Testimony re: docket number FDA-2019-N-1317

Thank you to the U.S. Food and Drug Administration (FDA) and members of the Antimicrobial Drugs Advisory Committee for this opportunity to offer testimony on behalf of Treatment Action Group (TAG).

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 (TB), and hepatitis C virus (HCV). As science-based treatment activists, we have a long history of productive engagement with the FDA, and of advocating for rigorous science and high regulatory standards for new medicines.

Today's review of the new drug application (NDA) for pretomanid when given with bedaquiline and linezolid in the so-called Nix-TB regimen (or BPaL) is significant. The world urgently needs simpler, shorter approaches to treating TB, especially the most difficult forms of TB. Yet, approving a new drug application on the basis of a small, single-arm, non-randomized clinical trial using retrospective, non-concurrent historical controls, would also mark a major departure from the regulatory stringency the FDA requires for new antimicrobials. Randomized, controlled studies (RCTs) have driven medical knowledge since the very first randomized trial, which was of streptomycin for pulmonary TB in 1948.[1]

Between 1948 and 1986, the TB field benefited from rigorous science. RCTs conducted during that period taught us to use combination treatment to prevent the development of resistance, and established regimens that could reduce relapse rates and shorten treatment for drug-sensitive TB to six months.[2]

But this halcyon period of good clinical science in TB ended by 1986, with the shuttering of the TB research programs at the British Medical Research Council and the U.S. Public Health Service.[3] Just as TB programs began to confront rising rates of drug-resistant TB and the syndemic of TB/HIV co-infection, policy shifted from being driven by thoughtful science based on RCTs to the less reliable standard of expert opinion and observational research. This lack of rigorous clinical science left us with many of the issues we are confronting today: TB treatment based on agents whose safety or efficacy is poor or unknown. Until very recently, most recommendations for drug-resistant TB treatment were based on low or moderate quality of evidence.

The FDA's accelerated approval of bedaquiline in 2012 based on several larger RCTs was a pivotal moment marking a return to quality evidence for decision-making on TB treatment. So while we are aware of the urgent need for new treatment, we are equally aware of the urgent need for quality clinical science and stringent regulatory standards. We refer the Committee's attention to the written testimony submitted to the FDA from the Global TB Community Advisory Board (Global TB CAB), which voiced concern that approval of this new drug application for pretomanid may "set a precedent with the potential to lower the evidentiary standard for the future approval of new TB drugs and regimens."[4] We share their concern, because we remember our history, having only been in such a period before. We cannot afford to backslide by accepting a lower evidentiary standard for pretomanid and the Nix-TB regimen.

As the Global TB CAB testimony notes, it is important that "well-intentioned efforts to expeditiously serve the needs of TB patients today do not inadvertently do a disservice to TB patients in the future."[5] The approach to TB drug and regimen development for pretomanid and the Nix-TB regimen may be considered innovative, but in accepting it for full approval of a new drug, we risk trading rigor for efficiency, and leave critical questions of clinical importance to prescribers and patients unanswered.

Since bedaquiline's FDA approval in 2012, and since the Nix-TB trial design was approved, the global landscape of drug-resistant TB treatment has changed dramatically. With the introduction of bedaquiline-containing regimens, the TB community has observed an inversion of cure and death rates for drug-resistant TB.[6] Before bedaquiline introduction, mortality rates for extensively drug-resistant TB (XDR-TB) were as high as 73 percent in endemic countries;[7] following bedaquiline introduction, treatment success rates have drastically improved, ranging from 65–93 percent.[8,9] HIV care also changed dramatically with the adoption of new policies, including the recommendation that all people living with HIV immediately initiate antiretroviral treatment upon diagnosis, regardless of CD4 cell count.[10] This shift is significant to today's deliberations given that half of the participants in the Nix-TB trial are HIV-positive. These dramatic improvements to the standards of care for drug-resistant TB and HIV could very well be driving the change attributed to pretomanid and the Nix-TB regimen.

Measuring pretomanid and the Nix-TB regimen against a non-concurrent, historic control could only be reasonably justified if there hadn't been any changes between the two periods of interest. Comparisons to history are only useful if there are no

major revolutions that upend the historical standard against which we are comparing. That is not the case for the comparison offered in the NDA for pretomanid.

