ECAT Discussion Questions

Access in Specific Countries

- **Is pretomanid registered in Azerbaijan?** Yes

- **As far as we know, pretomanid is not procured by the government in Belarus. Is there any information on what price will be offered to the government?** Pretomanid was procured by Belarus in 2023 and is available at GDF pricing.

- **Does TB Alliance plan to provide humanitarian aid to Central Asian countries, particularly Tajikistan?** Although we do not have any funding specifically for humanitarian assistance, TB Alliance helped arrange funding for operational research in Tajikistan for BPaL, resulting in the country becoming one of the first to use the regimen after U.S. FDA approval and initial WHO guidelines. Tajikistan is now procuring pretomanid with funding from the Global Fund. Pretomanid shipments to Tajikistan in 2022 and 2023 were similar in scale to the total caseload of DR-TB in WHO guidelines, so it appears the operational research was effective. No further requests for technical assistance or projects in Tajikistan have been communicated to us at this time.

- **Is pretomanid registered in Kazakhstan? What is the situation with the availability of the drug?** Pretomanid is registered in the country and can be accessed through GDF.

- **Only Viatris' pretomanid is registered in Kyrgyzstan, MacLeods is not registered. Did TB Alliance have conditions that upon licensing, companies should register their drugs in countries, including Kyrgystan?** Macleods is expected to file pretomanid in Kyrgyzstan later this year. The country is part of WHO's collaborative procedure, therefore Macleods is awaiting WHO PQ following submission in March 2022. Our agreements with licensees require that they use reasonable efforts to ensure our drugs are widely available in their respective territories in sufficient quantities to meet the need. Notably, Kyrgyzstan has procured pretomanid in volumes that reflect their annual caseload, which is a promising indicator of commitment.

- **When will the 6-month BPaLM regimen, including bedaquiline, pretomanid, linezolid (600 mg), and moxifloxacin, become available on the Russian market? Currently, it is unavailable due to the unavailability of pretomanid. How have your negotiations with Pharmstandard concluded?** Viatris had filed the dossier for pretomanid in Russia in early last year and is expecting approval in late 2024. We understand their negotiations with a local commercial partner for product launch in Russia are progressing well, and they expect to have the partnership in place before regulatory approval.

- **Does TB Alliance plan to withdraw patent application No. 201890614 for pretomanid to Eurasian Patent Office to ensure broader access to MDR-TB and XDR-TB treatment regimens?** As far as we know, the application has not been withdrawn.

- **Additional Eurasian patent applications related to pretomanid have been identified during the analysis, namely: EA 202391840 for the amorphous form of the substance, EA 202290150 for tablet granules, EA 202390502 for tablet suspension. If a patent is granted for the amorphous form, the patent monopoly will be in effect until 2044. These applications are essentially "evergreening," and we urge TB Alliance to withdraw them or issue a statement that these patents will not be enforced if granted.** Each of the patents referenced is pending in the patent office.

  Traditionally, pharmaceutical companies utilize a patent to secure a monopoly in the marketplace in order to maintain a high price for their drug as long as possible. As a nonprofit, TB Alliance works to secure patents in key countries, and then license those patents in the developing world on a royalty-free basis to multiple manufacturers with the capability of producing high-quality drugs and responsibly distribute those drugs to avoid misuse and resulting drug resistance. To help ensure our patented drug is used correctly, our licenses are also limited to marketing and using the drug only in regimens that have formed the basis of the drug's approval by the U.S. FDA, the EMA or the basis of WHO guidelines governing their proper use. *Use of new TB medicines in a manner inconsistent with global policy and evidence could result in proliferation of resistance and loss of novel medicines that are few and far between.*

  In addition, we require our licensees to adopt best practices to limit antibiotic resistance. While we also require licensees to make the licensed product available throughout their licensed territory on an affordable basis, we believe that enabling competition for the drug by licensing to multiple companies is the best means of keeping drug prices affordable. Licensing the drug to multiple, high-quality manufacturers also ensures that a consistent, sustainable supply of high-quality product is available to TB patients throughout the developing world. Although regulatory bodies and the WHO are committed to ensuring that only quality products meeting cGMP standards are made available to TB patients, not every country requires manufacturers to meet the standard of WHO prequalification or similar. Even in countries that do, enforcement of standards may be inconsistent. Imposing standards directly on our licensees and limiting our licenses to manufacturers with a track record in producing high-quality products provides an additional mechanism to ensure our products meet these standards throughout the world.

  If you are aware of any high-quality manufacturers who are not manufacturing and selling pretomanid because of the existence of patent applications for the drug, we urge you to refer them to us so that we can discuss and provide royalty-free licenses.

  Note that EA 202390502 referenced above does not cover pretomanid, but relates to a device and its use to mix tablets with liquid for pediatric patients and patients with difficulty swallowing tablets. The device ensures better delivery of the drug as compared to the traditional method of using spoons to crush the tablets and mixing the crushed tablets with a liquid.

