



Research, Regulatory, and Access Considerations Regarding Pretomanid

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In March 2019, the United States Food and Drug Administration (FDA) accepted a new drug application (NDA) for pretomanid, a drug candidate developed by the TB Alliance. The FDA will hold a public advisory committee meeting on the TB Alliance's application on 6 June 2019. Members of the public can submit written comments in advance of the hearing and apply to deliver oral testimony at the hearing itself. As stakeholders in the tuberculosis (TB) community prepare for this historic hearing, the Global TB Community Advisory Board (TB CAB) wishes to share its views on regulatory, research, and access considerations related to pretomanid.

We hope the considerations outlined in this document will stimulate dialogue among TB research stakeholders, inform the discussions and decisions of the FDA Antimicrobial Drugs Advisory Committee, FDA review staff, and other regulatory authorities, including the European Medicines Agency (EMA), and share our expectations for how further investigations of, and access to, pretomanid should be managed by the TB Alliance and its recently announced commercial partner, Mylan.¹

Introduction

Preliminary results from a small, uncontrolled study of a combination of new drug candidate pretomanid with existing drugs bedaquiline and linezolid (commonly referred to as the Nix-TB or BPaL – for bedaquiline, pretomanid, and linezolid – regimen) indicate that people with especially difficult to treat forms of drug-resistant tuberculosis (DR-TB) may be able to achieve cure with just six months of treatment.² This represents both a reduction in the number of drugs, and the length of treatment, from the current World Health Organization (WHO)-recommended 18-20 month, four-drug regimens that combine bedaquiline and linezolid with other older and repurposed TB medicines.

According to a modified intention-to-treat analysis of interim results presented at the 2018 Union World Conference on Lung Health, 88 percent (66/75) of participants treated with six-months of bedaquiline, pretomanid, and linezolid had a favorable outcome (sputum cultures negative for TB after six months of treatment and six months of post-treatment follow-up).³ These findings and the FDA acceptance of the TB Alliance's application to register pretomanid for extensively drug-resistant TB (XDR-TB), treatment intolerant multidrug-resistant TB (MDR-TB), and treatment non-responsive MDR-TB,⁴ have important implications for the field and for the future of TB drug and regimen development.

As civil society, including representatives and members of TB-affected communities, we understand well the need for better and shorter treatment options, especially for difficult-

to-treat forms of TB, and the importance of expediting access to the benefits of research into new TB medicines and regimens. As science-based treatment activists, we want to ensure that well-intentioned efforts to expeditiously serve the needs of TB patients today do not inadvertently do a disservice to the TB patients of the future.

Below, we share our concerns that the approval of the New Drug Application (NDA) for pretomanid may set a precedent with the potential to lower the evidentiary standard for the future approval of new TB drugs and regimens. We strongly believe that well-designed randomized controlled trials (RCTs) must remain the regulatory gold standard for sponsors seeking approval for new TB drugs and regimens in the future. We also discuss remaining research gaps, and our expectations regarding price, registration, pre-approval access, and how revenue generated from sale of the Priority Review Voucher (PRV) should be spent, if the pretomanid application before the FDA is approved.

Regulatory Considerations

The TB Alliance's NDA for pretomanid is precedent-setting in several ways. Pretomanid represents only the fourth new TB drug to go through stringent regulatory authority (SRA) review in the past half a century, and the first developed by a not-for-profit organization. It is the first regulatory filing for a TB medicine in the context of a regimen. Additionally, the primary basis for the TB Alliance's regulatory filing is a small uncontrolled, non-randomized study designed in one era of DR-TB care (the pre-bedaquiline era) and completed in another (the post-bedaquiline era). Evolutions in the standard of care available to people with DR-TB since the Nix-TB trial opened to enrollment, merit nuanced and open discussion. Regulators will need to weigh the need for new treatment options against concerns about maintaining regulatory stringency for TB drugs and regimens.

