TB Alliance Clinical Programs Update

CPTR Annual Meeting, April, 2017
Daniel Everitt, MD, for the TB Alliance
## TB Alliance Portfolio Partners

<table>
<thead>
<tr>
<th>Chugai</th>
<th>Roche Pharmaceuticals</th>
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<tr>
<td>Daiichi Sankyo</td>
<td>Sanofi</td>
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<td>Daiichi Sankyo Novare</td>
<td>Schrödinger</td>
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<td>Eli Lilly</td>
<td>Shionogi</td>
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<td>GlaxoSmithKline (GSK)</td>
<td>Stellenbosch University</td>
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<td>HyphaGenesis</td>
<td>Takeda Pharmaceuticals</td>
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<td>Institute of Materia Medica (IMM)</td>
<td>TB Drug Accelerator (TDBA)</td>
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<td>IMFAC</td>
<td>University College London (UCL)</td>
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<td>Janssen [Johnson &amp; Johnson]</td>
<td>University of Auckland (AUCK)</td>
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<td>Johns Hopkins University (JHU)</td>
<td>University of Dundee (Dundee)</td>
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<td>Macleods Pharmaceuticals</td>
<td>University of Illinois at Chicago (UIC)</td>
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<td>Medical Research Council (MRC) at UCL</td>
<td>University of Pennsylvania School of Medicine (UPenn)</td>
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<td>Médecins Sans Frontières (MSF)</td>
<td>Yonsei University</td>
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<td>US National Institutes of Health (NIH) OP-BIO</td>
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### Lead Identification

- Whole Cell Hit-to-Lead Programs
  - Sanofi
  - GSK
- RNA Polymerase Inhibitors
- Energy Metabolism Inhibitors
  - AUCK/UIC/UPenn
- ClpC/PIP2 Schrödinger
- PEPCK Roche/TAMU
- POA Produgs Yonsei

### Lead Optimization

- Macrolides Sanofi
- MmpL3 Inhibitors
- InhA Inhibitors
- Cyclopeptides Sanofi
- Squaramides Sanofi
- Pyrimidines GSK
- Arylsulphonamides GSK

### Preclinical Development

- TBA-7371 / DprE1 Inhibitor Eli Lilly
- TBI-223 / Oxazolidinone IMM
- TBAJ-597 / Diarylquinoline Janssen/AUCK/UIC

### Early Development

- Optimization of Rifampicin in Children <5kg Stellenbosch University
- Linezolid Dose-Ranging Study

### Late Development

- NC-005 Bedaquiline / Pretomanid / Moxifloxacin / Pyrazinamide (BPaMZ)
- STAND Pretomanid / Moxifloxacin / Pyrazinamide (PaMZ)
- Nix·TB Bedaquiline / Pretomanid / Linezolid (BPaL)

### Phase 4 / Marketed Products

- Rifampicin / Isoniazid / Pyrazinamide Macleods
- Ethambutol Macleods
- Pyrazinamide Macleods

### Optimized Pediatric Formulations

- Rifampicin / Isoniazid Macleods
- Isoniazid Macleods
TBAJ-587: a second generation BDQ

- **Efficacy**
  - More potent than BDQ *in vitro* against clinical TB isolates and BDQ-resistant *M. tb*
  - Superior bactericidal activity to BDQ, at similar exposures, in mouse models of TB
  - Superior treatment-shortening to BDQ with pretomanid and linezolid in BALB/c mice
  - Lower predicted clinical efficacious exposures than BDQ

- **DMPK**
  - 10 X Higher predicted clearance in humans than BDQ, suitable for daily dosing
    - Less potential for tissue accumulation

- **Safety/Tox**
  - Lower potential for QTc prolongation than BDQ
  - Higher safe exposure than BDQ in rats
  - Larger safety margins than BDQ, based on rat and dog toxicity study data

- **CMC**
  - Improved aqueous solubility (less lipophilic) than BDQ

### Table: MIC range (µg/mL)

<table>
<thead>
<tr>
<th>Compound</th>
<th>TBAJ-587</th>
<th>BDQ</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>0.001-0.064</td>
<td>0.02 – 0.64</td>
</tr>
</tbody>
</table>

