Tuberculosis Scientific Committee

Anneke C. Hesseling, Amita Gupta
Annual Meeting IMPAACT Network meeting
24 June 2021
Overall TB Scientific Committee Goals

“Evaluate novel approaches for TB prevention, diagnosis and treatment in HIV-infected and uninfected infants, children, adolescents, and pregnant and postpartum women that will lead to optimal dosing and regimens, licensing and improved care.”
Global burden of TB in children (< 15 years)

- 12% global burden
- Estimates of incident TB disease
  - 999,800\(^2\)
  - 847,000\(^1\)
  - 1,190,000\(^3\)
- >95% of disease burden is drug-susceptible TB
- Diagnosis remains challenging

Estimated mortality:
- <15 years: 240,000
- <5 years : 190,000
- Excess TB mortality in HIV: 17%
- TB: a top 10 cause of deaths in children < 5 years

## 2021 Global New TB Drug Pipeline

<table>
<thead>
<tr>
<th>Discovery</th>
<th>Preclinical Development</th>
<th>Clinical Development</th>
<th>Regulatory Market Approvals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lead Optimization</td>
<td>Early Stage Development</td>
<td>GMP / GLP Tox.</td>
<td>Phase 1</td>
</tr>
<tr>
<td>PanD inhibitors</td>
<td>JSF-3285*</td>
<td>GSK-839*</td>
<td>BVL-GSK098*</td>
</tr>
<tr>
<td>Indazole sulfonamides</td>
<td>MPL-446, 447*</td>
<td>OTB-658</td>
<td>GSK-286*</td>
</tr>
<tr>
<td>Diarylthiazoles</td>
<td>CPZEN-45*</td>
<td>Sanfetrinem</td>
<td>TBAJ-587</td>
</tr>
<tr>
<td>DprE1 Inhibitors</td>
<td>NTB-3119*</td>
<td></td>
<td>TBAJ-876</td>
</tr>
<tr>
<td>Direct InhA Inhibitors</td>
<td>TB-47*</td>
<td></td>
<td>TBI-223</td>
</tr>
<tr>
<td>Mtb energy metabolism</td>
<td>TZY-5-84</td>
<td></td>
<td>Macozinone* (PTBZ-169)</td>
</tr>
<tr>
<td>Macrolides</td>
<td>FNDR-20081*</td>
<td>Spectinamide – 1810*</td>
<td>TBI-166</td>
</tr>
<tr>
<td>Mycobacterial Gyrase Inhibitors</td>
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<td></td>
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<tr>
<td>Arvusulfonamides</td>
<td></td>
<td></td>
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<tr>
<td>Inhibitors of MmpL3, Translocase-1, Cip, PKS13, F-ATP synthase</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Oxazolidinones</td>
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</tbody>
</table>

*New chemical class. Known chemical classes for any indication are color coded: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diaryquinolone, 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](http://www.newtbdrugs.org/pipeline/clinical). Ongoing projects without a lead compound series identified: [http://www.newtbdrugs.org/pipeline/discovery](http://www.newtbdrugs.org/pipeline/discovery)

**Underline = updates since November 2020**

**Updated: March 2021**
DS TB prevention: birth – adolescence
HIV+/HIV-

Vaccines: pre-adolescents
HIV+/HIV-

P2024: 1 HP

P2035/HVTN 604: VPM

P2034: Pretomanid

P2020: BDQ, DLM, LFX

MDR-TB prevention: Household-based

A5300/P2003

P2005: DLM

P1108: BDQ

P2025: 1 HP vs. 3 HP in pregnancy: UNITAID?

MDR-TB treatment: birth-adolescence
HIV+/HIV-

2020 2021 2022 2023 2024 2025

IMPAACT TBSC ROADMAP 2021

P2026: DS and DR

Pregnancy

P2025: 1 HP vs. 3 HP in pregnancy: UNITAID?