Given challenges recruiting people with XDR-TB for trials, and the length, toxicity, lack of clinical trial evidence, and poor performance of the standard of care for the treatment of pre-XDR and XDR-TB at the time the Nix-TB trial opened,⁵ the single arm, open label design of the Nix-TB trial may have been considered acceptable. At the time, novel drugs bedaquiline and delamanid were not widely available, had not yet been shown to be able to be taken together safely, and five-year mortality rates with World Health Organization (WHO)-recommended regimens for XDR-TB were as high as 73 percent.⁶

A seminal article published in the *New England Journal of Medicine* (NEJM) in 1990 by Byar et al., *Design Considerations for AIDS Trials*—credited in part for reshaping the design and conduct of critical path regulatory trials of new treatments for HIV/AIDS—outlines the requirements under which an uncontrolled phase III trial to evaluate the efficacy of a new drug may be justified:

1. "There must be no other treatment appropriate to use as a control;
2. There must be sufficient experience to ensure that the patients not receiving therapy will have a uniformly poor prognosis;
3. The therapy must not be expected to have substantial side effects that would compromise the potential benefit to the patient;

4. There must be a justifiable expectation that the potential benefit to the patient will be sufficiently large to make interpretation of the results of a nonrandomized trial unambiguous; and
5. The scientific rationale for the treatment must be sufficiently strong that a positive result would be widely accepted.”⁷

In the case of pretomanid and the Nix-TB regimen, one could argue that these requirements were largely met at the time the study was designed. Over the course of the Nix-TB study, however, the standard of care and outcomes for drug-resistant forms of TB changed dramatically.⁸ As a result of these changes, the Nix-TB study no longer meets at least four of the five requirements (requirements 1, 2, 4, and 5) outlined by Byar et al.

Table 1. Applying Byar et al. requirements to Nix-TB

<p>Requirement 1: there must be no other treatment appropriate to use as a control</p>	<p>An appropriate control regimen for XDR-TB could be composed according to WHO treatment guidelines (using a number of new and repurposed medicines, including bedaquiline, linezolid, clofazimine, and delamanid (which shares the nitroimidazole class with pretomanid)).</p>
<p>Requirement 2: there must be sufficient experience to ensure that the patients not receiving therapy will have a uniformly poor prognosis</p>	<p>Since the Nix-TB trial opened to enrolment in 2015, the prognosis for people diagnosed with DR-TB has greatly improved with increased access to new and repurposed TB medicines, including bedaquiline. A retrospective cohort analysis of patients with rifampicin-resistant TB (RR-TB) treated with bedaquiline in South Africa showed bedaquiline’s inclusion in a treatment regimen was associated with a 41 percent increase in treatment success and a three-fold reduction in mortality compared with regimens that did not contain bedaquiline.⁹</p>
<p>Requirement 4: there must be a justifiable expectation that the potential benefit to the patient will be sufficiently large to make interpretation of the results of a nonrandomized trial unambiguous</p>	<p>While there are potential benefits to patients from receiving the Nix-TB regimen (including its short duration), the relative contribution of pretomanid to the regimen remains ambiguous. It is possible that the positive treatment outcomes observed in the Nix-TB study are driven by bedaquiline and linezolid, and that patients treated with regimens that contain these two drugs would do well regardless of whether they</p>

	received pretomanid. This uncertainty creates ambiguity in how the results from Nix-TB should be interpreted.
Requirement 5: the scientific rationale for the treatment must be sufficiently strong that a positive result would be widely accepted	Clear evidence of pretomanid's independent contribution in humans with TB disease to the Nix-TB regimen is limited to two phase II, 14 day, early bactericidal activity (EBA) studies (see Table 2). The endpoint evaluated in EBA studies, colony-forming units, is not a reliable surrogate marker for efficacy. The limited additional clinical data supporting pretomanid's contribution to the Nix-TB regimen challenge wide acceptance and agreement regarding how the study results should be interpreted and translated into policy and practice.

Interim results from the Nix-TB study have been presented at international conferences and in other forums, but peer-reviewed analyses had not been made available at the time of writing. In its public communications, the TB Alliance compares successful treatment outcomes among the XDR-TB patients enrolled in Nix-TB (88 percent) to those observed among XDR-TB patients treated under program conditions in South Africa from 2008–2012, establishing a historic control (16 percent treatment success).¹⁰ This historic control is now out of date. According to WHO cohort data from 2015, estimated treatment success rates among people with XDR-TB were 34 percent.¹¹ More recent data, including from cohorts in South Africa and Belarus, indicate treatment success rates for patients with XDR-TB with reported final outcomes range from 65–93 percent with the implementation of existing bedaquiline-based regimens.^{12,13}

Byar et al. warned that non-randomized, historic control participants may differ from patients receiving the new treatment in several ways, including that patients may not receive the same care and support. This could be the case with the Nix-TB study; in fact, other recent phase III MDR-TB trials have already demonstrated this risk: the control arms in both phase I of the STREAM study and Otsuka 213 performed surprisingly well compared to outcomes observed in program settings. In each study, roughly 80 percent of participants randomized to the control regimen had a favorable treatment outcome.^{14,15} In contrast, data from patients treated under program conditions indicate just 55–70 percent of patients treated for MDR-TB have a successful treatment outcome.¹⁶ If STREAM and Otsuka 213 were conducted as single arm studies and compared to historic controls (like Nix-TB), the effect of each intervention compared to the existing standard of care for MDR-TB would be dramatically overstated relative to the actual differences observed between the experimental and control arms in these trials.

