TB Alliance Stakeholders Association Annual Meeting

The webinar will begin momentarily
TB Alliance Stakeholders

Signatories of the 2000 Cape Town Declaration
SHA Meeting Agenda

Welcome Remarks – Mitchell Warren

Keynote Address – Nick Herbert (Lord Herbert of South Downs), Chair of the Global TB Caucus

State of the TB Alliance – Mel Spigelman, TB Alliance

Innovations in TB R&D – Eugene Sun and Nader Fotouhi, TB Alliance

Moderated Discussion: Treating TB during the COVID pandemic – Mitchell Warren
Dr. Francesca Conradie, WITS Health Consortium, South Africa
Dr. Nestani Tukvadze, National Center for TB and Lung Disease, Georgia
Bongiswa Mdaka, TB Survivor, South Africa

Q&A and Discussion
State of the TB Alliance

Mel Spigelman, MD, President & CEO

November 19, 2020
20 Years of Impact

FEBRUARY 2000

Declaration of Cape Town calls for **TB ALLIANCE**

a public-private partnership dedicated to developing new TB treatments.
Evolution of New TB Therapies

- 1943: Streptomycin (S)
- 1948: p-aminosalicylic acid (PAS)
- 1952: Isoniazid (H)
- 1954: Pyrazinamide (Z)
- 1955: Cycloserine (Cs)
- 1957: Kanamycin (Z)
- 1960: Ethionamide (ETO)
- 1961: Ethambutol (E)
- 1963: Capreomycin (Cm) & Rifampicin (R)
- 1975:isoniazid (H)
- 1984: Pyrazinamide (Z)
- 1996: Ethambutol (E)
- 1998: Rifapentine (P)
- 2006: Bedaquiline (BDQ)
- 2012: Delamanid (DLM)
- 2014: Pretomanid (Pa)
- 2016: RPAI: 6-month, all-oral therapy for highly resistant TB
- 2020: 2PM/2PHM: 4 months of therapy

First randomized trial: S Monotherapy
Led to S resistance

First regimen: S/PAS/R
24 months of therapy

PAS replaced by E: S/H/E
18 months of therapy

Addition of R: S/H/R/E
9–12 months of therapy

S replaced by Z: H/R/Z/E
6 months, oral therapy

1940s 1950s 1960s 1970s 1980s 1990s 2000s 2010s 2020s
Nix-TB Results

New England Journal of Medicine, March 2020

PARTICIPANT STATS

109 participants with confirmed TB

71 with XDR-TB

65%

38 with MDR-TB*

34%

THE RESULTS

Favourable outcomes

with XDR-TB

89%

79-85 (95% CI)

with MDR-TB*

92%

79-88 (95% CI)

90% of all participants had favourable outcomes

95% CI (83-95)

Clinical resolution

6 months after therapy

*Treatment intolerant or non-responsive MDR-TB
Shorter, Simpler Treatment for Highly Drug-Resistant Forms of TB

One day of typical BPaL regimen
6 months / <750 pills

One day of typical XDR-TB treatment
18+ months / 14,000+ pills

Please see Full Prescribing Information at: [www.accessdata.fda.gov](http://www.accessdata.fda.gov)
Ensuring Access

We partner at every stage to ensure improved TB regimens are adopted, available and affordable.

### Evidence Generation
- Perform and disseminate research in support of new therapeutics

### Policy and Guidelines
- Ensure new products are endorsed and recommended to drive use

### Supply and Availability
- Ensure consistent global supply of products at affordable prices
BPaL: Rapid Progress Toward Uptake

• Agreement with Global Commercialization Partner in April 2019
• In about 2 months from US FDA approval: pretomanid was made available for 150 low and middle-income countries though Stop TB Partnership’s Global Drug Facility (GDF) at a price of $364 for a six-month treatment course
• The World Health Organization (WHO) recommended the BPaL regimen under operational research conditions
• Enrollment was completed in TB Alliance’s Phase 3 ZeNix (linezolid optimization) trial, with results expected in 2021. The 24-month follow-up on all patients in the pivotal Nix-TB trial was recently completed
Support for Operational Research and Regulatory Submissions

• **Stop-TB / TB REACH**: early implementation of BPaL – Ukraine and Tajikistan

• **USAID**: BPaL Clinical Access Program planned in South Africa

• **EDCTP**: Project in Ethiopia, Nigeria, and South Africa to “triage-and-treat” patients using novel TB diagnostic technologies to guide implementation of short, all-oral regimens for DR-TB – in partnership with FIND

• **KOICA (South Korea)**: Project providing technical assistance for BPaL implementation in 7 countries in SE Asia and Eastern Europe

• Viatris (Mylan) prioritized regulatory submissions in key countries; Donating 50-100 treatments of pretomanid to help speed operations research (also, India and South Africa)

• Protocols include frequent data reporting to support timely guideline update by WHO
Impact of COVID-19

A New Pandemic Threatens Progress – Hard-won Gains May Be Erased

• By disrupting the testing and treatment of TB and HIV, the COVID-19 pandemic could cause an additional 6.3 million TB cases and 1.4 million additional TB deaths through 2025.

