TB Alliance

Our Progress in TB R&D

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February 17, 2022

Our Vision: Better TB Medicines for All

Discover, develop, and deliver better and faster TB regimens

Simple
All-oral, highly effective regimens

Short
Two to four months of treatment

Accessible
Adopted, available and affordable to people with TB

Millions of lives saved
Fight the TB epidemic and accelerate eradication

Achieving our mission will require:

- A sustainable pipeline of novel drugs to form the basis for universal regimens effective in all people with active TB
- An ultra-short and effective therapy for latent infection
- All TB treatments appropriately formulated for children

TB Drug Development Pipeline As of February 2022*

TB Alliance

Discovery

Lead Identification

ClpP1P2 Lead ID Programs
- CETR
- Harvard
- Texas A&M
- UIC

GHIT Hit ID Programs
- Daiichi Sankyo RD Novare
- Texas A&M
- UIC

GHIT Hit-to-Lead Programs
- Astellas
- Chugai
- Daiichi Sankyo RD Novare
- Takeda
- UIC

Intracellular Active Series
Evotec

Malate Synthetase Inhibitors
Texas A&M

Pantothenamide
- TropIQ
- WCM

PknB
- Schrödinger
- UoA

RNA Polymerase Inhibitors
CETR

Whole Cell Hit-to-Lead Program
GSK

Lead Optimization

Anti-TB Natural Products
Evotec

ClpC1
- CETR
- Harvard
- UIC

InhA Inhibitors
GHDDI

Intracellular Active Series
GSK

KasA
GSK

MmpL3 Inhibitors
- AbbVie
- ERA4TB

Preclinical Development

Preclinical TB Regimen Development
JHU

Early Development

Phase 1

TBAJ-876 / Diarylquinoline

TBAJ-587 / Diarylquinoline
ERA4TB

TBI-223 / Oxazolidinone
IMM

Phase 2A/2B

BPaMZ/SEM
UoSA

Sutezolid / Oxazolidinone
Gates MRI

TBA-7371 / DprE1 Inhibitor
- FNDR
- Gates MRI

Late Development

Phase 3

NixTB

Bedaquiline / Pretomanid / Linezolid
(BPaL)
Viatris

ZeNix

Bedaquiline / Pretomanid / Linezolid
(BPaL)
Viatris

SIMPLICITB

Bedaquiline / Pretomanid / Moxifloxacin / Pyrazinamide
(BPaMZ)
- PanACEA
- Radboud
- Viatris

Marketed Products

Optimized Pediatric Formulations

Ethambutol
Macleods

Isoniazid
Macleods

Pyrazinamide
Macleods

Rifampicin/Isoniazid
Macleods

Rifampicin/ Isoniazid / Pyrazinamide
Macleods

Pediatric Formulation Development

Pretomanid
Viatris

Pretomanid for use in BPaL

Pretomanid for use in BPaL Regimen
- Hongqi
- ITRC
- KNCV
- Lupin
- Macleods
- Viatris

TB Alliance Portfolio Partners

AbbVie
Astellas
Bill & Melinda Gates Medical Research Institute (Gates MRI)
Center for Excellence in Translational Research (CETR)
Chugai
Daiichi Sankyo RD Novare
ERA4TB Consortium
EU-Pearl Consortium
Evotec
Foundation for Neglected Disease Research (FNDR)
GlaxoSmithKline (GSK)
Global Health Drug Discovery Institute (GHDDI)
Harvard University
Hongqi Pharmaceutical
Institute of Materia Medica (IMM)
IMPAACT
International Tuberculosis Research Center (ITRC)
Johns Hopkins University (JHU)
KNCV Tuberculosefonds
Lupin Pharmaceuticals
Macleods Pharmaceuticals
Medical Research Council (MRC) at UCL
Médecins Sans Frontières (MSF)
National Institutes of Health (NIH)
PanACEA
PAN-TB Consortium
Schrödinger
Stellenbosch University
Takeda Pharmaceuticals
TB Drug Accelerator (TBDA)
Texas A&M University
TropIQ
UNITE4TB Consortium
University College London (UCL)
University of Auckland (UoA)
University of Illinois at Chicago (UIC)
University of St. Andrews (UoSA)
Viatris
Weill Cornell Medical (WCM)
Yonsei University

* Phase 3 clinical trials are added to the pipeline after enrollment of the first patient and are removed after publication of trial results. This document is updated on a quarterly basis.

