To: Members of the DR-TB Triple Therapy Working Group and Colleagues (see Appendix 1)

Cc: Anil Soni, Mylan
Kellen Thomas, Mylan
Mel Spigelman, TB Alliance
Sandeep Juneja, TB Alliance
Shelly Malhotra, TB Alliance
Willo Brock, TB Alliance
Zvia Shwirtz, TB Alliance

29 July 2019

OPEN LETTER RE: Transparency and access to pretomanid and the Nix-TB regimen

Dear Colleagues,

We write to you ahead of the meeting at The Rockefeller Foundation Bellagio Center. Preliminary results from the Nix-TB study of new drug candidate pretomanid in combination with existing drugs bedaquiline and linezolid (the Nix-TB 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.[1] **While we are encouraged by these findings and the prospect of shorter, all-oral treatment options for DR-TB, we write to share information and considerations related to pretomanid access and transparency, and concerns regarding the lack of community representation on the "DR-TB Triple Therapy Working Group," of which we understand you are a part. We appeal to you to address the issues discussed in this correspondence, especially as you consider supporting the introduction of pretomanid**.

Background
As civil society, including representatives and members of TB-affected communities, we have closely followed pretomanid's development. The TB Alliance developed pretomanid with foundation and public funding. As such, unlike with many other new products, there are no substantial research and development (R&D) costs for the sponsor to recoup through sales (as is often claimed by drug sponsors trying to justify high drug prices).

The Antimicrobial Drugs Advisory Committee to the US Food and Drug Administration (FDA) awarded the new drug application for pretomanid a favorable opinion in June 2019; the FDA's decision is expected in August 2019. If pretomanid is approved, the TB Alliance will receive a Priority Review Voucher (PRV), estimated to be worth between US$150 million and US$350 million. The TB Alliance has not articulated how it would use revenue generated through sale of a PRV.

The World Health Organization (WHO) will convene a guideline development group meeting to review data from the Nix-TB study in November 2019, meaning WHO guidelines will only be available as soon as 2020. Paediatric studies of pretomanid have been planned for several years, but have yet to begin, as further investigations of potential toxicities are required. No plan for the timing of their conduct has been publically communicated.

License terms and exclusivity
The TB Alliance and Mylan have rejected requests to share their licensing agreement publically.[2] In contrast, all licenses that go through the Medicines Patent Pool (MPP) are made public. The TB Alliance chose not to go through the MPP and instead directly granted Mylan a

global license for commercialization of pretomanid (the only countries not included in the license are China, Taiwan, Macau and Hong Kong). Under the agreement, Mylan has exclusive rights in high-income countries as well as several upper-middle income countries, though a list has not been made public.

Under this license, Mylan has noted it is responsible for registration (see below) and facilitating entry of other generics manufacturers, e.g. through right to reference and by making product available for bioequivalence testing. The specifics are not clear. We understand that, in addition to granting Mylan rights to pretomanid, the TB Alliance also granted Mylan a sublicense for bedaquiline for drug-susceptible TB (DS-TB) as bedaquiline is under investigation in combination with pretomanid (and moxifloxacin and pyrazinamide – BPaMZ) for shortening treatment for DS-TB. The exact terms and exclusivity of this part of the agreement are unknown. It is also unclear if the TB Alliance has received any financial gain from Mylan in exchange for granting an exclusive license in certain countries.

Pricing

Pricing for pretomanid is unknown. According to the TB Alliance, the licensing agreement contains affordability clauses; specifics have not been made public. Based on information contained in presentations by Mylan since the licensing agreement was announced, the price of pretomanid will be dependent on the costs of goods and manufacturing and volumes. Mylan has not shared the volume-based thresholds under consideration or its target profit margin, though they have indicated that volumes for substantial price reduction will require an indication for DS-TB (not expected until 2022 when the TB Alliance's phase III trial of BPaMZ [SimpliciTB; NCT03338621] is expected to complete).

The TB Alliance has said it will not use revenue generated by selling its assumed PRV to help lower the cost at which pretomanid can be introduced for difficult-to-treat forms of DR-TB. The TB Alliance strategy is to wait for competition driven by expanding the market to treating all forms of DR-TB and then DS-TB, which will take several years as studies to this end are several years from producing results.

Researchers from the University of Liverpool estimate that pretomanid can be produced and sold at a profit for USD $11–$34 per month once about 100,000 courses are reached.[3] Even with lower volumes, Mylan should be able to provide pretomanid at a low price in keeping with the USD $500 target regimen price[4] and still maintain a profit margin, especially given that it does not have any substantive R&D costs to recoup and even more so if its introduction is to be subsidized by donors including many of you in the room.