• Global TB incidence and deaths in 2021 could increase to levels last seen between 2013 and 2016 respectively – a setback of at least 5 to 8 years in the fight against TB.

• TB “brain drain” – partner capacity has been significantly impacted.
COVID-19 Research

Capitalizing on our existing activities

• In designing and testing protease inhibitors against TB, we also:
  – Screened our collection against SARS-Cov-2 protease
  – Designed and synthesizing specific inhibitors of the PLpro and 3CL

• A recent screen of select classes of proprietary compounds in a cell-based screen at Calibr have resulted in hits

• Currently following up on expanding the compound list and classes to select the best series to focus a medicinal chemistry approach
Strategic Overview

A new standard of TB drug development

- Nix-TB has provided proof of principle that the most resistant forms of TB can be treated in the same timeframe and with as few drugs as is used for DS-TB - and with comparable results
- Next challenge is one regimen for all patients with active TB (Universal Regimen)
- Initial goal is to shorten timeframe of treatment to 2-3 months
- Long term objective is a universal regimen that cures in days to weeks
- Needs of the market dictate our R&D agenda – requires a constant feedback loop
Innovations in TB R&D

Eugene Sun, SVP, Research & Development
Nader Fotouhi, SVP, Chief Scientific Officer

November 19, 2020
## TB Drug Development Pipeline

**As of October 2020**

### Lead Identification
- Clp Lead ID Programs
  - Harvard University
  - UIC
  - CETR

- GHT Hit ID Programs
  - Astellas
  - Fujifilm

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

- Malate Synthetase Inhibitors
  - Texas A&M

- Pantothenamide
  - TroplO
  - WCM

- PknB
  - USA/Schroedinger

- RNA Polymerase Inhibitors
  - CETR

- Whole Cell Hit-to-Lead Program
  - GSK

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

- InhA Inhibitors
  - GHDDI

- Intracellular Active Series
  - GSK

- KasA
  - GSK

- MmpL3 Inhibitors
  - AbbVie
  - ERA4TB

### Preclinical Development
- Preclinical TB Regimen Development
  - JHU

- TBAJ-876 / Diaryquinoline
  - ERA4TB

- TBI-223 / Oxazolidinone
  - IMM

- TBAJ-587 / Diaryquinoline
  - ERA4TB

### Phase 1
- Sutezolid / Oxazolidinone
  - Gates MRI

- TBAJ-876 / Diaryquinoline
  - JHU

- TBI-223 / Oxazolidinone
  - IMM

### Phase 2A/2B
- Bedaquiline / Pretomanid / Linezolid (BPaL)
  - Mylan

- TBAJ-7371 / DprE1 Inhibitor
  - FNDR
  - Gates MRI

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

- **ZeNix**
  - Bedaquiline / Pretomanid / Linezolid (BPaL)
  - Mylan

- **SIMPLICI TB**
  - Bedaquiline / Pretomanid / Moxifloxacin / Pyrazinamide (BPaMZ)
  - Parapharma
  - Mylan
  - Radboud

### Marketed Products
- Optimized Pediatric Formulations
  - Ethambutol
  - Macleods
  - Onyva

- Pyrazinamide
  - Macleods

- Rifampicin/Isoniazid
  - Macleods

- Pediatric Formulation Development
  - Pretomanid
  - Mylan

- Pretomanid for use in BPaL
  - Mylan
  - Macleods
  - Honyqi
  - KNDC

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**TB Alliance Portfolio Partners**

- AbbVie
- Astellas
- Bill & Melinda Gates Medical Research Institute (Gates MRI)
- Center for Excellence in Translational Research (CETR)
- Chuqai
- Daiichi Sankyo
- RD Novare
- ERA4TB Consortium
- Erasmus University Rotterdam
- Evotec
- Foundation for Neglected Disease Research (FNDR)
- Fujifilm
- GlaxoSmithKline (GSK)
- Global Health Drug Discovery Institute (GHDDI)
- Harvard University
- Hongqi Pharmaceutical
- Institute of Materia Medica (IMM)
- IMPAACT
- Johns Hopkins University (JHU)
- KNCV Tuberculosis
- Macleods Pharmaceuticals
- Medical Research Council (MRC) at UCL
- Médecins Sans Frontières (MSF)
- Mylan
- US National Institutes of Health (NIH)
- PanACEA
- Radboud University Nijmegen
- Schrödinger
- Stellenbosch University
- Takeda Pharmaceuticals
- TB Drug Accelerator (TBDA)
- Texas A&M University
- TroplO
- University College London (UCL)
- University of Auckland (UoA)
- University of Illinois at Chicago (UIC)
- Weill Cornell Medical (WCM)
- Yonsei University