Household-based
IMPAACT 2024: Phase I/II Dose Finding, Safety and Tolerability Study of Daily Rifapentine Combined with Isoniazid (1HP) for Tuberculosis Prevention in Infants, Children, and Adolescents

Protocol Chairs:
Nicole Salazar-Austin, MD, ScM
Christy Beneri, DO
**Design:** Phase I/II, multi-site, open-label study with two sequential cohorts

**Objectives:**

**Cohort 1:**
- To evaluate the relative bioavailability of RPT film-coated tablet when administered as a **crushed** or **whole** tablet

**Cohort 2:**
- To determine the weight-band-based dosing of daily RPT, as part of the 1HP regimen, that achieves targeted plasma PK exposures for infants, children, and adolescents with and without HIV
- To evaluate the safety and tolerability of the 1HP regimen over 28 days among infants, children, and adolescents with and without HIV

**Sites:** International and National,

**Timeline:** MPRG pre-review (ongoing) → DAIDS Signoff Sept/Oct 2021 → Start Q2 2022
A5300B/IMPAACT2003B

Protecting Households On Exposure to Newly Diagnosed Index Multidrug-Resistant Tuberculosis Patients

(A5300B/I2003B/PHOENIx)

Protocol Chairs
ACTG: GJ Churchyard, S Swindells
IMPAACT: AC Hesseling, A Gupta
• Multi-center, cluster-randomized, superiority trial
• Cluster = eligible high-risk contacts from same HH
  • Randomization balanced by site
• All eligible HHCs in same HH receive the same treatment
• 3452 high risk HHCs, assuming 2 HHCs per index case
Household Contacts: Enrolment

- **Accrual:** 370 Index Cases and 587 Household Contacts
- **Breakdown of HHC by age:**
  - <5 y: 44
  - >=5 to <18 y: 136
  - >=18 y: 407
High-Risk Household Contacts Enrolment
IMPAACT 2035 / HVTN 604: Phase I/II Study of the Safety and Immunogenicity of VPM1002 vaccination and BCG Revaccination against Tuberculosis in South African Pre-Adolescents Living with and without HIV

“Leveraging Early Adolescence to Prevent TB”

LEAP

Protocol Chairs:
Lisa Cranmer, MD, MPH, IMPAACT

Protocol Vice-Chairs: Cheryl Day, PhD, IMPAACT, Steven Innes, MD, PhD (HVTN)
LEAP Trial

Primary Objectives:

1. To evaluate the safety and tolerability of VPM1002 and BCG revaccination

2. To evaluate the cellular immunogenicity of VPM1002 and BCG revaccination

Randomized 1:1:1
Double-blinded

Each arm stratified by HIV and IGRA status:

- HIV−, IGRA− (n=40)
- HIV−, IGRA+ (n=40)
- HIV+, IGRA− (n=40)
- HIV+, IGRA+ (n=40)

160 per arm, 480 Total

Timeline: Protocol Development (current) → MPRG/SRC (Aug/Sept) → Start (June ‘22)

International sites
TUBERCULOSIS TREATMENT
# TB Treatment Research (DR-TB)

