TB Alliance Stakeholders Association Annual Meeting

The webinar will begin momentarily

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2020 Stakeholders Association Annual Meeting

November 19, 2020

TB Alliance Stakeholders

Community Representative, Ksenia Shchenina

Community Representative, Roger Paul Kamugasha

★ 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

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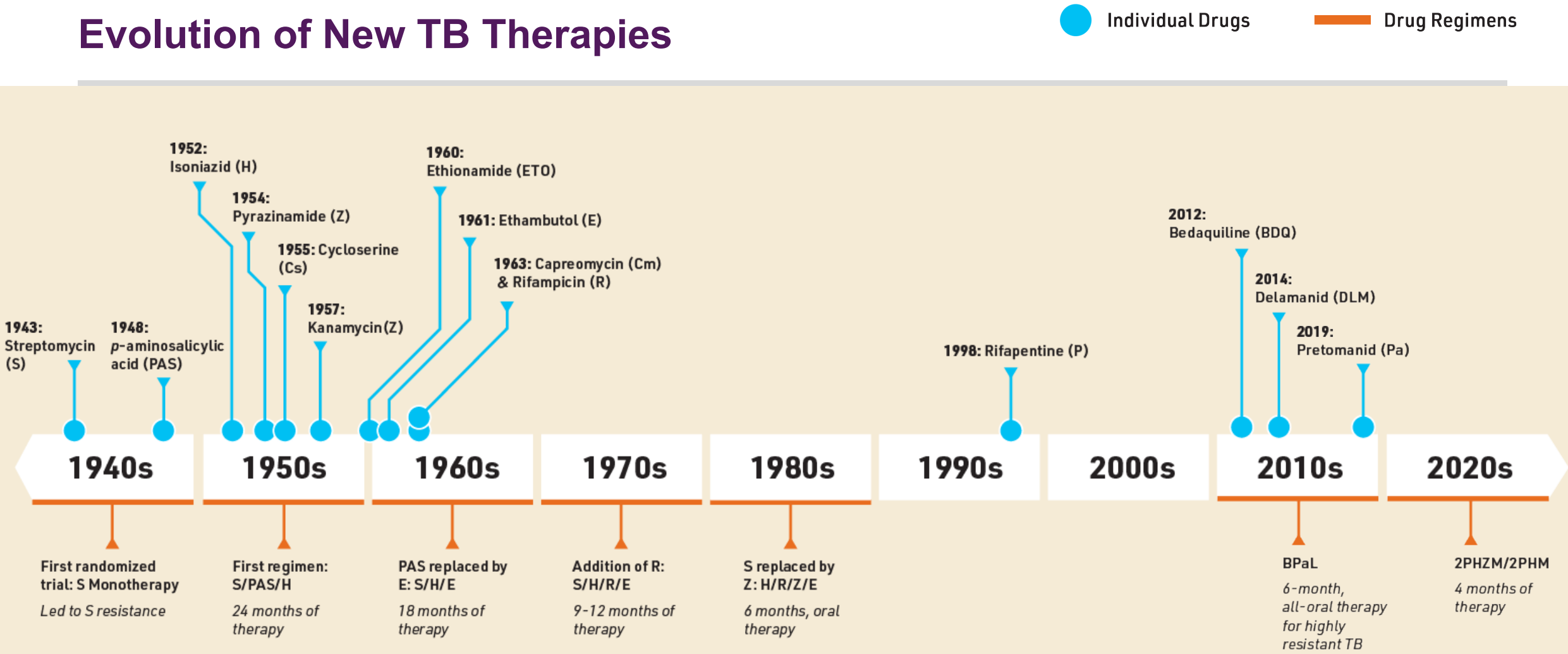
State of the TB Alliance