Fixed Dose Combinations

- **This news is particularly concerning in light of the consultations on the development of a fixed-dose combination - we consider all this as part of the process of creating a patent monopoly. Is this the case? Do you plan to launch FDC and use patents to create a monopoly?** No. Any patent we might file to protect an FDC would be driven by the same considerations described above, and not for creating any monopoly. It should also be pointed out that it's actually quite challenging to obtain a patent for an FDC when simply combining drugs known to have an effect on the treatment of TB. That's because you're required to demonstrate "surprising results" for the FDC beyond the additive effects of combining the drugs. Our goal for FDCs is to create competition that drives prices down to the lowest sustainable price. For example, in the development of a BPaMZ FDC, we discovered that the combination of pretomanid and pyrazinamide in an FDC produced a surprising result because pyrazinamide had an incipient effect when combined with pretomanid, meaning that the quantity of drug material could be significantly reduced when combined in an FDC as compared to combining as single drugs. This led us to file a patent for the BPaMZ FDC, which we ultimately abandoned when the clinical results of the BPaMZ trial did not support the regimen's further clinical development.

Drug Accessibility Policy

- **What measures does TB Alliance take to ensure guaranteed access to tuberculosis medications and therapies for the most vulnerable groups, including refugees and people with low income?** The disproportionate disease burden of TB on our most vulnerable communities means that every discovery we pursue and the subsequent development and delivery strategies to get drugs to patients is an investment in the most at-risk populations. And as a mission-driven organization, every drug we develop must be accessible to those in need. By ensuring the lowest possible cost for our medications, advocating for inclusion of TB in national budgets, and supporting capacity building and technical assistance at the national and community levels, we're helping advance widespread access to BPaL/M regimens in high-burden countries, helping all populations – and especially those who rely on government programs – to access treatment and mitigate the often catastrophic economic burden of TB.

  On the topic of cost, we've demonstrated the cost-effectiveness and cost-saving potential of the BPaL/M regimen through a number of studies that have compelled countries to adopt the regimen. One analysis, in fact, showed savings exceeding $740 million if BPaL/M was available to all people who qualify. We've also developed a model for countries to rapidly undertake cost analyses of their own and free of charge – an exercise that can otherwise be expensive and protracted.

  Lastly, we supported the price reduction of pretomanid through a volume guarantee by MedAccess after WHO guidelines in December 2022 expanded the use of the drug from pre-XDR-TB to almost all DR-TB.

- **Is a decrease in the price of pretomanid expected?** We're working to reduce the cost of pretomanid in two ways. First, by improving the manufacturing process for raw materials (Active

Pharmaceutical Ingredients). Second, by increasing volumes through demand creation.

This increase in volume is a powerful factor. Case in point: we enabled a low starting price for pretomanid. At the time, based on WHO guidelines, the market size for the drug was 10-12,000 treatments annually, with only a tiny fraction of that converted into commercial supplies. When we knew that the market may grow due to WHO guidelines expanding the drug's usage to almost all DR-TB, we were able to stimulate a price reduction by 34% through a volume guarantee.

Efforts by communities to advocate for use of newer WHO-recommended treatments in all countries – especially those with the highest burden and without access to BPaL/M – will help put downward pressure on cost in addition to improving treatment outcomes.

- **Are there pricing policies or standards for specific countries?** While we require that our licensees make our products available on an affordable basis, the competition we enable through multiple licensees in the developing world is a key driver in ensuring our products will, in fact, be affordable. To date, we have licensed Viatris, Macleods, Hongqi, Lupin and Remington Pharmaceuticals to market pretomanid in the developing world.

Research and Development

- **Why is operational research still ongoing in countries when WHO has already announced the programmatic use of BPaL regimens?** Treatment of people in operational research supported by TB Alliance began in 2020 and ended in early 2023 when all enrolment in OR finished. Through LIFT-TB, research was undertaken in seven countries, including Kyrgyzstan, Uzbekistan, Ukraine, Vietnam, Myanmar, Indonesia and the Philippines. However, due to Covid-19-related disruptions and various logistical challenges, some countries experienced delays in starting enrollment. OR enrollment was completed in five LIFT-TB countries in December 2022, coinciding with the release of WHO guidelines. Indonesia and Myanmar finished in March 2023. Current OR-related activities include data collection and verification, and support for 6-month and 12-month post-treatment follow-up, data analysis, publication and an exchange of learnings from OR sites to expand capacity.

  It's noteworthy that when we were approached by countries to support OR after WHO's communication in May 2022 signaling the imminent programmatic use of BPaL/M, we encouraged them to consider alternative mechanisms to enable faster rollout of the regimens. In Pakistan, for example, where we supported a local nonprofit to conduct a pilot project rather than operational research, the country became one of the fastest worldwide to scale up treatment. This also underscores the invaluable role of civil society and the advocacy community in education and implementation support.

- **At what stage is the development of pediatric formulations?** The first clinical study – a single dose study – in pediatric patients is ongoing and being conducted in partnership with the IMPAACT network.