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Duration</th>
<th>For Treatment of</th>
<th>BDQ</th>
<th>DLM</th>
<th>PTD</th>
<th>LZD</th>
<th>CFZ</th>
<th>FQ</th>
<th>PZA</th>
<th>Other(s)</th>
<th>Estimated to Complete</th>
</tr>
</thead>
<tbody>
<tr>
<td>SimpliciTB</td>
<td>6 months</td>
<td>MDR-TB (DS-TB)</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td>M</td>
<td>X</td>
<td></td>
<td></td>
<td>February 2022 [fully enrolled]</td>
</tr>
<tr>
<td>Nix-TB</td>
<td>6-9 months</td>
<td>XDR-TB, pre-XDR-TB, Ti/NR MDR-TB</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>December 2021 [fully enrolled]</td>
</tr>
<tr>
<td>ZeNix</td>
<td>6-9 months</td>
<td>XDR-TB, pre-XDR-TB, Ti/NR MDR-TB</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Final results presented CROI 2021</td>
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<tr>
<td>TB-PRACTECAL</td>
<td>6 months</td>
<td>MDR-TB Pre-XDR-TB XDR-TB</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>(X)</td>
<td>(M)</td>
<td></td>
<td></td>
<td>February 2023</td>
</tr>
<tr>
<td>BEAT-Tuberculosis</td>
<td>6 months</td>
<td>RR-TB</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>(X)</td>
<td>(Lx)</td>
<td></td>
<td></td>
<td>March 2023</td>
</tr>
<tr>
<td>endTB</td>
<td>9 months</td>
<td>MDR-TB</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>M/Lx</td>
<td>X</td>
<td></td>
<td>January 2023</td>
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<tr>
<td>endTB-Q</td>
<td>6-9 months</td>
<td>FQ-R MDR-TB</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td></td>
<td></td>
<td>September 2023</td>
</tr>
<tr>
<td>NEXT</td>
<td>6-9 months</td>
<td>MDR-TB</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>Lx</td>
<td>X</td>
<td>Eto or Hdh or Tzd</td>
<td>December 2020 [fully enrolled]</td>
</tr>
<tr>
<td>STREAM stage II</td>
<td>6-9 months</td>
<td>MDR-TB</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td>Lx</td>
<td>X</td>
<td>Hdh; Pto or Kan; +/- Emb</td>
<td>July 2022 [fully enrolled]</td>
</tr>
<tr>
<td>MDR-END</td>
<td>9-12 months</td>
<td>MDR-TB</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>Lx</td>
<td>X</td>
<td></td>
<td>June 2021</td>
</tr>
</tbody>
</table>

Focused on shortening treatment to 6–12 months and improving outcomes and tolerability by optimizing linezolid dose and duration, and/or by evaluating different combinations of new and repurposed medicines (e.g., J, D, Pa, C, M, Lx, Lz).
IMPAACT P1108: Phase I/II: PK, safety and tolerability of BDQ in HIV+ and -children with RR-TB

Enrollment

Wk 1 sparse PK

Wk 2 intensive PK

Sparse PK

30-day screening window

2 wks daily BDQ

22 wks thrice-weekly BDQ

96 wks follow-up post-BDQ

Protocol chairs:
Anneke C. Hesseling, MD, PhD
Simon Schaaf, MD, PhD
- **Modified age de-escalation trial**: 0-17 years; n=54
- Younger cohorts open in parallel (0-2 and 3-5 years)
- Dose-finding: PK modeling, dose adjustment; adaptive design, semi-real time PK modeling in mini-cohorts, real time safety assessment
- Adult formulation: whole/crushed (access)
- Long-term safety; treatment outcome. Sites: South Africa, Haiti, India

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Age and</th>
<th>BDQ Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort 1</td>
<td>≥ 6 to &lt; 18 years</td>
<td>400 mg once per day for two weeks and then 200 mg three times per week on Monday, Wednesday, and Friday for 22 weeks</td>
</tr>
<tr>
<td></td>
<td>□ 30 kg</td>
<td>○ 15 to &lt;30 kg</td>
</tr>
<tr>
<td></td>
<td>≥ 6 to &lt; 18 years</td>
<td>200 mg once per day for two weeks and then 100 mg three times per week on Monday, Wednesday, and Friday for 22 weeks</td>
</tr>
<tr>
<td></td>
<td>□ 15 to &lt;30 kg</td>
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</tbody>
</table>

| Cohort 2 | ≥ 2 to < 6 years | Participants >7 to ≤ 30 kg: 200 mg once per day for two weeks and then 100 mg three times per week on Monday, Wednesday, and Friday for 22 weeks |
|          | □ 7 kg          | Participants 7 kg: 100 mg once per day for two weeks and then 60 mg three times per week on Monday, Wednesday, and Friday for 22 weeks |

