Application of Phase 2C – The CRUSH-TB Trial

(Combination Regimens for Shortening TB Treatment)

TBTC CRUSH TB Working Group
INTER-TB Meeting, London, UK
September 9, 2019
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Microbiology, pharmacology, pediatrics, community, clinicians, biomarkers, drugs, international/US, young/old
TBTC mission (from By Laws):

“... to conduct programmatically relevant clinical, laboratory, and epidemiologic research concerning the diagnosis, clinical management, and prevention of tuberculosis infection and disease.”
CRUSH-TB Working Group Mandate

- **Middle Development**
  - Identify **regimens** likely to successfully shorten TB treatment
  - Working in the phase 2b/2c space
    - At least early evidence for efficacy (EBA/Phase 2a)
    - Efficiently select candidates for further study (phase 3)

- **Programmatically Relevant**
  - Regimens have potential for administration under routine program conditions

- **Unmet medical need**
  - Choice/options, for patients and clinicians
  - Shortened duration, for patients and programs
Some innovations, broadly useful to TB field

Phase 2C

• Treatment consists of promising new regimen(s) (focus on shorter-course), typically given for intended duration, plus a standard control
  • Microbiologic endpoint (8-wk culture conversion/time to conversion) is primary, but follows all patients for failure/relapse to capture this crucial endpoint
  • The failure/relapse endpoint is critical, can provide a probabilistic assessment of how likely the novel regimens will be successful if studied in a phase III trial that enrolls similar participant population

Adaptive design

• Allows you to add regimens later in the trial, when more safety/efficacy information is available for promising drugs

Parallel animal model studies examining same regimens

Embedded biomarker (sputum LAM?)

**ADVANTAGES:** safety/microbiology for full duration (e.g. 4 mos); early information about relapse for decision-making; flexibility in light of emerging data in a rapidly evolving field; building translational and inter-phase modeling

Study Schema

Study treatment

DS-TB*

BZM + Rifabutin

BZM + DLM

R+H+Z+E

R+H

2 months

4 months

6 months

Follow for relapse (Ph 2C design)

Key:
B=bedaquiline
Z=pyrazinamide
M=moxifloxacin
E=ethambutol
DLM=delamanid

*B Patients with INH-mono resistant TB could be randomized in parallel, but only to arms without H.
The Drugs
Regimen components—rationale

**Drug #1: Bedaquiline (highest treatment shortening potential of new drugs to date)**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>M1</th>
<th>M2</th>
<th>M3</th>
<th>M4</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>15/15 (100%)</td>
<td>13/15 (87%)</td>
<td>6/13 (46%)</td>
<td></td>
</tr>
<tr>
<td>RH</td>
<td>14/15 (93%)</td>
<td>7/13 (54%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>10/15 (67%)</td>
<td>0/15 (0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>13/15 (87%)</td>
<td>2/14 (14%)</td>
<td>4/14 (28%)</td>
<td></td>
</tr>
</tbody>
</table>

**Lung CFU counts after 1 month of treatment**

**Relapse rates after treatment**

Bedaquiline (B) has sterilizing activity ≥ rifampin (R) in mice.
Fig. 10. Forest-plot of adjusted Hazard Ratios on a number of co-variates for Cox regressions and Logistic regression analyses

2. Logistic regression
   a. Excluding BCAP patients 0.39 (0.31, 0.51)
   b. No history of TB treatment 0.42 (0.28, 0.62)
   c. History of TB treatment 0.38 (0.28, 0.53)
   d. MDR-TB patients 0.51 (0.37, 0.68)
   e. MDR-TB (+FQ or +SL1) patients 0.49 (0.25, 0.97)
   f. XDR-TB patients 0.34 (0.19, 0.58)
   g. HIV negative patients 0.67 (0.43, 1.06)
   h. HIV positive patients not on ART 0.11 (0.02, 0.48)
   i. HIV positive patients on ART 0.35 (0.26, 0.47)
Regimen components – rationale

**Drug #2: Pyrazinamide**
(Do we need this drug? What does it add?)

**IV infxn of outbred Swiss mice**

- **Group**
  - Untreated
  - J
  - JZ
  - JR
  - JH
  - JM
  - RZ
  - RM
  - RH
  - HZ
  - JZM
  - JZR
  - JZH
  - JRM
  - JZR
  - JRM
  - RMZ
  - RHZ