- **Are there any other combinations with pretomanid for TB treatment besides BPaL(M)?** Other combinations with pretomanid are being explored in a number of clinical studies.

- **Are people who use psychoactive substances involved in TB Alliance's studies to test the compatibility of TB drugs with narcotics and the effectiveness of therapy in this patient group?** Our clinical trials typically exclude people using narcotics. In one current Phase 2 trial, for example, the following criterion is included: "Abuse of alcohol or illegal drugs that in the opinion of the investigator would compromise the participant's safety or ability to follow through with all protocol-specified restrictions, visits, and evaluations."

Pharmacovigilance and Quality Control

- **What adverse events associated with pretomanid and BPaL and BPaLM regimens are most frequently reported at the global level?** The most frequent events reported are gastrointestinal reactions (including nausea, dyspepsia, vomiting and decreased appetite) and lower grade increase in transaminases. While anemia and peripheral neuropathy were initially reported more frequently, their incidence has significantly decreased with the lower dose of linezolid (600 mg). No new safety signal was identified since the approval of pretomanid in 2019.

- **TB Alliance representatives claim that the patent for pretomanid is not intended for use, as it is supposedly needed only for quality control. Why isn't the WHO prequalification enough for quality control? Why was a mechanism chosen that is not intended for quality control at all?** An important aspect and responsibility of a partner that commercializes our compounds – in addition to production of high-quality product – is pharmacovigilance. For example, Viatris is responsible for the management of all aggregate safety reports associated with post-marketing safety surveillance activities where Viatris is the marketing authorization holder (MAH). These documents are shared with TB Alliance, which in turn is responsible for the fulfilment of aggregate safety reports associated with the clinical development of the product or a clinical trial sponsored by the organization.

Strengthening Healthcare Systems, Cooperation

- **Is there a plan to expand the number of participating countries in the LIFT-TB project?** The LIFT-TB project as co-funded by TB Alliance and the Korean development agency (KOICA) will end in mid-2025. As LIFT-TB countries are quickly scaling up BPaL/M implementation, we've started to involve other countries to learn from the LIFT-TB experience, as well as offer technical assistance (at their request) to countries like Bangladesh. In fact, building on the success of LIFT-TB, we launched an initiative called PeerLinc Knowledge Hub in March – a peer-to-peer platform in which countries learn from other BPaL/M-implementing countries to strengthen PMDT and rapidly implement new DR-TB treatments. Peru and Rwanda have already benefitted from capacity building activities, with a growing cohort of new countries coming on board. Learn more about the program at peerlinc.org.

- **What new steps will be taken to eradicate tuberculosis in the ECA countries during the period of unstable relations between Russia and Ukraine?** Ukraine, Kyrgyzstan and Uzbekistan

will continue to be supported as part of LIFT-TB while funding is available, estimated now to be until the end of 2024. PeerLinc also provides an important source of technical support for any country globally, including ECA countries. That technical assistance includes all clinical, lab, programmatic and community aspects of BPaL/M implementation. Additional TA requests from countries can be accommodated based on need and availability of funds.

- **How does the company collaborate with international partners and organizations to ensure the availability of TB treatment worldwide?** As a nonprofit organization, we work closely with a range of partners, including civil society, to ensure that every patient in need receives the best treatment science can deliver. Our nonprofit status also means that we operate largely with public funding and are committed to ensuring our research benefits the broadest population possible.

TB Treatment in the Penitentiary System

- **What additional measures are you taking to improve the accessibility of tuberculosis treatment in the penitentiary system of your countries?** We have not received any request for support in any penitentiary systems. However, assistance provided to implement new treatments, update national clinical guidelines, build capacity and engage the community can be leveraged to implement the regimens in other sectors, including among incarcerated populations. PeerLinc Knowledge Hub may also be an opportunity to explore how to provide support within the unique conditions of the penitentiary system.

- **How do you assess the effectiveness of the early tuberculosis diagnosis system among inmates in penitentiary institutions?** While our projects have not been tailored specifically to assess the effectiveness of the early TB diagnosis system within incarcerated populations, the tools already developed may be shared within any community if requested by the country.

- **How do you cooperate with government structures to ensure tuberculosis treatment in penitentiary institutions?** See above.

- **What opportunities do you see for improving the treatment and care of tuberculosis among prisoners in the future?** See above.

General Questions

- **Could you share tools and practices for enhancing research literacy to train community members?** We've worked with numerous community groups over the years and would be happy to share our extensive resources. Please reach out to Stephanie Seidel for more information on our community engagement (stephanie.seidel@tballiance.org).

- **What are the plans of the company for the next five years?** TB Alliance is continuing to grow our pipeline of possibilities to achieve a TB-free world. By exploring new compounds and working with new populations, we're optimistic that we'll reach a universal regimen in the near future. And through continued expansion of our peer-to-peer and community-based networks, that universal regimen can get in the hands of more patients, more quickly, to save more lives.

Contact communications@tballiance.org for more information.