| Cohort 3 | ≥ 0 to < 2 years | Participants >7 to ≤ 30 kg: 200 mg once per day for two weeks and then 100 mg three times per week on Monday, Wednesday, and Friday for 22 weeks |
|          | □ 3 kg          | Participants ≥ 3 to ≤ 7 kg: 100 mg once per day for two weeks and then 50 mg three times per week on Monday, Wednesday, and Friday for 22 weeks |
Paused to accrual: March 2020: COVID-19
- Re-opened: February 2020: Cohorts 2 and 3 in parallel
- First participant < 6 years enrolled in November 2020
- Accrual targets met: interim analysis: May 2021: cohort 2
- SMC review completed: May 2021: targets met for PK and safety
- Data shared with WHO upon request: May 2021
- Cohort 3 targets met for accrual and interim analysis: June 2021
- N=8 enrolled cohort 3, n=8 enrolled, cohort 2 (min = 6 “mini-cohort”)
- Collaboration with Janssen: data sharing
- Version 2.0 to be released to sites: July 2021: paediatric BDQ formulation, broader eligibility
IMPAACT 2005: A Phase I/II Open-Label, Single-Arm Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of Delamanid in Combination with Optimized Multidrug Background Regimen for MDR-TB in Children with and without HIV

Chairs: Ethel Weld, MD, Pharm D, Anthony Garcia-Prats, MD, PhD, Kelly Dooley, MD, Pharm D,
• **Primary objectives**
  • To evaluate the PK of DLM at doses determined most likely to achieve exposures similar to those achieved in adults with 100 mg twice-daily
  • To evaluate the safety of DLM when added to OBR over 24 weeks of children

• **Design**
  • Phase I/II open-label, single—arm, multisite study
  • Sites: India (BJMC), Botswana (Gaborone, Molepolole), South Africa (DTTC, Sizwe, PHRU Matlosana), Tanzania (KCMC)

• **Accrual status:** n=4, Paused to accrual pending approval of protocol amendment

• **Challenges**
  • After pause for protocol amendment to revise dosing based on emerging data, paused to due to COVID
  • Paused for protocol amendment to address unexpected new safety signal

• **Other**
  • Evaluating model-optimized dosing strategy across the weight spectrum, based on data from Otsuka's 232/233 trials
  • Will identify DLM dosing in smallest children, current critical knowledge gap
IMPAACT 2034: Phase I Study of the Pharmacokinetics, Safety, and Acceptability of Pretomanid in Children with Rifampicin-Resistant Tuberculosis

Protocol chairs:
Ethel Weld, MD, Pharm D,
Pauline Howell, MD,
Anthony Garcia-Prats, MD, PhD
• Objectives
  • Primary: Evaluate the pharmacokinetics of a single-dose of pretomanid in children with RR-TB
  • Secondary: Evaluate the safety, tolerability, acceptability and palatability of a single-dose of pretomanid in children with RR-TB
• Design: Phase I, multi-site, open-label, single-dose study
  • Minimum: n= 36 evaluable children in 4 weight groups
• Status
  • In protocol development, sites TBD
  • For MPRG review Q3 2021
• Other
  • Collaboration with TB Alliance
  • FDA IND, EMA
  • Followed by a multiple-dose study, pending safety data from adult male fertility study
IMPAACT 2020: All oral short course treatment for RR-TB in children and adolescents

**Screening**
- Up to 28 Days

**Enrollment**
- 8
- 26
- 48
- 72
- 96

**Primary outcomes assessed**
- 48

**Completion of follow-up**
- 96

**Arm 1: FQN-Susceptible, All-Oral, Short-Course Regimen**
- 26 weeks: LFX + BDQ + DLM
- Follow-up for 70 weeks (96 weeks total follow-up)
- 8 weeks: LZD

**Arm 2: FQN-Resistant, All-Oral, Short-Course Regimen**
- 26 weeks: CFZ + BDQ + DLM
- Follow-up for 70 weeks (96 weeks total follow-up)
- 8 weeks: LZD

*Participants assigned to Arm 1 in Step 1 will be reassigned to Arm 2 in Step 2 if FQN-resistance is identified post-treatment assignment.*
Advancing priority new studies: addressing gaps for treatment of DS TB