It is unknown whether a similar effect would have been observed in the context of a RCT comparing the pretomanid-containing Nix-TB regimen to the pre-bedaquiline standard of

care for XDR-TB and treatment intolerant or non-responsive MDR-TB. Any comparisons made between the outcomes observed in the Nix-TB study and those observed under program conditions in the pre-bedaquiline era should be interpreted with the above risks in mind. The meaningful comparison regulators should consider today is how the Nix-TB regimen compares to other regimens that contain bedaquiline and linezolid as these make up the current standard of care for DR-TB.

Given the above-described considerations resulting from changes to the standard of care and outcomes for drug-resistant forms of TB, the non-randomized, uncontrolled approach to evaluating pretomanid and the Nix-TB regimen is not an acceptable trial design upon which full approval should be granted.

Granting full marketing approval to pretomanid based on the amount and quality of data behind the Nix-TB regimen has the potential to seriously lower regulatory standards and absolve product sponsors of their responsibility to adequately demonstrate proof of safety and efficacy before receiving authorization to market new TB drugs and regimens. The TB CAB feels strongly that large, randomized controlled trials (RCTs) must remain the regulatory gold standard for sponsors seeking approval for new TB drugs and regimens.

Under accelerated or conditional approval pathways, regulatory authorities can require additional studies, including those to confirm efficacy. Once full marketing approval is granted, however, there is little recourse for regulatory authorities to require additional studies, especially for demonstrating further proof of efficacy. While regulatory authorities still have leverage, they should require RCTs of pretomanid and the Nix-TB regimen to better establish proof of efficacy and safety, and to address a number of other remaining research gaps and uncertainties (see Research Considerations). In the meantime, we reiterate our call—first issued in 2014 and unanswered up to now—for the TB Alliance to establish a pre-approval access program for pretomanid (see Access Considerations).

Research Considerations

Bedaquiline and delamanid were developed independent of each other and as add-ons to an 18-24 month regimen of toxic medicines. This approach left the field with two new drugs and no evidence to inform how they might be used together or to shorten and/or optimize treatment by replacing older toxic medicines. The development of pretomanid as part of a novel regimen is a welcome advance, but the relatively limited experience with pretomanid and the design of the Nix-TB study, leave pretomanid's safety and efficacy unconfirmed. In addition, there are a number of research gaps concerning questions of critical importance to patient care and normative guidance that remain unfilled.

Pretomanid has been administered in clinical trial settings to more than 1,200 people in 14 countries.¹⁷ However, far fewer people have received pretomanid for the indication and duration of the Nix-TB regimen (see Table 2).

Table 2. Phase II and III studies of pretomanid

Study Identifier	Phase	Treatment duration	Population	Actual enrollment (Total)	Intervention(s)	Comparator	Status
PA-824-CL-007 NCT00567840	II	14 days	DS-TB	69	Pa	HRZE	Complete
CL-010 NCT00944021	II	14 days	DS-TB	69	Pa	HRZE	Complete
NC-001 NCT01215851	II	14 days	DS-TB	85	PaB PaZ PaMZ	HRZE	Complete
NC-002 NCT01498419	II	8 weeks	DS-TB MDR-TB	207	PaMZ	HRZE	Complete
NC-003 NCT01691534	II	14 days	DS-TB	105	BPaZC BPaZ BPaC BZC Z C	HRZE	Complete
NC-005 NCT02193776	II	8 weeks	DS-TB MDR-TB	240	BPaMZ	HRZE	Complete
APT trial NCT02256696	II	12 weeks	DS-TB	183	HRZPa/HRPa HRbZPa/HRbPa	HRZE	Recruiting
STAND/ NC-006 NCT02342886	III	4-6 months	DS-TB	284	PaMZ	HRZE	Discontinued
Nix-TB NCT02333799	III	6-9 months	Pre-XDR-TB XDR-TB MDR-TB	109	BPaL	None	Active, not recruiting
ZeNix/ NC-007 NCT03086486	III	6-9 months	Pre-XDR-TB XDR-TB MDR-TB	180	BPaL	None	Recruiting
SimpliciTB/ NC-008 NCT03338621	III	4-6 months	DS-TB MDR-TB	450	BPaMZ	HRZE	Recruiting
TB-PRACTECAL NCT02589782	II/III	6 months	MDR-TB	630	BPaLM BPaLC BPaL	Local MDR-TB SOC	Recruiting