Nix-TB: 6-month BPaL study in highly drug-resistant TB

New England Journal of Medicine, March 2020

PARTICIPANTS

109 enrolled

71 with **XDR-TB**

65%

38 with **TI/NR* MDR-TB**

34%

RESULTS

90% had **favorable outcomes**

XDR-TB

89%

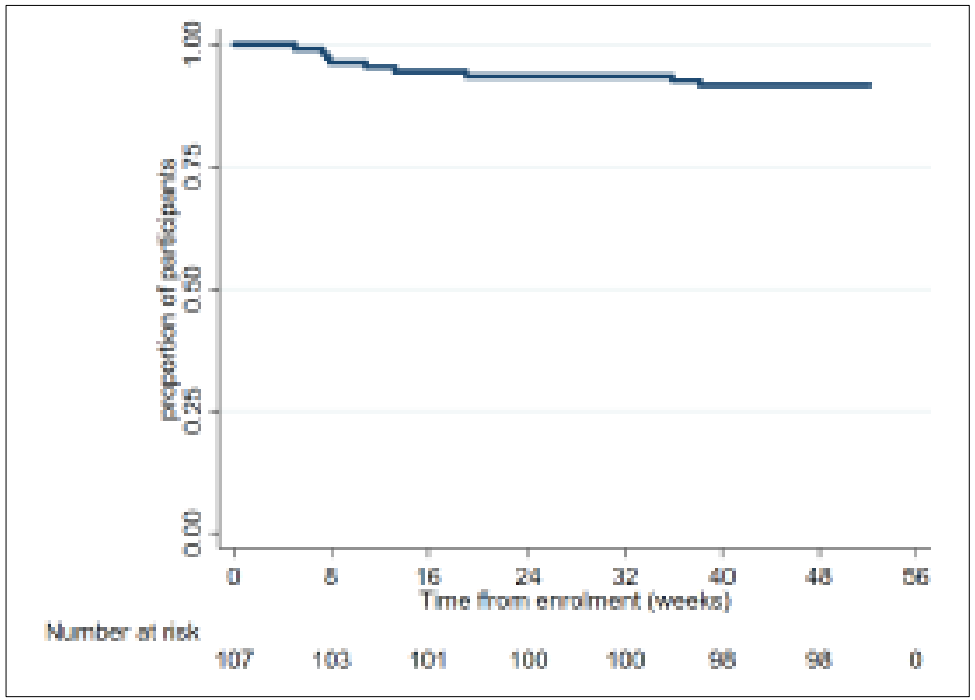
79-95 (95% CI)

TI/NR* MDR-TB

92%

79-98 (95% CI)

Nix-TB Efficacy: Time to Unfavorable Outcome



*Treatment intolerant or non-responsive MDR-TB

NixTB Conclusions

- 90% of subjects with highly resistant TB achieved relapse-free cure status six months after the end of treatment with this simplified, shortened, all-oral regimen
- This high efficacy was sustained through two-year follow-up (88%)
- Peripheral neuropathy from linezolid was common, but manageable with dose modification, and symptoms generally improved or resolved over 24 months of follow-up
- A follow-on trial, ZeNix, investigates the optimal dose and duration of linezolid in the BPaL regimen
- Data through primary endpoint presented at International AIDS Society Meeting, July 2021

ZeNix: BPaL study in highly drug-resistant TB

ZeNix

LINEZOLID DOSING	FAVORABLE OUTCOMES
1200 mg x 6 mo	93% (81.3-98.6 (95% CI))
1200 mg x 2 mo	89% (75.9-96.3 (95% CI))
600 mg x 6 mo	91% (78.3-97.5 (95%) CI)
600 mg x 2 mo	84% (69.9-93.4 (95% CI))