• Disease burden (>95%); 75% PTB
• Considerable existing investment in DR-TB – at cost of DS-TB
• Different disease spectrum vs. adults; paucibacillary, lymph nodes
• Priority: treatment shortening: building on results of SHINE and TBTC Study 31 (Q4 2020): 4 months non-inferior to 6 months
• Optimizing role of rifamycins
SHINE: PHASE III TRIAL - EFFICACY AND SAFETY OF 4 MONTHS STANDARD TB TREATMENT

Children aged <16 years with minimal TB (n=1200)

Randomisation (1:1)

6 month (n=600)
Intensive phase: 8 weeks
Continuation phase: 16 weeks

4 month (n=600)
Intensive phase: 8 weeks
Continuation phase: 8 weeks

72 weeks follow-up for primary outcome assessment

Nested PK substudies undertaken in selected centres

Primary Outcome Measure(s)
Main Trial:
Efficacy: Unfavourable outcome, defined by the composite endpoint of TB treatment failure, relapse (or re-infection) or death
Safety: Grade 3/4 adverse events
Pharmacokinetic Studies:
Pharmacokinetic (PK) parameters (AUC, Cmin, Cmax) of HRZ(E) and of antiretrovirals (ARVs), from full pharmacokinetic curves determined per age group and by HIV status
TBTC S31/A5349
Design Summary
Adults adolescents
>= 12 years

Consent/screen/enroll
Randomize 1:1:1

Control
2RHZE/4RH
26 weeks

RPT
2PHZE/2PH
17 weeks

RPT-MOX
2PHZM/2PHM
17 weeks

Evaluation for primary outcome at 12 months after randomization

Notes:
• All treatment: daily 7/7
• Flat P dose of 1200 mg
• M dose of 400 mg
• Food guidance: food with RPT-MOX, no food with RPT

No daily RFPT PK in children
Optimizing rifamycin exposure in children

**Cohort 1**
- 15-20 mg/kg (Days 1-14)
- 35 mg/kg (Day 15)

**Cohort 2**
- ~35 mg/kg (Days 1-14)
- ~50 mg/kg (Day 15)

**Cohort 3**
- ~60 mg/kg (Days 1-14)
- ~75 mg/kg (Day 15)

**n = 20 per cohort 0-12 years**

Monitoring for adverse events:
- 0, 1, 2, 4, 6, 8, 24 h
- 0, 2, 4, 8, 24 h

Single high-dose rifampicin

Svensson, under review
Advancing TB therapeutics: priority studies

1. Rifapentine PK and safety (high-dose; 1200 mg daily): bridging TBTC S31: high dose daily RFPT, with MFX

2. Rifampicin: PK and safety, tolerability of high dose rifampicin: long-term
Other priorities

1. **Vaccine trials:** following VPM: subunit vaccines? ID-93, inclusion of HIV+

2. **Diagnostic studies:** POC, in context of clinical algorithms non sputum based - diagnostic and treatment response
TBSC mentored investigator programme (and graduates)

- Ethel Weld
- Yael Hirch-Moverman
- Sylvia La Course
- Lisa Cranmer
- Jyothi Mathad
- Jeff Tornheim
- Mandar Paradkar
- Pauline Howell
- Christy Beneri
- Jennifer Hughes
- Nicole Salazar-Austin
- Louvina van der Laan
- Graeme Hoddinott
- Jennifer Hughes
- Megan Palmer
- Marije van Schalkwyk
Motivations for joining and benefits of program participation

- Improving knowledge of TB
- Gain understanding of TB trial design/conduct
- Becoming involved in protocol design and writing
- Contributing to TB publications
- Networking/building community
- Learning from senior investigators
- Gaining leadership opportunities at site
- Improving knowledge of TB
- Informing the TB IMPAACT agenda
- Gaining leadership opportunities on protocol teams
THANK YOU

Photo taken with permission, Sue Purchase
Desmond Tutu TB Centre, Cape Town, South Africa

Elin Svensson
Lindsay McKenna
Tony Garcia-Prats
Ethel Weld
Nicole Salazar-Austin
Christy Beneri