Further, while decisions taken by the FDA are influential globally, the agency's principal mission is to protect the health of the American public.[11] In this case, the burden and type of TB disease and available standard of care vary greatly between the United States—where approval for pretomanid as part of the Nix-TB regimen is being sought—and South Africa, the source of data for the non-concurrent historical control and where the Nix-TB study was conducted.

Based on recent data from the U.S. Centers for Disease Control and Prevention, fewer than 60 patients would have been eligible to receive pretomanid for the proposed indication in the United States in 2017.[12,13] Rates of treatment success for drug-resistant TB in the United States far exceed the 50 percent historical control significance threshold against which the Nix-TB regimen is being measured. Even before broader use of new and repurposed TB medicines, U.S. TB programs were achieving treatment success rates of 78 percent for patients with drug-resistant TB.[14] This raises questions about the relevance and utility of the comparison upon which the foundation of the NDA for pretomanid has been built.

We call the Committee's attention to the written comments submitted by the National TB Controllers Association, which raises an important question: If pretomanid is granted approval, will U.S. clinicians will feel comfortable prescribing the Nix-TB regimen, given the available evidence regarding the efficacy and safety of pretomanid, much of which has not been previously made available for public review?[15]

People given the Nix-TB regimen appear to have done well in the trial so far; this is clear. What is less clear is pretomanid's contribution to the regimen, given the potency of the two other drugs that make up the Nix-TB regimen: bedaquiline and linezolid. The NDA relies heavily on pre-clinical data from studies in mice to establish pretomanid's contribution to the Nix-TB regimen.

Further complicating discussions on this NDA is the fact that linezolid does not have a TB indication and bedaquiline does not have full regulatory approval in the United States. This raises a number of questions. As a thought exercise, should the FDA grant full approvals to bedaquiline and linezolid for XDR-TB and treatment intolerant and non-responsive MDR-TB (recognizing that the FDA conditions for bedaquiline's accelerated approval in 2012 have not yet been met)?

After reviewing the Sponsor and FDA briefing documents, we ask the FDA and the Advisory Committee to consider a number of questions critical to determining where the balance rests between being bold and being stringent in evaluating the NDA for pretomanid and the Nix-TB regimen. In making its recommendation to the FDA regarding the new drug application for pretomanid, **we ask the Committee to consider the following:**

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 treatment-intolerant or non-responsive multidrug-resistant TB (TI/NR-MDR-TB), pre-XDR-TB, and XDR-TB?

2. Does the analysis presented in the NDA cherry pick data from the non-Nix-TB pretomanid-containing studies?

    a. Should efficacy and safety data from the only phase III randomized controlled trial of pretomanid (NC006 or the STAND trial) be more prominently considered (acknowledging differences in regimen and patient population under evaluation, and the trial's early termination)?

    b. Should the safety dataset include all available pretomanid data (1,618 patients vs. 107 patients)?

3. Are the people living with HIV that were enrolled in the Nix-TB trial representative of people co-infected with HIV and TB in South Africa?

    The mean CD4 count among people with HIV enrolled in the Nix-TB study was around 400 cells/uL (mean duration since HIV diagnosis of 4.7 years; all were on ART). Data from the Western Cape in South Africa suggests that the median CD4 count among people with HIV treated for XDR-TB is 100 cells/uL.[16]

4. How many people in the Nix-TB trial with a favorable outcome were classified as being culture negative based on clinical response to treatment (rather than culture)?

5. 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?[17] 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. Did the propensity scores used to match Nix-TB participants with control patients from Brooklyn Chest Hospital in Cape Town, South Africa[18] take into account all relevant categories for making a meaningful comparison?

   b. Why did the propensity scores not account for CD4 count (in addition to HIV status), severity of disease (as measured by extent of cavitation on chest X-ray and/or smear grade or Xpert cycle threshold), and body mass index (rather than body weight)?

      We know from a pooled analysis of patient-level data from three pivotal phase III randomized, controlled trials of fluoroquinolone-based treatment-shortening regimens for drug-susceptible pulmonary tuberculosis (i.e., OFLOTUB1, NCT00216385; REMoxTB2, NCT00864383; and RIFAQUIN3, ISRCTN number 44153044) that these are among the most important factors affecting TB treatment outcomes.[19]

   c. 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/NR-MDR-TB, pre-XDR-TB, and XDR-TB become the Nix-TB regimen?

   d. 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?