<table>
<thead>
<tr>
<th>Group</th>
<th>Day 0</th>
<th>1 mo</th>
<th>2 mo</th>
<th>% of mice culture negative at 2 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated</td>
<td>7.2 ± 0.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>J</td>
<td>4.1 ± 1.8</td>
<td>2.3 ± 0.7</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>JZ</td>
<td>1.6 ± 1.6</td>
<td>0.0</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>JR</td>
<td>4.7 ± 1.1</td>
<td>1.9 ± 1.0</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>JH</td>
<td>3.8 ± 1.9</td>
<td>1.9 ± 1.0</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>JM</td>
<td>4.6 ± 0.5</td>
<td>2.1 ± 1.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RZ</td>
<td>5.4 ± 0.6</td>
<td>1.9 ± 0.9</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>RM</td>
<td>5.5 ± 0.9</td>
<td>3.1 ± 0.5</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>RH</td>
<td>5.1 ± 0.4</td>
<td>3.1 ± 1.1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>HZ</td>
<td>5.5 ± 0.6</td>
<td>3.9 ± 0.7</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>JZM</td>
<td>1.4 ± 1.2</td>
<td>0.03 ± 0.13</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>JZR</td>
<td>2.3 ± 1.5</td>
<td>0.07 ± 0.24</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>JZH</td>
<td>1.7 ± 1.4</td>
<td>0.18 ± 0.59</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>JRM</td>
<td>4.4 ± 1.1</td>
<td>1.2 ± 1.1</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>JRZ</td>
<td>4.4 ± 0.3</td>
<td>1.4 ± 0.8</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>RMZ</td>
<td>4.6 ± 0.8</td>
<td>1.4 ± 0.4</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>RHZ</td>
<td>3.9 ± 0.7</td>
<td>2.2 ± 0.6</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

**Aerosol infxn of inbred BALB/c mice**

- **Regimen**
  - D0
  - RHZ
  - JZPa
  - JZ
  - JZM
  - JZL
  - JZR
  - JZP
  - JZC

- **Lung log CFU count**
  - * p < 0.05 vs. JZ
  - ** p < 0.01 vs. JZ

**Slide from Eric**

- Ibrahim et al, AAC 2007
- Tasneen et al, AAC 2011

**B + Z = Potent sterilizing combo**
Clinical results: JZ in *extended* EBA

**Figure 2:** Bilinear regression showing the fall in mean \( \log_{10} \) CFU from baseline. CFU = colony forming unit.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Days 7-14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bedaquiline</td>
<td>14 (0.123 [0.097])</td>
</tr>
<tr>
<td>Bedaquiline-pyrazinamide</td>
<td><strong>15 (0.152 [0.120])</strong></td>
</tr>
<tr>
<td>Bedaquiline-PA-824</td>
<td>14 (0.114 [0.069])</td>
</tr>
<tr>
<td>PA-824-pyrazinamide</td>
<td>14 (0.124 [0.080])</td>
</tr>
<tr>
<td>PA-824-moxifloxacin-pyrazinamide</td>
<td>13 (0.175 [0.146])</td>
</tr>
<tr>
<td>Isoniazid-rifampicin-pyrazinamide-ethambutol</td>
<td><strong>10 (0.136 [0.102])</strong></td>
</tr>
</tbody>
</table>

Diacon et al 2012 Lancet
Clinical results: BZM(Pa) in NC-005 (TB Alliance)

**Design**

- Randomize
- MDR
- DS
- Dosing for 8 weeks
- \( B_{\text{registered dosing}} \) - Pa - Z
- \( B_{\text{200mg daily}} \) - Pa - Z
- Rifafour
- \( B_{\text{200mg daily}} \) - Z - M - Pa

**Results**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Population</th>
<th>Overnight</th>
<th>Overnight</th>
</tr>
</thead>
<tbody>
<tr>
<td>( B_{\text{loading}} )ZPa</td>
<td>DS</td>
<td>66%</td>
<td>89%</td>
</tr>
<tr>
<td>( B_{\text{200mg}} )ZPa</td>
<td>DS</td>
<td>75%*</td>
<td>84%</td>
</tr>
<tr>
<td>BZM-Pa Z-sensitive</td>
<td>MDR</td>
<td>96%*</td>
<td>100%*</td>
</tr>
<tr>
<td>BZM-Pa Z-resistant</td>
<td>MDR</td>
<td>78%*</td>
<td>95%*</td>
</tr>
<tr>
<td>HRZE control</td>
<td>DS</td>
<td>51%</td>
<td>86%</td>
</tr>
</tbody>
</table>