Registration

The TB Alliance is responsible for registering pretomanid with the FDA and the European Medicines Agency (EMA). Mylan is responsible for registration in other countries, and has indicated its preliminary list of priority countries. However, the terms of what Mylan's actual obligations may be under the agreement (number of countries, timeline, etc.) remain unknown.

Civil society has long-advocated for the TB Alliance to establish a pre-approval access programme for pretomanid. Mylan has stated its intent to set up such a programme, but its approach to "compassionate use" or preapproval access has yet to be announced.

Community Engagement

We note with severe disappointment the lack of community representation on the DR-TB Triple Therapy Working Group. In keeping with the 1983 Denver Principles, members of affected communities have *a right to be involved at every level of decision-making and to be included in all forums with equal credibility as other participants, to share their own experiences and knowledge*.[5] This has been a central tenant of the AIDS movement since its inception, and has become an ethical standard for the responses to TB and other global health issues.

Further investments in pretomanid should be made responsibly, and include terms that promote transparency and equitable access as well as a strong return on public investment. We respectfully request your support to:

1. **Make publicly available the full terms of the TB Alliance's licensing agreement with Mylan;**
2. **Secure from the TB Alliance an articulation of how it will use revenue generated from sale of an FDA PRV if received as expected;**
3. **Ensure a low global price based on costs of production plus a reasonable margin;**
4. **Ensure availability and proper stewardship of pre-approval access to pretomanid;**
5. **Expedite the additional toxicity studies required for paediatric investigations of pretomanid to begin; and**
6. **Meaningfully consult with communities while determining access plans and before committing any resources to the roll out of this regimen.**

To further discuss any of the issues described in this urgent appeal or how they might best be addressed, please write to the co-chairs of the Global TB Community Advisory Board (TB CAB), Patrick Agbassi (ayjpatrick@gmail.com) and Carolina Moran Jara (kromoran28@gmail.com).

Respectfully submitted,
on behalf of the undersigned organizations and individuals:

Organizations
Act Up-Basel, Switzerland/ France
ACT! AP / APCASO, Asia Pacfic
Advance Access & Delivery, United States
Afghan Youth Services Organization (AYSO), Afghanistan
Afrihealth Optonet Association (CSOs Network), Nigeria
AIDS Action Baltimore, United States
AIDS-Free World, Canada
Ambassadeurs de Lutte contre la Tuberculose (former TB patients NGO), Democratic Republic of the Congo
Association for Supporting MDR-TB Patients (ASPTMR), Romania
Assoication Burkinabe D'Action Communautaire (ABAC/ONG), Burkina Faso
Balajee Sewa Sansthan, India
BrookCherith Support, Nigeria
Burundian Alliance for Against Tuberculosis and Leprosy (ABTL), Burundi
Community and Family Aid Foundation, Ghana
Drug Resistant TB Scale Up Treatment Action Team (DR-TB STAT), Global
Dynamic Youth Development Organisation, Nigeria
Empower India, India
European AIDS Treatment Group (EATG), Europe
Facilitators of Community Transformation, Malawi
Gateway Health Institute, South Africa
Global Coalition of TB Activists, Global

Global Tuberculosis Community Advisory Board (TB CAB), Global
Grassroots Development and Empowerment Foundation, Nigeria
Health Action International (HAI), Netherlands
Health GAP, Global
Kenya Aids NGO Consortium (KANCO), Kenya
Life Concern, Malawi
Mongolian TB Coalition, Mongolia
Nirmaan Rehabilitation Facility, India
Partners In Health, United States/ Global
Positive Malaysian Treatment Access & Advocacy Group (MTAAG+), Malaysia
Radanar Ayar Association, Myanmar
Sos Enfance et Jeunesse Africaine/UNICO, Cote d'Ivoire
Synergy Care Development Initiative, Nigeria
TB and HIV Investigative Network- South Africa, South Africa
TB Association Charsadda Pak, Pakistan
TB Europe Coalition, WHO Europe Region
TB People Kyrgyzstan, Kyrgyzstan
TB Proof, South Africa
The Sentinel Project on Pediatric Drug-Resistant Tuberculosis, United States
Treatment Action Group, United States
Vivir. Participación, Incidencia y Transparencia, A.C., Mexico
Volunteers for Development Nepal (VFDN), Nepal
Women United for Economic Empowerment, Nigeria
Women's Initiative for Self-Actualization, Nigeria
Yayasan Menara Agung (MAP Internasional Indonesia), Indonesia
Judith Chikonde Foundation (JCF), Zambia/ Southern Africa Region
Zambia Tuberculosis and Leprosy Trust (ZATULET), Zambia
Wote Youth and Development Projects, Kenya