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*Phase 3 clinical trials are added to the pipeline after enrollment of the first patient and are removed after completion of the Clinical Study Report. This document is updated on a quarterly basis.*
Phase 3 Results in 2021

- 24 month Nix-TB results
- ZeNix top-line results
- SimpliciTB top-line results
ZeNix: Linezolid Optimization Trial

Patients with XDR-TB, Pre-XDR-TB or who have failed or are intolerant to MDR-TB treatment

Enrollment completed Dec 2019. 181 patients enrolled from Georgia, South Africa, Russia and Moldova
The SimpliciTB clinical trial seeks to test a novel regimen consisting of bedaquiline (B), pretomanid (Pa), moxifloxacin (M) and pyrazinamide (Z) (BPaMZ). This trial evaluates:

- The efficacy of a 4-month regimen of BPaMZ in people with DS-TB versus six months of HRZE (control/standard of care).
- The safety, tolerability and efficacy of a 6-month BPaMZ regimen for patients with DR-TB.


*Specifically MDR-TB and mono-resistance to isoniazid or rifampicin. B: bedaquiline 200 mg x 8 weeks, then 100 mg | Pa: pretomanid 200 mg | M: moxifloxacin 400 mg | Z: pyrazinamide 1500 mg | H: isoniazid | R: rifampicin | Z: pyrazinamide | E: ethambutol
Additional Pretomanid Studies

Pretomanid Pediatric Program
Pretomanid Pediatric Program
Pediatric Investigational Plan finalized and agreed with EMA in early 2019
3 clinical studies
• Bioavailability study of pediatric formulation in healthy adult volunteers - completed
• Single-dose pretomanid study in children with MDR-TB and XDR-TB – Estimated start mid-2021
• Multiple-dose BPaL study in children with XDR-TB, non-responsive MDR-TB and treatment-intolerant MDR-TB

Semen Studies
Male reproductive safety study. Estimated start date is May 2021
Paternity Survey. Estimated start date is mid-Nov 2020
### Preliminary dose/exposure-response evaluation for TBAJ-587 and TBAJ-876 with PaO*

*O = TBI-223

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<th>Proportion of Mice Relapsing After:</th>
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<td>D0</td>
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<tr>
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<td>3/15</td>
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BPaL typically cures all mice in 3-4 months, and would perform similarly to BPaO here.
We initiated a program to develop treatments against certain nontuberculous mycobacteria (NTM) infections.

- Establish NTM drug discovery and regimen development engines
  - Develop predictive chronic animal models of NTM lung disease
  - Leverage TB Alliance’s existing anti-TB portfolio to identify novel NTM drug candidates
  - Identify regimens with potential to treat NTM infections in the cystic fibrosis population
- Identify one preclinical development candidate by 2021
Innovations in TB Discovery

Nader Fotouhi, SVP, Chief Scientific Officer

November 19, 2020
Setting a New Course for TB Drug Development

Exploring Immunotherapy and Leveraging Artificial Intelligence

2000s
Establishing the PDP Paradigm for TB Drugs

2010s
Proving the Theory of Regimen Development and Advancing New Drugs

2020s
What comes next?

TB Alliance
Stakeholders Association
The Next Innovations in TB Treatments: Immunotherapy

Harnessing the Immune System to Shorten Treatment Duration

Available TB Therapies

- **1st line regimen (HRZE)**
  - 6+ months to cure

- **BPaL**
  - 12 weeks to cure

Universal Regimen

- **All-novel regimen**
  - ≤3 months to cure

The Next Paradigm

- **All-novel regimen**
  - + Immunotherapy
  - 7-10 days to cure
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

**Al-Assisted Screening Process**

- Combine large scale screening approach such (DNA encoded Library) and AI to select advanced drug like lead (ZebiAI)
- Could significantly reduce the time and cost to discover novel leads against traditional targets as well as potential immunotherapy targets of value
What Could the Patient Experience Look Like in the Future?

Available Therapies

Universal Regimen

Universal Regimen + Immunotherapy

6+ Months

≤3 Months

7-10 Days
TB Alliance Stakeholders Association Annual Meeting

Moderated Discussion

Please submit your questions through the Q&A function.
TB Alliance Stakeholders Association
Annual Meeting

Thank you for participating!