* statistically significant vs HRZE

**n.b.** M added to shore up the B-Z-Pa regimen in patients with MDR-TB
Regimen components—rationale

Drug #3: Moxifloxacin—bactericidal (we need this) AND gets into lesions AND has anaerobic/sterilizing activity

### BALB/c mice, Aerosol infection

<table>
<thead>
<tr>
<th>Treatment</th>
<th>1 month</th>
<th>2 months</th>
<th>4 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>2RHZ/3RH</td>
<td>100% (15/15)</td>
<td>100% (15/15)</td>
<td>100% (15/15)</td>
</tr>
<tr>
<td>PZM</td>
<td>100% (15/15)</td>
<td>100% (15/15)</td>
<td>100% (15/15)</td>
</tr>
<tr>
<td>BZM</td>
<td>100% (15/15)</td>
<td>33% (5/15)</td>
<td>0% (0/14)</td>
</tr>
</tbody>
</table>

1. BZM shortens treatment by ≥3 months compared to RHZ
2. BZM is superior to PZM

### Swiss mice, IV infection

<table>
<thead>
<tr>
<th>Treatment</th>
<th>3 month</th>
<th>4 months</th>
<th>5 months</th>
<th>6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>2RHZ/3RH</td>
<td>50% (10/20)</td>
<td>27% (5/18)</td>
<td>100% (20/20)</td>
<td>32% (5/19)</td>
</tr>
<tr>
<td>PZM</td>
<td>100% (20/20)</td>
<td>32% (5/19)</td>
<td>100% (20/20)</td>
<td>32% (5/19)</td>
</tr>
<tr>
<td>BZM</td>
<td>18% (3/16)</td>
<td>0% (0/20)</td>
<td>18% (3/16)</td>
<td>0% (0/20)</td>
</tr>
</tbody>
</table>

1. BZM is superior to RHZ
2. BZM is comparable to PMZ

BZM is treatment-shortening in mice

Tasneen et al, AAC (2011);55:5485
Andries et al, AAC (2010);54:4540
M contributes to efficacy of BMZPa regimen

<table>
<thead>
<tr>
<th>Drug regimen</th>
<th>M1</th>
<th>M1.5</th>
<th>M2</th>
<th>M3</th>
<th>M4</th>
<th>M5</th>
</tr>
</thead>
<tbody>
<tr>
<td>RHZ</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BPaZ</td>
<td>25/29 (86)</td>
<td>2/30 (7)</td>
<td>0/15 (0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BPaMZ</td>
<td>15/15 (100)</td>
<td>7/32 (22)</td>
<td>0/30 (0)</td>
<td>0/15 (0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Proportion (%) of mice relapsing after treatment for:

Composite results of 2 experiments

Li et al, AAC (2017);61
Lesion PK and activity—new findings in rabbits and humans

Vehicle (control)
Moxifloxacin
Gatifloxacin
Levofloxacin

Proportion patients meeting target, by lesion type

Sarathy et al AAC 2019
Strydom 2019 PLoS Medicine
Back to NC-005...

**Design**

- Randomize
- MDR
- Dosing for 8 weeks

**Regimen**

- B\(_{\text{registered dosing}}\) - Pa - Z
- B\(_{\text{200mg daily}}\) - Pa - Z
- Rifafour
- B\(_{\text{200mg daily}}\) - Z - M - Pa

*n.b. M added to shore up the B-Z-Pa regimen in patients with MDR-TB*

**Results**

% culture negative at 2 months

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Population</th>
<th>Liquid cx</th>
<th>Solid cx</th>
</tr>
</thead>
<tbody>
<tr>
<td>B(_{\text{(loading)}})ZPa</td>
<td>DS</td>
<td>66%</td>
<td>89%</td>
</tr>
<tr>
<td>B(_{\text{200mg}}})ZPa</td>
<td>DS</td>
<td>75%*</td>
<td>84%</td>
</tr>
<tr>
<td>BZPa+M</td>
<td>MDR Z-sensitive</td>
<td>96%*</td>
<td>100%*</td>
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</tr>
<tr>
<td>HRZE control</td>
<td>DS</td>
<td>51%</td>
<td>86%</td>
</tr>
</tbody>
</table>