B = bedaquiline; C = clofazimine; E = ethambutol; H = isoniazid; L = linezolid; M = moxifloxacin; Pa = pretomanid; R = rifampicin; Rb = rifabutin; Z = pyrazinamide
DS-TB = drug-sensitive tuberculosis; MDR-TB = multidrug-resistant tuberculosis; XDR-TB = extensively drug-resistant tuberculosis

The results of studies including pretomanid have not always been favorable or transparently and comprehensively reported. In 2015, following the deaths of three participants in the TB Alliance’s STAND trial (PaMZ) associated with hepatotoxicity, recruitment was suspended, and then followed by a partial clinical hold by the FDA. The hold was eventually removed, but the TB Alliance never reinitiated recruitment to the study. In 2016, the TB Alliance permanently discontinued recruitment, at which point it had enrolled just 284 of a planned 1,200 participants with DS-TB and 300 participants with MDR-TB. Upon this decision, the TB Alliance stated its plans to instead re-focus its resources to launch a phase III study (SimpliciTB) to test the STAND regimen (PaMZ) plus bedaquiline, which “appears to be much more promising compared to the PaMZ regimen” alone.¹⁸

Several aspects of this story concern us. There was no public communication regarding the cause(s) of the three deaths in the STAND trial, and pretomanid’s potential contributions to these hepatotoxic events. The only public record that these deaths occurred is the “study

results” tab of the ClinicalTrials.gov page for the STAND trial (NCT02342886). Under “limitations and caveats” it says, “following three deaths associated with hepatotoxicity, recruitment was suspended, followed by a partial clinical hold by the FDA. The hold was removed but the Sponsor permanently stopped recruitment in December 2016.”¹⁹ To date, the TB Alliance has not published any findings, or its Drug Safety Monitoring Board’s (DSMB) review of the deaths that occurred in the STAND trial. Both the FDA and the South African Health Products Regulatory Authority (SAHPRA) reviewed the deaths that occurred in the STAND trial, but neither agency published anything in the public domain. The STAND trial deaths and study discontinuation, and the lack of transparency around these events, have left us concerned about pretomanid’s safety, especially for people living with HIV, given that a majority of antiretroviral medications also are processed through, and have an effect on, the liver.

In addition to the need for more data to support the safety of pretomanid, further work is necessary to define the background regimen and improve its tolerability. Linezolid, a key component of the Nix-TB regimen has several difficult side effects, including myelosuppression and peripheral neuropathy. In February 2017, at the Conference on Retroviruses and Opportunistic Infections (CROI), the TB Alliance reported 71 percent of patients had at least one linezolid dose interruption (22 percent of all participants due to myelosuppression and 28 percent due to peripheral neuropathy).²⁰ This finding underscores the importance of additional research to further improve the safety and tolerability of the Nix-TB regimen, particularly to reduce linezolid toxicity. The TB Alliance is evaluating linezolid dosing and duration in the ZeNix study, also referred to as NC-007, but final results are only expected in 2022.²¹ As pretomanid undergoes SRA review in the context of the Nix-TB regimen, and the TB Alliance and Mylan plan for its market introduction, the optimal dose and duration of linezolid, a critical component of the regimen, remains unknown.

Another critical knowledge gap is how pretomanid compares to delamanid, a drug from the same class as pretomanid. Delamanid has completed a phase III trial, is SRA-approved and WHO-recommended, and is being rolled out for the treatment of MDR-TB. The possibility that replacing pretomanid with delamanid could produce a regimen similar or superior in efficacy or safety (or both) to the Nix-TB regimen begets the need for additional research.

Finally, drug-resistant TB affects 32,000 children each year, and developing pretomanid for children will be necessary to close equity gaps and ensure that children are able to benefit from scientific progress. Though pretomanid has been in phase III development since 2015, the TB Alliance only submitted a pediatric investigation plan (PIP) to the European Medicines Agency (EMA) in 2019. The TB Alliance is working with the U.S government-funded International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) to develop a pediatric pharmacokinetic and safety study protocol for pretomanid, but it will be years before the information needed to appropriately and safely treat children with pretomanid is available.

In summary, continued investigations of pretomanid and the Nix-TB regimen are urgently required to: (1) confirm pretomanid’s safety and efficacy; (2) optimize the dose and

duration of linezolid; (3) compare pretomanid and delamanid; and (4) determine the safety and appropriate dose of pretomanid for children. If full SRA-approval is granted, it will be very difficult to hold the sponsors accountable for conducting studies to fill the first three of these critical knowledge gaps (the pediatric investigations, as noted, are required by the EMA).