Mel Spigelman, MD, President & CEO

November 19, 2020

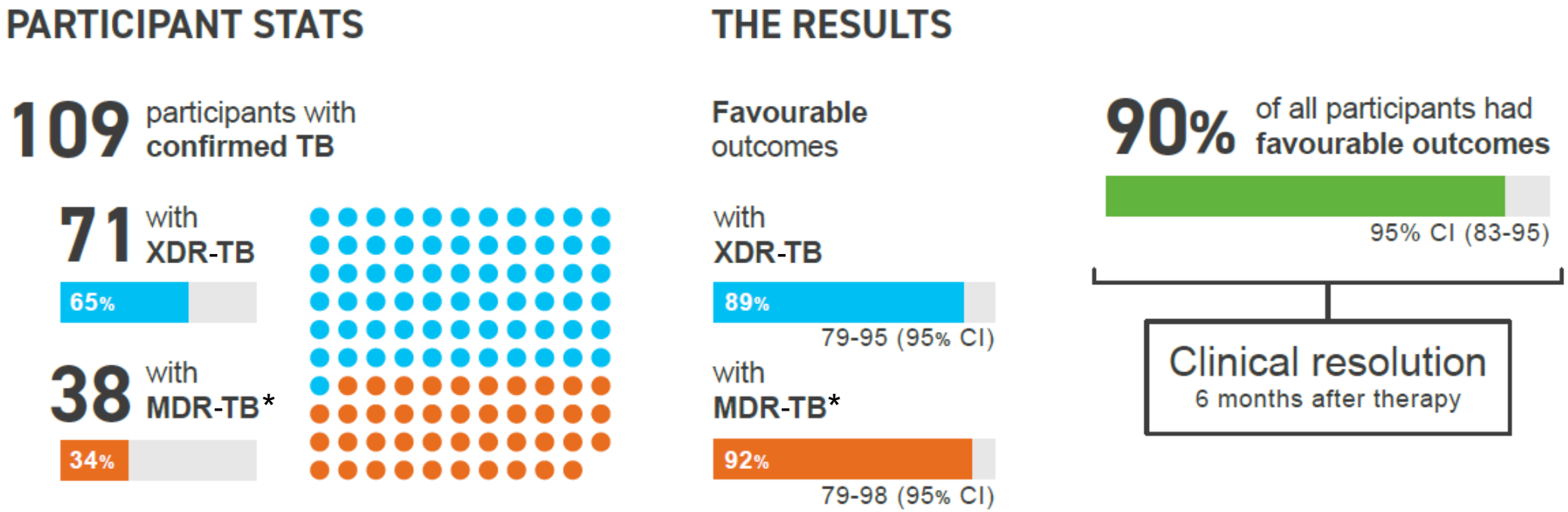
20 Years of Impact

Evolution of New TB Therapies



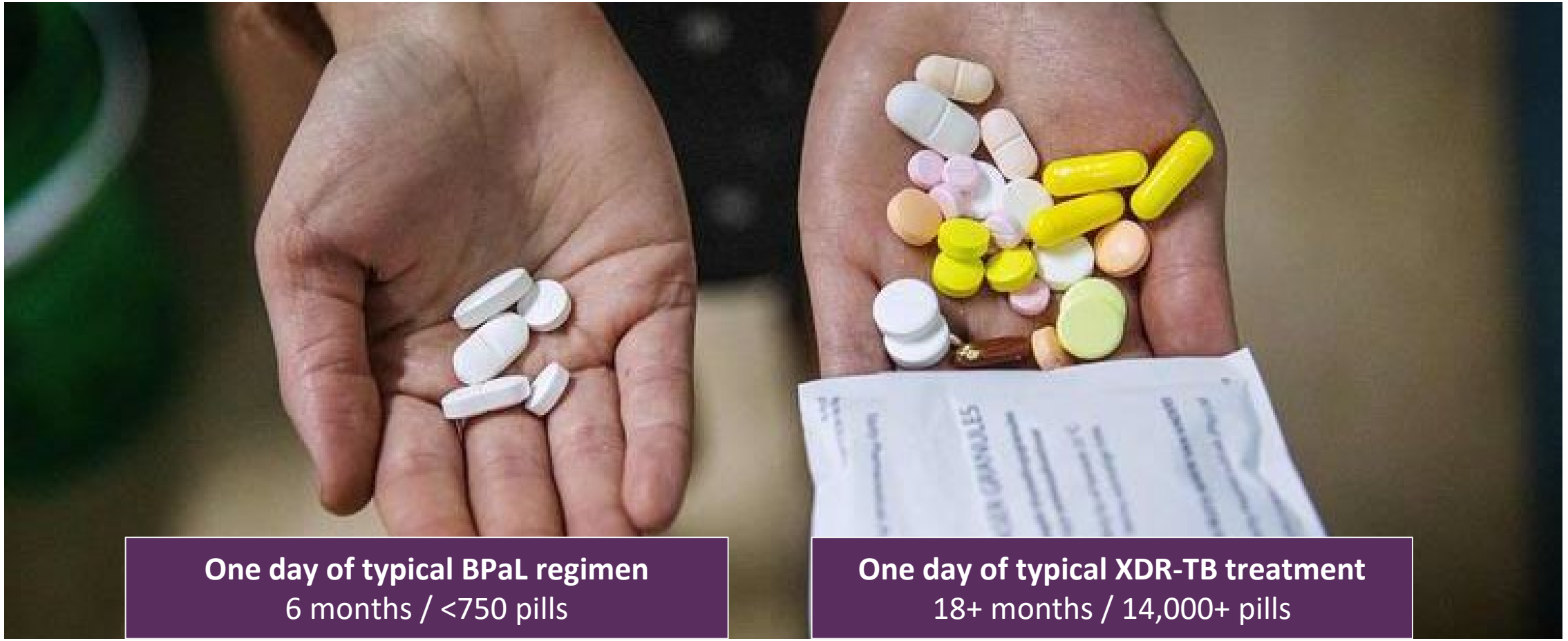
Nix-TB Results

New England Journal of Medicine, March 2020



*Treatment intolerant or non-responsive MDR-TB

Shorter, Simpler Treatment for Highly Drug-Resistant Forms of TB



Please see Full Prescribing Information at: 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

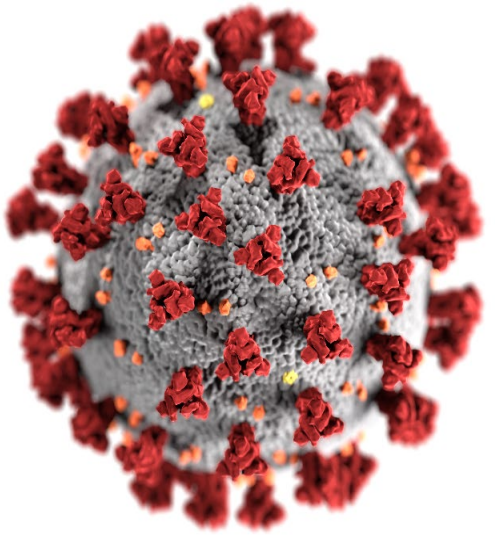
Impact of COVID-19

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

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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*

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Discovery

Lead Identification

Clp Lead ID Programs
- Harvard University
- UIC
- CETR

GHIT Hit ID Programs
- Astellas
- Fujifilm

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

Malate Synthetase Inhibitors
Texas A&M

Pantothenamide
- TropIQ
- WCM

PknB
UoA/Schrödinger

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-587 / Diarylquinoline
ERA4TB

Early Development

Phase 1

TBAJ-876 / Diarylquinoline

TBI-223 / Oxazolidinone
IMM

Phase 2A/2B

Sutezolid / Oxazolidinone
Gates MRI

TBA-7371 / DprE1 Inhibitor
FNDR
Gates MRI

Late Development

Phase 3

NixTB

Bedaquiline / Pretomanid / Linezolid
(BPaL)
Mylan

ZeNix

Bedaquiline / Pretomanid / Linezolid
(BPaL)
Mylan

SIMPLICITB

Bedaquiline / Pretomanid / Moxifloxacin / Pyrazinamide
(BPaMZ)
PanACEA
Mylan
Radboud