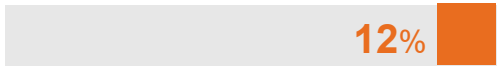
PARTICIPANTS

181 participants with **confirmed TB**

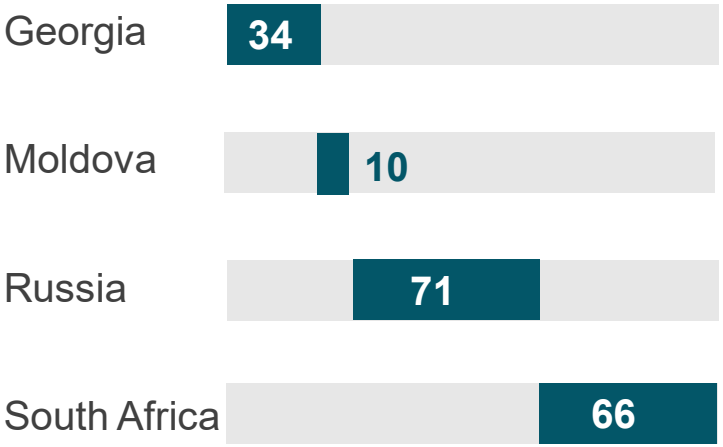
75 with **XDR-TB**

85 with **pre-XDR-TB**

21 with **TI/NR* MDR-TB**



Country

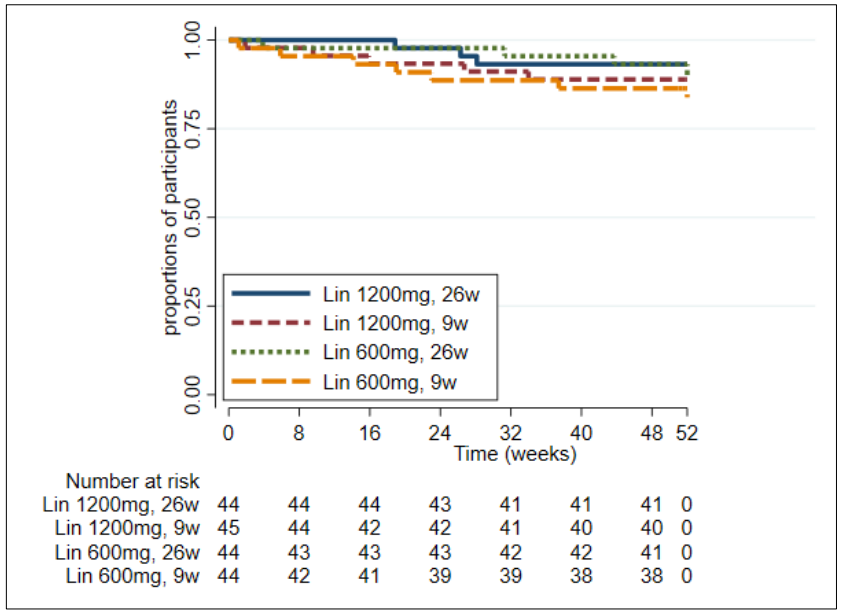


*Treatment intolerant or non-responsive MDR-TB

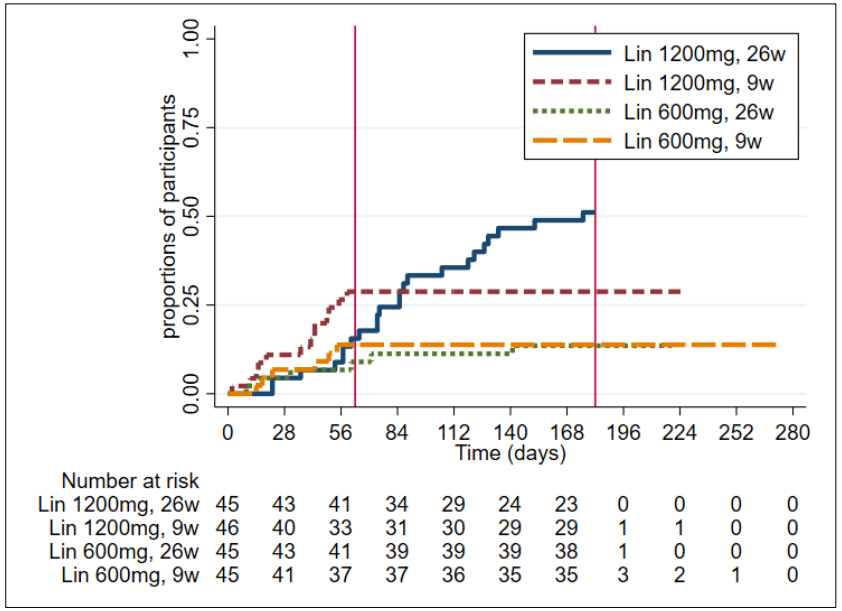
ZeNix Results at Primary Endpoint

ZeNix

ZeNix Efficacy: Time to Unfavorable Outcome



ZeNix Safety: Time to First Dose Modification



- High success rate of Nix-TB replicated in all four treatment arms
- Lower and/or shorter dosing of linezolid showed substantially improved safety and tolerability
- Extends Nix-TB results to broader patient populations (demographics, geography, drug resistance)