### Table: Number of mice (%) with CFU after M months of treatment (+3 months no Rx)

<table>
<thead>
<tr>
<th>Regimen</th>
<th>M1.5 (+3)</th>
<th>M2 (+3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDQ_{25Pa_{100L}}</td>
<td>15/15 (100%)</td>
<td>15/15 (100%)</td>
</tr>
<tr>
<td>S_{25PaL}</td>
<td>10/14 (71%)*</td>
<td>4/13 (31%)**</td>
</tr>
</tbody>
</table>

### Table: Pharmacological markers

<table>
<thead>
<tr>
<th>Compound</th>
<th>BDQ</th>
<th>TBAJ-587</th>
</tr>
</thead>
<tbody>
<tr>
<td>hERG IC_{50} (µM)</td>
<td>0.37*</td>
<td>28.6</td>
</tr>
<tr>
<td>Nav 1.5 IC_{50} (µM)</td>
<td>NA</td>
<td>&gt;30</td>
</tr>
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</table>
TBI-223: Safer Oxazolidinone

• Efficacy
  – Similar potency to LZD in vitro against clinical TB isolates
  – Similar activity to LZD, at similar exposures, in BALB/c and Kramnik mice
  – Similar treatment-shortening to LZD in combination with bedaquiline and pretomanid in BALB/c mice

• DMPK
  – Predicted clearance suitable for daily dosing

• Safety/Tox
  – Larger safety margins than LZD, comparing rat and dog safe/mouse efficacious or safe/predicted clinical efficacious exposure
  – No bone marrow toxicity observed at 4-10X (dog/rat) over mouse/predicted clinical efficacious exposures

• CMC
  – Similar to Linezolid
### In Vivo Safety and Toxicity - MPS vs. Bone Marrow Toxicity and Hematological

Reduced activity against MPS led to reduced bone marrow toxicity

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<thead>
<tr>
<th></th>
<th>Linezolid</th>
<th>TBI-223</th>
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<tbody>
<tr>
<td><strong>MPS (µM)</strong></td>
<td>8.5</td>
<td>&gt; 74</td>
</tr>
<tr>
<td>Mouse/human bone marrow progenitor cell suppression assay (µM)</td>
<td>24-60</td>
<td>&gt;150</td>
</tr>
<tr>
<td><strong>MED AUC (hr·µg/mL)</strong></td>
<td>131</td>
<td>179</td>
</tr>
<tr>
<td>Bone Marrow Histopathology, platelet↓, reticulocyte↓ (Rat 28 day study at mg/kg dose)</td>
<td>150 mg/kg (AUC 425 µg·hr/mL) NOAEL at 20 mg/kg (IB)</td>
<td>&gt; 300 mg/kg (AUC 1685 µg·hr/mL)</td>
</tr>
<tr>
<td>Bone Marrow Histopathology, platelet↓, reticulocyte↓ (Dog 14 day study at mg/kg dose)</td>
<td>NOAEL at 20 mg/kg (IB)</td>
<td>&gt; 150 mg/kg (AUC 789 µg·hr/mL)</td>
</tr>
<tr>
<td><strong>Comments</strong></td>
<td>Death (day 11,12) at 300 mg/kg Death (day 21) at 150 mg/kg</td>
<td></td>
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Nix-TB Trial in XDR-TB

Patients with XDR-TB or Who Have Failed MDR-TB Treatment

XDR-TB

- Pretomanid 200 mg
- Bedaquiline 200 mg tiw after 2 week load
- Linezolid 1200 mg qd**

Follow up for relapse-free cure over 24 months

6 months of treatment

Additional 3 months if sputum culture positive at 4 months

**Just amended from 600 mg bid strategy

Sites: Sizwe and Brooklyn Chest, South Africa
75 Participants Enrolled 15 March 2017