6. 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 of TI/NR-MDR-TB, pre-XDR-TB, and XDR-TB, and at the intended duration of six months, and been evaluated for the clinical efficacy endpoint of interest, i.e. 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 TI/NR-MDR-TB, pre-XDR-TB, and XDR-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?

7. 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?

8. 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 Global TB CAB.[20]

9. 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?

10. 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?

11. How will approval of pretomanid and the Nix-TB regimen based on the available evidence (exclusively from South Africa) be received and interpreted by TB clinicians in the United States?

Given these questions, **we encourage the Committee to consider** recommending the TB Alliance's application for pretomanid be considered for accelerated approval, and that the FDA mandate the following additional studies:

- A randomized controlled trial comparing the Nix-TB regimen to the global standard of care for the treatment of drug-resistant TB (18-20 months of bedaquiline, linezolid, moxifloxacin [or levofloxacin], clofazimine and/or cycloserine, or the highest available standard of care pending further guidance from WHO);

- A randomized controlled trial comparing pretomanid to delamanid, a drug from the same class as pretomanid that has completed a phase III trial, is SRA-approved and WHO-recommended, and is being rolled out for the treatment of DR-TB;

- A randomized study to determine the optimal dose and duration of linezolid, a critical component of the Nix-TB regimen, and whether other oxazolidinones in development improve the tolerability of the regimen without compromising efficacy; and

- A pharmacokinetic and safety study to determine the appropriate dose and safety of pretomanid for children.

In 2012, when Janssen's new drug application for bedaquiline was under review, we asked the FDA Advisory Committee to "be bold," but to "do it stringently."[21] Today, we challenge the FDA Advisory Committee:

- to determine whether the evidence we have of pretomanid's safety and efficacy is strong enough to support full approval;

- to consider how the many outstanding questions will be answered, and by whom; and

- to ensure that the trade we would be making in approving pretomanid—one of scientific rigor for efficiency in the face of serious unmet medical need—will not set a precedent that lowers the evidentiary standard for future TB drug and drug regimen approvals, thereby doing a disservice to the interests of TB patients in the future.[22]

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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.

References

[1] Medical Research Council. Streptomycin treatment of pulmonary tuberculosis. Br Med J. 1948; 2: 769–782. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2091872/.

[2] 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 publications. IJTLD. 1999 Oct; 3(10 Suppl 2): S231-79. https://www.ingentaconnect.com/search/article?option1=tka&value1=Studies+on+the+treatment+of+tuberculosis+undertaken+by+the+British+Medical+Research+Council+Tuberculosis+Units.+1946%251986.&pageSize=10&index=1.

[3] World Health Organization. Global investments in TB research: past, present, and future. Geneva: World Health Organization; 2017. https://www.who.int/tb/publications/2017/Global_Investments_in_Tuberculosis_Research_Investment/en/.

[4] Global TB Community Advisory Board. Research, Regulatory, and Access Considerations Regarding Pretomanid. May 15, 2019. http://www.tbonline.info/media/uploads/documents/tb_cab_pretomanid_nda_considerations_final_05.14.19.pdf.

[5] Ibid.

[6] 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.

[7] Pietersen E, Ignatius E, Streicher EM, et al. Long-term outcomes of patients with extensively drug-resistant tuberculosis in South Afria: a cohort study. Lancet. 2014 April 5; 383 (9924): 1230–1239.

[8] Schnippel K, Ndjeka N, Maartens G, et al. Effect of bedaquiline on mortality in South Africa patients with drug-resistant tuberculosis: a retrospective cohort study. Lancet Respir Med. 2019 July 9; 6(9): 699–706. doi: https://doi.org/10.1016/S2213-2600(18)30235-2.

[9] Skrahina, Alena. Bedaquiline containing regimens in the treatment of multi- and extensively drug-resistant tuberculosis at the programmatic level: prospective cohort study [OA18-308-26]. Presented at: 49th Union World Conference on Lung Health, 26 October 2018; The Hague, the Netherlands.

[10] World Health Organization. Guideline on when to start antiretroviral therapy and pre-exposure prophylaxis for HIV. Geneva: World Health Organization; 2015. https://www.who.int/hiv/pub/guidelines/earlyrelease-arv/en/.