Marketed Products

Optimized Pediatric Formulations

Ethambutol
Macleods

Isoniazid
Macleods

Pyrazinamide
Macleods

Rifampicin/Isoniazid
Macleods

Rifampicin/ Isoniazid / Pyrazinamide
Macleods

Pediatric Formulation Development

Pretomanid
Mylan

Pretomanid for use in BPaL

Pretomanid for use in BPaL Regimen
Mylan
Macleods
Hongqi
KNCV

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
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 Tuberculosefonds
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
TropIQ
University College London (UCL)
University of Auckland (UoA)
University of Illinois at Chicago (UIC)
Weill Cornell Medical (WCM)
Yonsei University

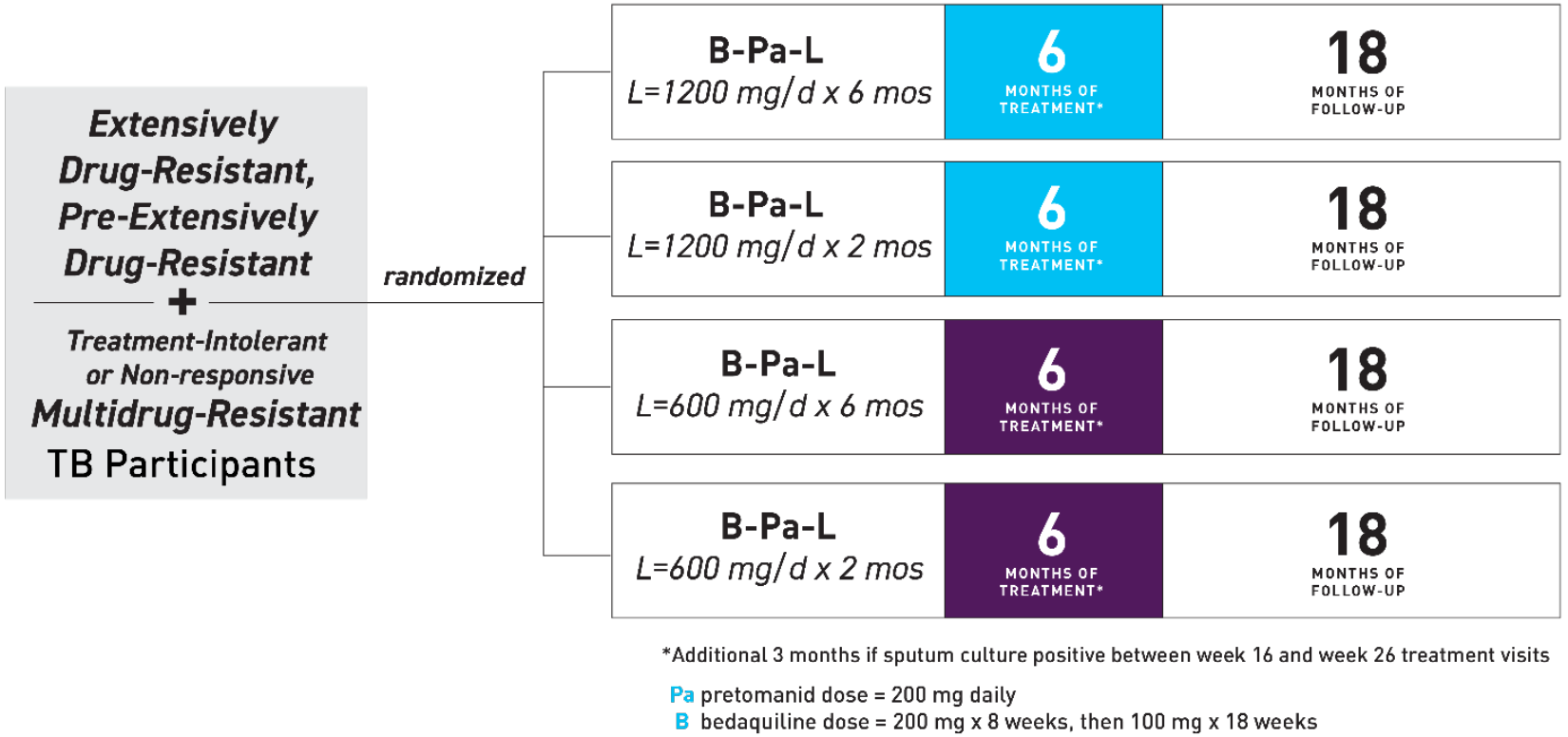
* Phase 3 clinical trials are added to the pipeline after enrollment of the first patient and are removed after completion of the Clinical Study Report. This document is updated on a quarterly basis.