Access Considerations

Pre-approval access

The TB Alliance and Mylan's most urgent priority should be to establish a pre-approval access program for pretomanid. A pre-approval access program would enable access to pretomanid for individual patients with an unmet medical need, and generate additional data and experience while the TB Alliance and Mylan are working to fill the research gaps described in the previous section (see Research Considerations). To expedite the generation of additional data on pretomanid, the TB Alliance and Mylan should also ensure that pretomanid is made available to TB research networks and independent investigators interested in adding to the evidence-base for pretomanid.

The TB CAB has called for the TB Alliance and donors to set up a pre-approval access program since 2014, when the TB Alliance was in the process of launching its first phase III trial of pretomanid. Pre-approval access— which usually spans late-stage (phase IIb) development through SRA approval and even past WHO recommendation—is critical not only for DR-TB patients in need, but also to laying a foundation for the market entry of pretomanid (assuming it is found to be adequately safe and effective), including by creating familiarity with the product and providing additional data on its use in a range of settings.

Though imperfect, the pre-approval access programs established by Janssen for bedaquiline and by Otsuka for delamanid demonstrate the potential impacts of such programs on policy and uptake of new medicines for DR-TB.²² Janssen's pre-approval access program for bedaquiline started nearly three years earlier and was more extensive than Otsuka's pre-approval access program for delamanid. Early experience with bedaquiline gained by country programs and clinical providers, and the additional data generated through pre-approval access programs, including the B-CAP (bedaquiline clinical access program) in South Africa, may explain some of the differences between current policies and uptake for bedaquiline and delamanid globally.²³ Currently, the WHO recommends bedaquiline as a core component of regimens for RR-/MDR-TB, while delamanid remains listed among the medicines to be added to RR-/MDR-TB regimens that cannot otherwise be composed using bedaquiline, linezolid, moxifloxacin or levofloxacin, and cycloserine and/or clofazimine. Donor support is essential for providing pre-approval access to pretomanid.

Registration

When we do reach the point where we have sufficient proof of efficacy and safety, and adequate progress has been made to fill other gaps in the evidence base for pretomanid and the Nix-TB regimen, we expect Mylan and the TB Alliance to register pretomanid widely. The TB Alliance and Mylan should prioritize registration in countries with high burdens of DR-TB, starting with those where it has conducted research on pretomanid and

the Nix-TB regimen (e.g. South Africa, Georgia, Moldova, and Russia). As we have learned from the rollouts of bedaquiline and delamanid, prompt registration is required to ensure equitable and sustainable access to new TB medicines.²⁴ This is especially true given ongoing and further anticipated shifts in the donor landscape, including the trend toward increasing use of domestic financing for the procurement of TB medicines and other commodities.

Pricing

Pretomanid is a drug developed by a nonprofit organization for public benefit using philanthropic and public funding. In developing pretomanid for a small, overlooked, and neglected patient population, the TB Alliance was seeking to correct a market failure. Its pricing and access plans must be set with respect to this original objective. The common (yet contested) justification for high drug prices—that drug sponsors must recoup their investments in research and development—does not apply to pretomanid since its development was supported by philanthropic and public funds. Researchers from the University of Liverpool estimate that pretomanid can be produced and sold at a profit for USD \$11–\$34 per month.²⁵ We encourage the TB Alliance and Mylan to set a flat, low price of USD \$1 per day for pretomanid for all countries, in keeping with the Médecins sans Frontières (MSF) call for a USD \$500 DR-TB regimen and with estimates from University of Liverpool.

Priority Review Voucher

Finally, if pretomanid is approved, we reiterate our call for the TB Alliance to commit to reinvesting earnings from selling the Priority Review Voucher (PRV) it will receive from the FDA into innovative mechanisms that support the future of TB research, such as the Life Prize.²⁶

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About the Global Tuberculosis Community Advisory Board (TB CAB)

The Global TB Community Advisory Board (TB CAB) is a group of science-literate, treatment research activists from HIV and TB networks across the world. Founded in 2011, the TB CAB acts in an advisory capacity to product developers and institutions conducting clinical trials of new TB drugs, drug regimens, diagnostics, and vaccines by providing input on study design, early access, regulatory approval, post marketing, and implementation strategies. The TB CAB is dedicated to increasing meaningful community engagement in TB research and to mobilizing political will to advance the development and uptake of new tools to fight TB.

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