Our Progress in TB R&D

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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

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
### TB Drug Development Pipeline

**As of February 2022**

#### Lead Identification
- **ClpP1P2 Lead ID Programs**
  - CETF
  - Harvard
  - Texas A&M
  - UIC

- **GHT HIT ID Programs**
  - Daiichi Sankyo RD Novare
  - Texas A&M
  - UIC

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

- **Intracellular Active Series**
  - CETF
  - GSK
  - Evotec

- **Malate Synthetase Inhibitors**
  - Texas A&M

- **Pantothenamide**
  - Troplol
  - WCM

- **PknB**
  - Schrödinger
  - UoA

- **RNA Polymerase Inhibitors**
  - CETF

- **Whole Cell Hit-to-Lead Program**
  - GSK

### Lead Optimization
- **Anti-TB Natural Products**
  - Evotec

- **ClpC1**
  - CETF
  - Harvard
  - UIC

- **InHA Inhibitors**
  - GHDDI

- **Intracellular Active Series**
  - GSK
  - Kasa
  - GSK

- **MmpL3 Inhibitors**
  - AbiVie
  - ERA4TB

### Preclinical Development
- **Preclinical TB Regimens Development**
  - JHU

### 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

### Phase 3
- **Bedaquiline / Pretomanid / Linezolid**
  - (BPaL)
  - Viatris

- **SimplificaTB**
  - Bedaquiline / Pretomanid / Moxifloxacin / Pyrazinamide (BPaM) / PBPaMZ
  - PanACEA
  - Redbox
  - Viatris

### Marketed Products
- **Optimized Pediatric Formulations**
  - Ethambutol
  - Macrolides
  - Isoniazid
  - Macrolides
  - Pyrazinamide
  - Macrolides
  - Rifampicin/isoniazid
  - Macrolides

### Pediatric Formulation Development
- **Pretomanid**
  - Viatris

### Pretomanid for use in BPaL
- **Pretomanid for use in BPaL, Regimen**
  - Hongqi
  - ITRC
  - KNCV
  - Lupin
  - Macrolides
  - 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)
- IMRACCT
- International Tuberculosis Research Center (ITRC)
- Johns Hopkins University (JHU)
- KNCV Tuberculosisfonds
- Lupin Pharmaceuticals
- Macleods Pharmaceuticals
- Medical Research Council (MRC) at UCL
- Medecine Sans Frontieres (MSF)
- National Institutes of Health (NIH)
- PanACEA
- PAN-TB Consortium
- Schrödinger
- Stellenbosch University
- Takeda Pharmaceuticals
- TB Drug Accelerator (TBDA)
- Texas A&M University
- Troplol
- UNITE4TB Consortium
- University College London (UCL)
- University of Auckland (UoA)
- University of Illinois at Chicago (UIC)
- University of St. Andrews (UoSAT)
- 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)

*N: Treatment intolerant or non-responsive MDR-TB
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

<table>
<thead>
<tr>
<th>LINEZOLID DOSING</th>
<th>FAVORABLE OUTCOMES</th>
<th>PARTICIPANTS</th>
<th>COUNTRY</th>
</tr>
</thead>
<tbody>
<tr>
<td>1200 mg x 6 mo</td>
<td>93%</td>
<td>181</td>
<td></td>
</tr>
<tr>
<td></td>
<td>81.3-98.6 (95% CI)</td>
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</tr>
<tr>
<td>1200 mg x 2 mo</td>
<td>89%</td>
<td>75</td>
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<tr>
<td></td>
<td>75.9-96.3 (95% CI)</td>
<td>41%</td>
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<tr>
<td>600 mg x 6 mo</td>
<td>91%</td>
<td>85</td>
<td></td>
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<tr>
<td></td>
<td>78.3-97.5 (95% CI)</td>
<td>47%</td>
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<tr>
<td>600 mg x 2 mo</td>
<td>84%</td>
<td>21</td>
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<tr>
<td></td>
<td>69.9-93.4 (95% CI)</td>
<td>12%</td>
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</tbody>
</table>

*Treatment intolerant or non-responsive MDR-TB
ZeNix Results at Primary Endpoint

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

**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
# 2021 Global New TB Drug Pipeline

## Discovery
- PanD inhibitors
- Indazole sulphonamides
- 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

## Preclinical Development
- Early Stage Development
- GMP / GLP Tox.

## Clinical Development
- Phase 1
- Phase 2
- Phase 3

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

### Underline = updates since March 2021

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

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*New chemical class. Known chemical classes for any indication are color coded: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diaryquinoline, 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

Updated: October 2021
Special thanks to clinical trial participants and all our partners