**Primary Endpoint**

- 31 patients have reached 6 months since completion of treatment
  - One relapse/reinfection
  - XDR TB on LPA- Genome sequencing will determine whether relapse or new infection
- Four patients have died (all in the first 8 weeks)
  - 3 had multi-organ TB on autopsy
  - 1 had a GI bleed due to erosive esophagitis
- All surviving patients were culture negative at 4 months
- 26 (74%) negative at 8 weeks as of December 2016.
Plans for Next BPaL Trial

- Evaluate Linezolid dose
- Evaluate Linezolid duration
Patients with XDR-TB, Pre-XDR-TB or who have failed or are intolerant to MDR-TB Treatment

Randomize

- **B-L-Pa**
  - L=1200 mg/d x 6 mos

- **B-L-Pa**
  - L=1200 mg/d x 2 mos

- **B-L-Pa**
  - L=600 mg/d x 6 mos

- **B-L-Pa**
  - L=600 mg/d x 2 mos

N=45 per group; total 180 (30/group XDR)

6 months of treatment

- 1° follow up for relapse-free cure 6 months after end of treatment; Full f/u 24 mos after end of treatment

Extension study for patients who relapse or who are sputum positive at end of 6 months of regimen dosing

Pa dose = 200 mg daily; B Dose = 200 mg daily X 8 wks, then 100 mg daily
NC-005: Testing Combinations of Bedaquiline, Pretomanid, Pyrazinamide and Moxifloxacin (BPaZM)

Key Results
NC-005 – 8 week SSCC Study of B-Pa-Z-M

B, Pa, Z and M containing regimens

Participants with newly diagnosed smear positive DS- and MDR-TB

- \[ B_{\text{registered dosing}} - Pa - Z \]
- \[ B_{(200\text{mg daily})} - Pa - Z \]
- \[ \text{Rifafour} \]
- \[ B_{(200\text{mg daily})} - Pa - Z - M \]

Randomize

60 per DS group
Up to 60 MDR

Survival Follow-up Visits at 6, 12, 18 and 24 Months

\[ Z = \text{pyrazinamide (1500mg daily)} \]
\[ M = \text{moxifloxacin 400mg daily} \]
\[ Pa = \text{PA-824 200mg daily} \]
\[ J_{\text{registered dosing}} = \text{bedaquiline 400mg for 14 days then 200mg three times a week} \]
\[ J_{(200\text{mg daily})} = \text{bedaquiline 200mg daily} \]
Percent of Patients Culture Negative at 2 Months
Kaplan-Meyer Analysis

<table>
<thead>
<tr>
<th></th>
<th>Liquid Culture</th>
<th>Solid Culture</th>
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<tbody>
<tr>
<td></td>
<td>Overnight</td>
<td>Spot</td>
</tr>
<tr>
<td>B/loading)PaZ</td>
<td>66%</td>
<td>84%*</td>
</tr>
<tr>
<td>B(200mg)PaZ</td>
<td>75%*</td>
<td>79%</td>
</tr>
<tr>
<td>BPaZM (MDR) Z-sensitive</td>
<td>96%*</td>
<td>89%*</td>
</tr>
<tr>
<td>BPaZM (MDR) Z-resistant</td>
<td>78%*</td>
<td>95%*</td>
</tr>
<tr>
<td>HRZE control</td>
<td>51%</td>
<td>63%</td>
</tr>
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*Statistically significant vs HRZE
Paradigm Shift: Treatment For All

People with XDR-TB/pre-XDR (<1% of TB Patients)

People with MDR-TB (~4% of TB Patients)

People with Drug Sensitive TB (~95% of TB Patients)

Treatment using...

BPaMZ

BPaL
Proposed Treatment Algorithm

GenXpert or Empiric Assessment

Rif sensitive
- BPaMZ (3-4 months)

Rif resistant
- Rapid quinolone test
  - Quinolone sensitive
    - BPaMZ (duration dependent on PZA sensitivity; if unknown 6 mo)
  - Quinolone resistant
    - BPaL (6 months)

- Common backbone of BPa for all
  - Common therapy for virtually all DS and MDR
- All treatments conducive to FDCs
- Marked simplification and rationalization of present state
Thank You to the Trial Participants, Investigators, TB Alliance Staff, Partners & Funders who have Made our Studies Possible