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



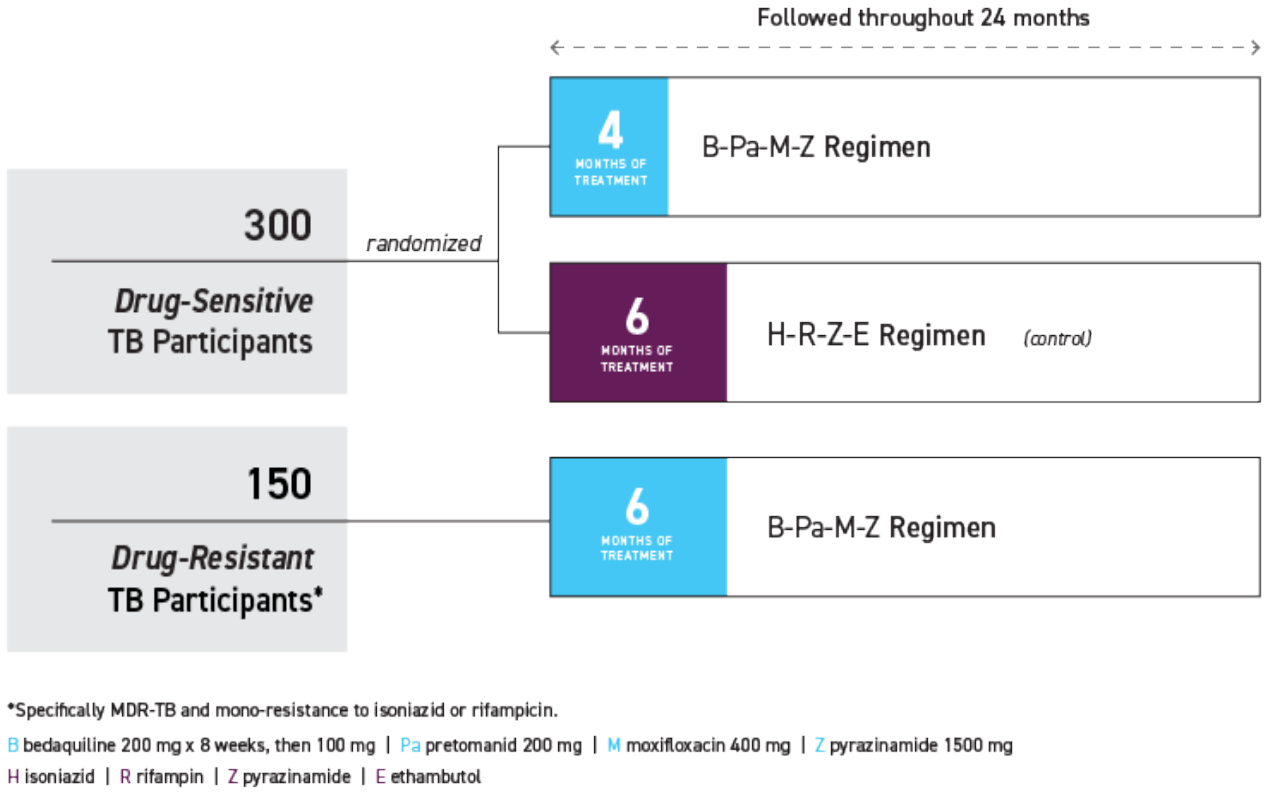
*Additional 3 months if sputum culture positive between week 16 and week 26 treatment visits