Novelty and Significance of Pretomanid and the BPaL Regimen

- FDA approval of pretomanid in 2019
  - Utilized new, expedited regulatory pathway (LPAD)
  - Approval of a new drug in a specific drug regimen: BPaL
  - Indicated for highest-need patients – extensively drug-resistant TB
- Represents dramatic improvement in treatment and outcome
  - Three-drug, six-month, all-oral, once daily regimen
  - Achieved 90% treatment success in the most difficult-to-treat patients
- Additional regulatory approvals by EMA, high-burden countries (India, South Africa) and 10 other countries; WHO issued rapid guidance in December 2019
- Multiple commercialization partnerships established, providing worldwide access and fostering generic competition

Broadening the Evidence Base for BPaL-Containing Regimens

- TB-PRACTECAL Trial (MSF)
  - Two-stage trial evaluating three BPaL-based regimens in rifampicin-resistant TB
  - Randomized vs control arm local standard-of-care
- Initial WHO guidance for BPaL implementation in Operational Research (OR) setting
  - At least 14 countries have commenced or are planning OR or similar programs
    - Stop-TB/TB REACH
    - USAID
    - WHO/TDR
    - LIFT-TB

Building Upon BPaL, and Beyond

- Second generation drugs – improved safety and efficacy
  - Bedaquiline → Novel Diarylquinolines TBAJ-876, TBAJ-587
  - Linezolid → Novel Oxazolidinones TBI-223, Sutezolid
- Incorporate novel drug classes, without preexisting resistance
- Further shortening of treatment: Months → Weeks
- Develop “universal” regimens, irrespective of drug resistance

Early-Stage Research: Filling the Pipeline

A three-pronged approach

- TB Alliance leverages industry and other partners to support the continued growth of the global TB drug pipeline.

Optimize known compound classes

Fully capitalize on the success of compounds already in development or approved

Develop novel classes based on known targets

Leverage validated drug targets, discover novel classes to address resistance

Develop novel classes based on novel targets

Discover new drug classes with novel modes of action

Advancing the Pipeline

- **TBI-223 (novel oxazolidinone)**
  - Three-month and six-month animal GLP studies confirmed the lack of bone marrow toxicity
  - SAD (single ascending dose) and MAD (multiple ascending dose) studies completed
- **Sutezolid (novel oxazolidinone)**
  - Potentially safer oxazolidinone
  - Several Phase 2 combination studies planned
- **TBAJ-876 (novel diarylquinoline)**
  - Completing Phase 1; preparing for Phase 2
- **TBAJ-587 (novel diarylquinoline)**
  - Completed Phase 1 SAD in partnership with Innovative Medicines Initiative (IMI)
- **TBA-7371 (DprE1 inhibitor)**
  - Phase 2A study in progress
- **MmpL3 Inhibitors**
  - Nearing preclinical lead identification

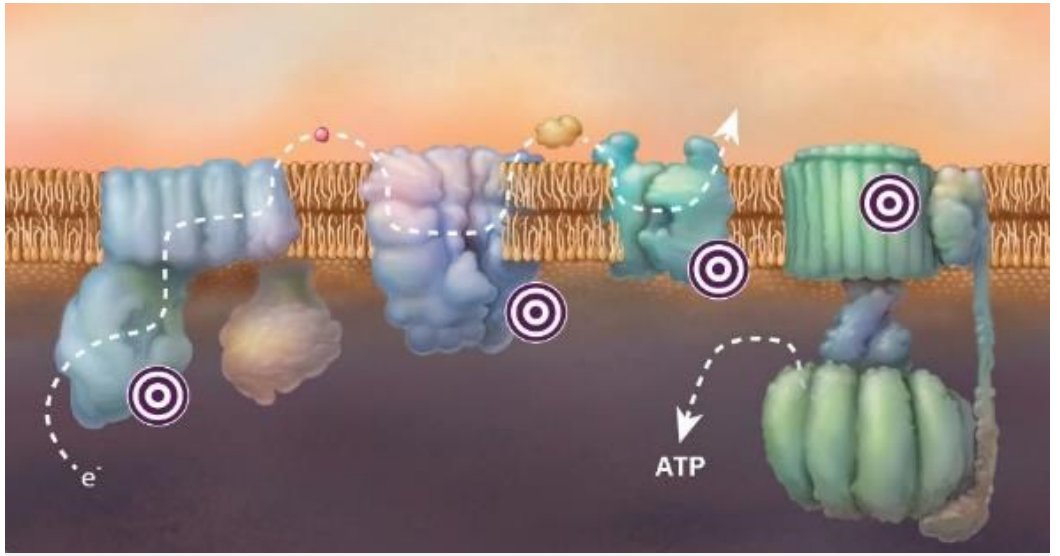
TBAJ-876: next generation Diarylquinoline