Individuals
Amanda Brumwell, Advance Access & Delivery, Inc., United States
Arumugam Sankar, Empower India, India
Billy Sichamba, Chichetekelo Outreach Partners, Zambia
Brian Citro, Northwestern Pritzker School of Law, United States
Candice Sehoma, Doctors Without Borders, South Africa
Cathy Rowan, Maryknoll Sisters, United States
Colleen Daniels, CD Global Consult, United States
Dean E Schraufnagel, United States
Uzodinma Adirieje, Afrihealth Optonet Association, Nigeria
Heny Akhmad, Stop TB Partnership Indonesia, Indonesia
Jennifer Furin, Harvard Medical School, United States
Joel Lexchin, York University, Canada
Joseph Senyo Kwashie, Community and Family Aid Foundation, Ghana
Pauline Londeix, France
Peter Ngola Owiti, Wote Youth Development Projects, Kenya
Peter Wiessner, Germany
Philip Waweru Mbugua, National Organization of Peer Educators (NOPE), Kenya
Renbonthung tongue, Indian Drug Users' Forum, India
Rosa Herrera, Mexico
Thura Aung, Radanar Ayar Association, Myanmar
Wim Vandevelde, Global Network of People living with HIV/AIDS (GNP+), South Africa

Appendix 1: Presumed Members of the DR-TB Triple Therapy Working Group and other colleagues involved in TB treatment access

Adrian Thomas, Johnson & Johnson
Amy Bloom, United States Agency for International Development
Ariel Pablos-Mendez, Columbia University
Benafsha Tasmim, Strongheart Group
Bill Foege, Emory University
Brenda Waning, Global Drug Facility
Carol Leland, Johnson & Johnson
Carolyn Reynolds, World Bank
Catherine Oyler, Johnson & Johnson
Christian Gunneberg, World Health Organization
Daisy Lekharu, the Global Fund Against AIDS, Tuberculosis and Malaria
David Wilson, World Bank
Draurio Barreira, Unitaid
Eliud Wandwalo, the Global Fund Against AIDS, Tuberculosis and Malaria
Fuad Mirzayev, World Health Organization
Jaak Peeters, Johnson & Johnson
Jacob Creswell, Stop TB Partnership
Jaime Nicolas Bayona Garcia, World Bank
Jamie Bayona, World Bank
Janet Ginnard, Unitaid
Janet Tobias, Ikana Health Action Lab
Jeremy Knox, Wellcome Trust
Joanne Carter, Results
John Fairhurst, the Global Fund Against AIDS, Tuberculosis and Malaria
Judith Kallenberg, Johnson & Johnson
Kara Adamon, World Bank
Katherine Fitzgerald, the Global Fund Against AIDS, Tuberculosis and Malaria
Kefas Samson, World Health Organization
Lars Hartenstein, McKinsey & Company
Lucica Ditiu, Stop TB Partnership
Marek Sienkiewicz, McKinsey & Company
Marie Sieghold, McKinsey & Company
Mehreen Khalid, the Global Fund Against AIDS, Tuberculosis and Malaria
Mukadi YaDiul, United States Agency for International Development
Nina Probst, McKinsey & Company
Peter Small, Rockefeller Foundation
Sahu Suvanand, Stop TB Partnership
Sally Davies, Government of the United Kingdom
Sanne Fournier-Wendes, Unitaid
Shantanu Nundy, World Bank
Soumya Swaminathan, World Health Organization

Tereza Kasaeva, World Health Organization
Timothy Grant Evans, World Bank
Yogan Pillay, Government of South Africa
Zoe Adams, Strongheart Group

References

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[2] Open Letter Urging Halt to Publication of pretomanid licensing agreement between the TB Alliance and Mylan in the public domain. Global Tuberculosis Community Advisory Board. 10 June 2019. Available from: http://www.tbonline.info/media/uploads/documents/open_letter_to_tb_alliance_and_mylan_make_pretomanid_agreement_public_6.7.19_final.pdf.

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[5] The Denver Principles (1983). People with AIDS Advisory Committee. Available from: http://www.actupny.org/documents/denver_principles.pdf.