Pa pretomanid dose = 200 mg daily
B bedaquiline dose = 200 mg x 8 weeks, then 100 mg x 18 weeks

Enrollment completed Dec 2019. 181 patients enrolled from Georgia, South Africa, Russia and Moldova

BPaMZ Regimen

- 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
- Enrollment commenced on 30 July 2018
  - Enrollment completed on 2 March 2020
  - Patients enrolled in 27 sites in 8 countries on 4 continents
  - Last patient completed treatment 30 August 2020



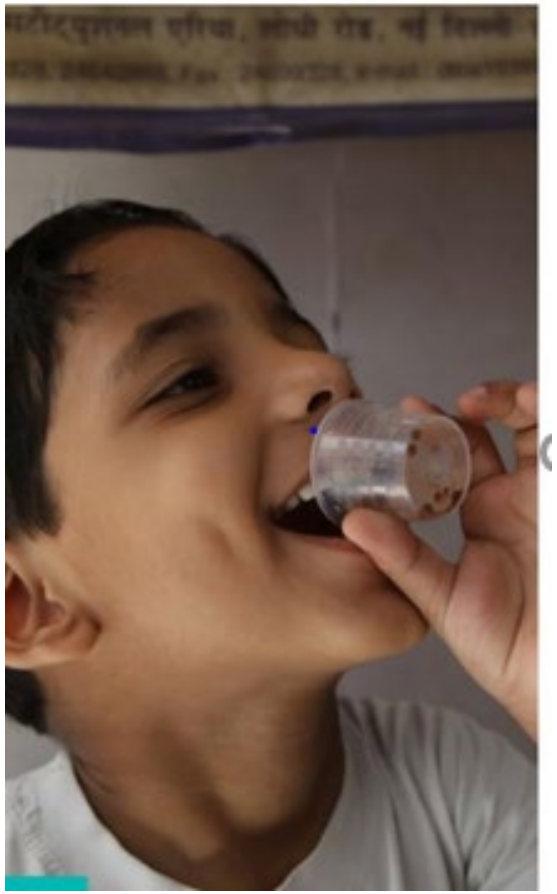
Additional Pretomanid Studies

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

What's Next: Combination Studies

Preliminary dose/exposure-response evaluation for TBAJ-587 and TBAJ-876 with PaO*

*O = TBI-223

	Lung CFUs		Proportion of Mice Relapsing After:		
Regimen	W-2	D0	W4 (+12)	W6 (+12)	W8 (+12)
Untreated	4.0	6.6			
B25 PaO				11/15	2/14
587_{25}PaO			7/13	3/15	0/15
587_{50}PaO			2/15	0/15	
$876_{6.25}$PaO				2/15	1/15
$876_{12.5}$PaO			3/15	0/15	

BPaL typically cures all mice in 3-4 months, and would perform similarly to BPaO here

Developing Treatments Against Non-tuberculous Mycobacteria

In Collaboration with the Cystic Fibrosis Foundation and JHU

- 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

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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?