Preclinical profile

- Increased potency
  - Treatment shortening demonstrated in mouse model
  - Potential to overcome BDQ resistance
- Improved safety profile
  - Minimal potential for QTc prolongation, avoiding need for ECG monitoring

Development status

- Phase 1 SAD study completed
- MAD study ongoing
- Excellent tolerability
- Preparations for Phase 2 underway



Mechanism of Action

Electron Transport Chain

Compounds stop the generation of cell energy, impeding the growth of the TB bacteria.

The Next Innovations in TB Treatments: Artificial Intelligence

New Partnerships to Identify the Components of Tomorrow's TB Regimens

AI to Support Immunotherapy

- AI driven analysis of immunomodulatory pathways and targets with greatest impact on bacterial clearance (InveniAI)
- Targets and pathways have either clinical or research compounds available
- With Advisory group select top candidates to evaluate in a relapse mouse model on top of a novel regimen and SOC

InveniAI
Innovate with Intelligence

AI-Assisted Screening Process

- Combine large scale screening approach such (DNA encoded Library) and AI to select advanced drug like lead (Relay Therapeutics)
- Could significantly reduce the time and cost to discover novel leads against traditional targets as well as potential immunotherapy targets of value

RELAY THERAPEUTICS

2021 Global New TB Drug Pipeline [1]

Discovery | **Preclinical Development** | **Clinical Development**

Lead Optimization → **Early Stage Development** → **GMP / GLP Tox.** → **Phase 1** → **Phase 2** → **Phase 3** → **Regulatory Market Approvals**

PanD inhibitors
Indazole sulfonamides
Diarylthiazoles
DprE1 Inhibitors
Direct InhA Inhibitors
Mtb energy metabolism
Macrolides
Mycobacterial Gyrase Inhibitors
Arylsulfonamides
Inhibitors of MmpL3, Translocase-1, Clp, PKS13, F-ATP synthase
Oxazolidinones

JSF-3285*
MPL-446, 447*
CPZEN-45*
NTB-3119*
TZY-5-84
MBX-4888A (1810)*
FNDR-10045*
FNDR-20364*

FNDR-20081*
TB-47*
GSK-839*
OTB-658
Sanfetrinem

BVL-GSK098*
GSK-286*
TBAJ-587
TBAJ-876
TBI-223
Macozinone* (PBTZ-169)
Pyrifazimine (TBI-166)

Delpazolid
Sutezolid
BTZ-043*
TBA-7371*
OPC-167832*
GSK-656* (070)
SQ-109*
Telacebec*
SPR720*
Macozinone*

Pretomanid* / Moxifloxacin / Bedaquiline*/ PZA (4-month regimen)
Truncate TB (2-month regimens)
Rifapentine / Moxifloxacin / INH/PZA (4-month regimen)

Bedaquiline*
Delamanid*
Pretomanid*

Underline = updates since March 2021

*New chemical class. Known chemical classes for any indication are color coded: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone, imidazopyridine amide, beta-lactam.

[1] New Molecular Entities not yet approved, being developed for TB or only conditionally approved for TB. Showing most advanced stage reported for each. Details for projects listed can be found at http://www.newtbdrugs.org/pipeline/clinical

Ongoing projects without a lead compound series identified: http://www.newtbdrugs.org/pipeline/discovery

WORKING GROUP ON NEW TB DRUGS
www.newtbdrugs.org

Updated: October 2021

Special thanks to clinical trial participants and all our partners