[11] U.S. Food and Drug Administration. What we do [Internet]. Silver Spring, MD: U.S Food and Drug Administration; 2018. https://www.fda.gov/about-fda/what-we-do#mission.

[12] Talwar A, Tsang CA, Price SF, et al. Tuberculosis – United States, 2018. MMWR. 2019 Mar 22;68(11):257–262. https://www.cdc.gov/mmwr/volumes/68/wr/mm6811a2.htm?s_cid=mm6811a2_w. "Among the 6,684 TB cases reported in 2017 with available drug-susceptibility testing results, 128 (1.9%) were multidrug-resistant TB. […]. Three cases of extensively drug-resistant TB were reported."

[13] Bonnet M, Bastard M, du Cros P, et al. Identification of patients who could benefit from bedaquiline or delamanid: a multisite MDR-TB cohort study. IJTLD. 2016 February; 20(2): 177–186. doi: https://doi.org/10.5588/ijtld.15.0962.

[14] Marks SM, Flood J, Seaworth B, Hirsch, Moverman Y, Armstrong L, Mase S, et al. Treatment practices, outcomes, and costs of multidrug-resistant and extensively drug-resistant tuberculosis, United States, 2005–2007. Emerg Infect Dis. 2014;20(5):812–821. doi: https://dx.doi.org/10.3201/eid2005.131037. "Of the 134 patients alive at diagnosis, 78% completed treatment, 11% transferred within or outside the United States or were lost to follow-up, and 1% stopped treatment because of adverse events (Table 6). For no patients did treatment fail or TB recur within the year after treatment completion. Of the 134 patients, 12 (9%) died during treatment; 75% of these deaths were considered TB related. No XDR TB patient died."

[15] National TB Controllers Association. Public comment. Docket ID: FDA-2019-N-1317

 FDA-2019-N-1317. 22 May 2019. https://www.regulations.gov/document?D=FDA-2019-N-1317-0020.

[16] von Delft, Arne and Boulle, Andrew (University of Cape Town, Cape Town, South Africa). Personal communication with: Lindsay McKenna (Treatment Action Group, New York, NY). 2019 June 5. "Of 18,665 HIV-infected patients started on TB treatment in the Western Cape Province in 2018 for whom data were available, 76.0% had a recent (between 1 year prior and a month post TB treatment start date) CD4 count available (median 128 cells/µl; IQR: 52; 275), and 57.6% had started ART prior to or on the same day as TB treatment, a median of 1,330 days (IQR: 538; 2343) or 3.6 years prior, though retention on ART at time of TB diagnosis and treatment was not known. The CD4 breakdown by drug-resistance status for patients with HIV is given in the table below."

DR-Status of TB	n	CD4 available (%)	CD4 (median, IQR) cells/µl
Drug sensitive or unknown	17,279	75.3	130 (53; 278)
Mono/Poly Resistance	221	86.0	134 (60; 300)
MDR/RR	1,012	83.8	102 (41; 236.5)
XDR	153	81.0	78.5 (38; 228)

[17] 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."

[18] Olayanju O, Limberis J, Esmail A, et al. Long-term bedaquiline-related treatment outcomes in patients with extensively drug-resistant tuberculosis from South Africa. Eur Respir J. 2018 May 30;51(5). pii: 1800544. doi: 10.1183/13993003.00544-2018. Print 2018 May.

[19] Imperial MZ, Nahid P, Phillips P, et al. A patient-level pooled analysis of treatment-shortening regimens for drug-susceptible pulmonary tuberculosis. Nature Medicine. 2018 Nov 5; 24: 1708–1715. https://www.nature.com/articles/s41591-018-0224-2.

[20] Global TB Community Advisory Board. Research, Regulatory, and Access Considerations Regarding Pretomanid. May 15, 2019. http://www.tbonline.info/media/uploads/documents/tb_cab_pretomanid_nda_considerations_final_05.14.19.pdf.

[21] Harrington, Mark. Statement on bedaquiline to the FDA [Internet]. New York: Treatment Action Group; 2012. http://www.treatmentactiongroup.org/tb/publications/2012/statement-bedaquiline-fda.

[22] Global TB Community Advisory Board. Research, Regulatory, and Access Considerations Regarding Pretomanid. May 15, 2019. http://www.tbonline.info/media/uploads/documents/tb_cab_pretomanid_nda_considerations_final_05.14.19.pdf.