TB Alliance
Upcoming Clinical Trials

CPTR Meeting
September, 2014
Overarching Clinical Strategy

• Goal: entirely novel regimen
  – TBA 354 (Phase 1, First in Human)  New NCE
  – PaMZ (STAND; ph 3):  One NCE
    • Target treatment duration 4 months
  – JPaZ (NC-005; ph 2b):  Two NCEs
    • Target treatment duration 3 months
  – JPaOx (NiX-TB; ph 3):  Three NCEs
    • Target treatment duration 6 weeks (Z) to 3 months
  – Newer regimens:  Three NCEs, safer

• Path forward
  – Forward development (EBA, etc.)
  – Simultaneous reverse-direction development (phase 3 in XDR)
STAND – PaMZ Ph 3
PaMZ Value Proposition

• Possible 4 mo treatment for DS-TB
  – Requires DST in areas where MDR
    • As does HRZE
    • GenXpert can serve as proxy DST for PZA resistance

• Possible 4-6 mo treatment for MDR-TB
  – In patients whose *M. tb* is sensitive to PZA and moxifloxacin
  – Requires DST

• HIV/ART compatible

• Low cost of goods
STAND: Phase 3 Trial of the Pa-M-Z Regimen

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

- **Pa(100mg)-M-Z**
  - N=350

- **Pa(200mg)-M-Z**
  - N=350

- **Pa(200mg) - M-Z**
  - N = 350

- **Rifafour**
  - N=350

- **Pa(200mg) - M-Z**
  - N = up to 350

4 months of treatment

6 months of treatment

Randomize

12 & 24 mos f/u after randomization

Z = pyrazinamide at 1500mg  Pa = PA-824  M = moxifloxacin

TB ALLIANCE
NC-005 – JPaZ Ph 2b
NC005 Design – 8 week SSCC Study of J-Pa-Z

J, Pa, Z and M Containing Regimens
Participants with newly diagnosed smear positive DS and MDR TB

Z=pyrazinamide (1500mg daily),  M = moxifloxacin 400mg daily, Pa = PA-824 200mg daily , J_{\text{registered dosing}} = \text{bedaquiline 400mg for 14 days then 200mg three times a week}, \ J_{\text{(200mg daily)}} = \text{bedaquiline 200mg daily}
NiX-TB – JPaOx Ph 3
The Dismal Prognosis of Patients with XDR-TB

http://dx.doi.org/10.1016/S0140-6736(13)62675-6

107 Patients with XDR-TB in S. Africa dx’d 2002 – 2008
Treated empirically with median of 8 drugs

<table>
<thead>
<tr>
<th></th>
<th>Died</th>
<th>Failed Treatment</th>
<th>Defaulted</th>
<th>Cured or Continuing</th>
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</thead>
<tbody>
<tr>
<td>24 mo f/u</td>
<td>46%</td>
<td>23%</td>
<td>7%</td>
<td>16%</td>
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<tr>
<td>60 mo f/u</td>
<td>73%</td>
<td>10%</td>
<td>4%</td>
<td>11%</td>
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Patients with XDR TB or Who Have Failed MDR Treatment

NiX-TB “Rescue” Study

Pa-824 200 mg
Bedaquiline 200 mg tiw after 2 week load*
Linezolid 600 mg bid**

XDR TB

Follow up for relapse-free cure over 24 months

6 months of treatment
Additional 3 months if sputum positive at 4 months

Serial 16 early morning sputum samples in liquid culture

Sites: Durban, Sizwe, Brooklyn Chest, SA

*May adjust dosing based on NC-005
**May adjust based on linezolid EBA study
LIN-CL001 Dose-Ranging Linezolid Study

2 Week Safety, Tolerability and Bactericidal Activity Study
Participants with newly diagnosed smear positive DS TB

- Linezolid 300 mg QD
- Linezolid 300 mg BID
- Linezolid 600 mg QD
- Linezolid 600 mg BID
- Linezolid 1200 mg QD
- Rifafour

Randomize
15 per group

14 daily doses

Serial 16 hour pooled sputum samples for CFU Count
TBA-354 Update

Steve Murray
Town Hall, September 11, 2014
Next Generation Nitroimidazole Program

Goal: Deliver a next generation nitroimidazole that has potential to shorten TB treatment as part of a regimen superior to that of PA-824 and delamanid:

1. Improve anti-TB potency compared to PA-824
2. Improve bioavailability and gain longer half-life (for once daily PO dosing)
3. Improve safety window

Secondary goal: Deliver a back-up compound to PA-824 in the event that PA-824 fails to reach registration due to unacceptable risk/benefit ratio.
TBA-354 CL001

Single Ascending Dose Study

• First in human dosing of TBA-354

• 6 Cohorts of 8 normal, healthy volunteer subjects
  – 6 dosed, 2 placebo

• Planned Dosing
  – 10mg Starting Dose
  – Escalation dependent on PK and safety of prior cohort
  – Current plan: 10, 25, 75, 150, 300 and 450mg

• Cardiovascular and CNS safety monitoring
  – 24 hour monitoring and telemetry
  – Safety and ECG on-site review. Build in CNS effect observation parameters
  – 48 hour, 12-lead holter data collection for interval and rate/rhythm analysis
TB Alliance Supporters

Thanks to all those who support our mission for better, fast TB drugs