortality for patients with multidrug-resistant or rifampicin-resistant tuberculosis (hazard ratio [HR] 0·35, 95% CI 0·28–0·46) and extensively drug-resistant tuberculosis (0·26, 0·18–0·38) compared with standard regimens.”*
3. Is the evidence base sufficient to establish the safety and efficacy for pretomanid given that pretomanid is being considered for approval as part of the Nix-TB regimen, which just 109 people have received for the intended indication (XDR-TB, TI/DR-TB, and treatment non-responsive DR-TB) and duration (six months), and been evaluated for the clinical efficacy endpoint of interest (relapse-free cure)?

   a. If the evidence is sufficient for full approval of pretomanid as part of the Nix-TB regimen, should the FDA provide full approval for bedaquiline and linezolid for the same indication and duration?

   b. Did the FDA request supplemental NDA (sNDA) filings from Johnson & Johnson (J&J) for bedaquiline and from Pfizer for linezolid to revise their labeling and package insert to accommodate new indications for treatment of XDR-TB, TI/DR-TB, and treatment non-responsive DR-TB as a result of the Nix-TB study results? And if not, why?

   In 1995, while it was evaluating Abbott Laboratories’ NDA for full approval for ritonavir [brand name Norvir], the FDA requested that Merck & Co. submit its new protease inhibitor, indinavir [brand name Crixivan] for accelerated approval based on phase II study results. The FDA did this to ensure that two potent protease inhibitors would be released on the market in the same month in March 1996, thereby launching the era of highly-active antiretroviral therapy (HAART).

   c. If the FDA approves pretomanid under this NDA with data from the Nix-TB trial, will J&J and Pfizer (and other manufacturers) be allowed to use the new pretomanid label as a back-door implicit license to market bedaquiline and linezolid for off-label indications? If so, what are the possible unanticipated and unintended downstream consequences on the future of regulatory- and guidelines-directed clinical trials necessary to support the evolving standards of care for TB and other diseases?

4. As the optimal dosing of linezolid is still under investigation (and linezolid currently lacks an indication for TB, despite its apparent importance and position alongside bedaquiline as a core component of the new standard of care for all forms of drug-resistant TB established by the latest WHO treatment recommendations), does the Committee feel comfortable recommending approval of new drug pretomanid in the context of the linezolid-containing, three-drug Nix-TB regimen?

5. What future research on pretomanid and/or the regimen under consideration does the TB field need and would the Committee want to see?

   We understand that pretomanid is under consideration for full approval (as opposed to accelerated approval) by the FDA, which limits the type and scope of research the FDA can require as a condition of approval. However, several significant research gaps of critical
importance to patient care and normative guidance remain unfilled, as detailed in the testimony of the TB CAB.\textsuperscript{12}

6. Would it be preferable, given the small sample size, short duration of follow-up, and lack of a concurrent active control arm, for the FDA to grant pretomanid an accelerated approval, which would strengthen the FDA’s ability to mandate required post-marketing studies?

a. If pretomanid is granted full approval how will commitments to conduct necessary post-approval studies be secured?

A pressing question for the TB field is how the performance of pretomanid compares to that of delamanid in the same population studied in the Nix-TB trial – e.g., a study with bedaquiline plus linezolid with either delamanid or pretomanid. Another series of important questions involve studying pretomanid-containing regimens in pregnant women, adolescents, children, infants, and neonates.

b. If full approval is granted now, what will induce the Sponsor – or other clinical trials implementers and networks – to carry out such studies?

7. If pretomanid is approved, what efforts will FDA take to uphold regulatory stringency for future TB drugs and regimens, and prevent this approval from setting a precedent for the acceptance of small, non-controlled, non-randomized trials as sufficient evidence of efficacy and safety?

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**About TAG:** Treatment Action Group (TAG) is an independent, activist and community-based research and policy think tank fighting for better treatment, prevention, a vaccine, and a cure for HIV, tuberculosis, and hepatitis C virus. TAG works to ensure that all people with HIV, TB, or HCV receive lifesaving treatment, care, and information. We are science-based treatment activists working to expand and accelerate vital research and effective community engagement with research and policy institutions. TAG catalyzes open collective action by all affected communities, scientists, and policy makers to end HIV, TB, and HCV.

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