The Next Innovations in TB Treatments: Immunotherapy

Harnessing the Immune System to Shorten Treatment Duration

Available TB Therapies

1st line regimen (HRZE)

BPaL

6+ months 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

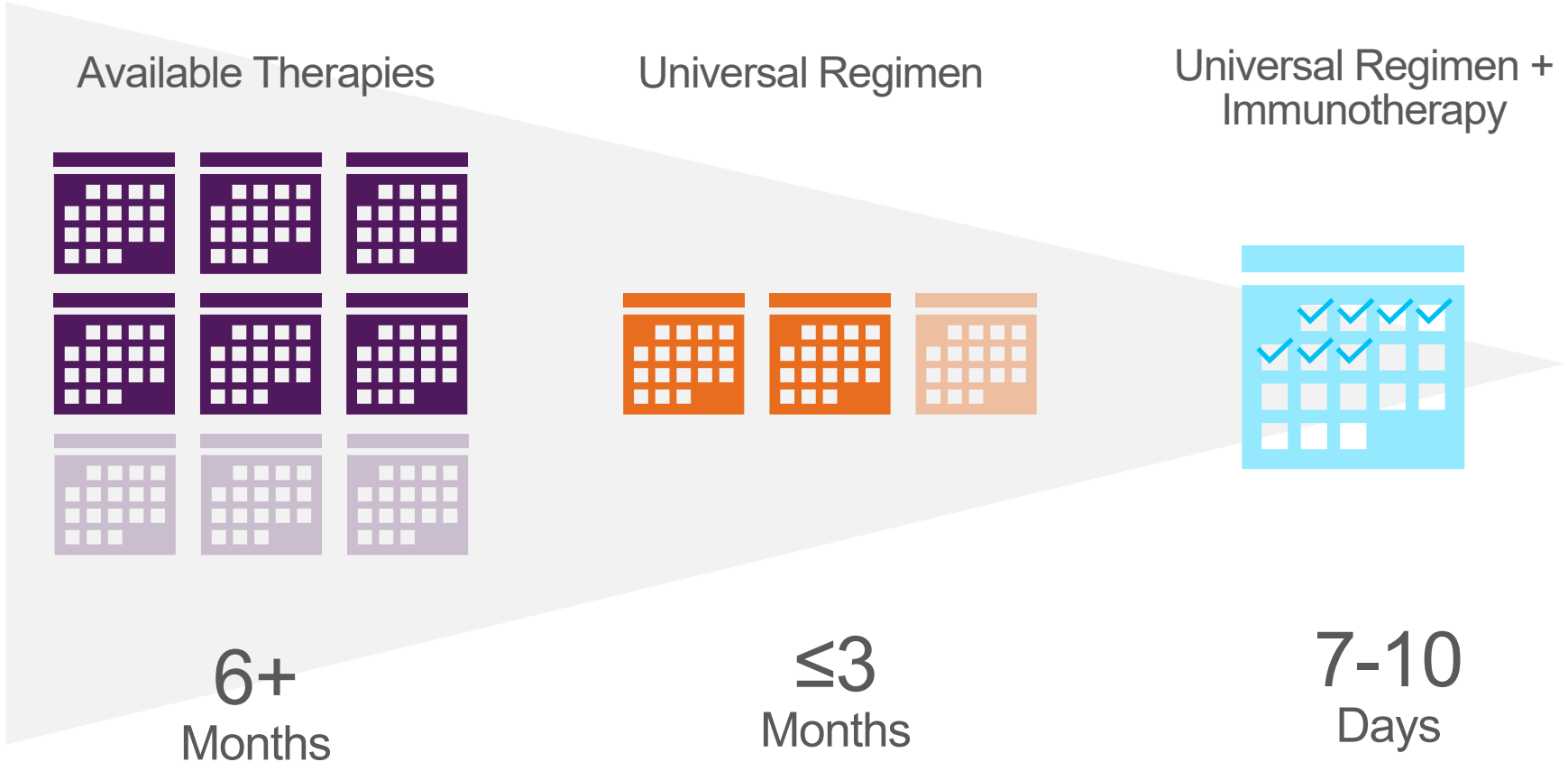
InveniAI
Innovate with Intelligence

AI-Assisted Screening Process

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

zebi AI

What Could the Patient Experience Look Like in the Future?



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Moderated Discussion

Please submit your questions through the Q&A function.

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Thank you for participating!

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