* statistically significant vs HRZE
QTc considerations

- Change in QTcF interval from baseline in NC-005 trial

<table>
<thead>
<tr>
<th></th>
<th>Mean Change (msec)</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>B(loading)PaZ</td>
<td>21.9</td>
<td>18.2 – 25.7</td>
</tr>
<tr>
<td>B(200mg)PaZ</td>
<td>20.4</td>
<td>15.1 - 25.7</td>
</tr>
<tr>
<td>BPaZM (MDR)</td>
<td>21.9</td>
<td>18.7 – 25.0</td>
</tr>
<tr>
<td>HRZE control</td>
<td>10.2</td>
<td>7.0 – 13.4</td>
</tr>
</tbody>
</table>

- In US, when BDQ is used for 24 weeks—
  - ECG at baseline, 2, 12, and 24 weeks
  - Note that ECG changes with BDQ peak at 8 weeks and then stabilize
  - Note that M’s QT effects go away immediately when drug stopped

- French cohort- Among patients getting BDQ for prolonged course, QT prolongation >500ms associated with high-dose MXF (800mg) or methadone, not moxifloxacin 400mg  
  Guglielmetti Eur Resp J 2017

- ACTG A5343, DLM Phase 3– Adding DLM to any regimen increases QT by just 8 ms
Regimen components—rationale

Drug #4: Do we need one? What are best options?

**Proportion relapsing after treatment for:**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>1 month</th>
<th>1.5 months</th>
<th>2 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>JMZ</td>
<td>13/13</td>
<td>2/15 (13%)</td>
<td>0/15</td>
</tr>
<tr>
<td>JMZPa</td>
<td>n.d.</td>
<td>3/15 (20%)</td>
<td>0/16</td>
</tr>
</tbody>
</table>

**Proportion relapsing after treatment for:**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>2.5 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>JMZ</td>
<td>4/16 (25%)</td>
</tr>
<tr>
<td>JMZPa</td>
<td>1/18 (6%)</td>
</tr>
</tbody>
</table>

Pa contributed bactericidal activity to the JMZPa regimen but no significant contribution to sterilizing activity was detected.

Yes, probably--4th drug may reduce relapse in hard-to-treat patients.
Regimen components—rationale

Drug #4: What are best options? Argument for delamanid

Nitroimidazoles kill those bacilli that are hard-to-kill in necrotic lesions

Gengenbacher (Dartois, Barry, Cole, Kaufmann)
2017 Scientific Reports
Regimen components—rationale

**Drug #4: What are best options? Argument for rifamycin**

### Relapse data, chronic mouse model

<table>
<thead>
<tr>
<th></th>
<th>PZM</th>
<th>BZ</th>
<th>BZP</th>
</tr>
</thead>
<tbody>
<tr>
<td>W6 (+12)</td>
<td>47%</td>
<td>93%</td>
<td>33%</td>
</tr>
<tr>
<td>(7/15)</td>
<td>(14/15)</td>
<td>(5/15)</td>
<td></td>
</tr>
<tr>
<td>W8 (+12)</td>
<td>13%</td>
<td>67%</td>
<td>0%</td>
</tr>
<tr>
<td>(2/15)</td>
<td>(10/15)</td>
<td>(0/15)</td>
<td></td>
</tr>
<tr>
<td>W10 (+12)</td>
<td></td>
<td>53%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(13%)</td>
<td>(8/15)</td>
<td></td>
</tr>
</tbody>
</table>

Day -17: log CFU 4.41; Day 0: log CFU 8.32

Relapse data, chronic mouse model: Williams et al, AAC (2012); 56:3114

Adding a rifamycin to BZ gives impressive increase in activity

### Swiss mice, IV infection

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>2 months</th>
<th>3 months</th>
<th>4 months</th>
<th>6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>2RHZ/4RH</td>
<td>17%</td>
<td>(5/30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2RMZ/2RM</td>
<td>84%</td>
<td>(16/19)</td>
<td>42%</td>
<td>(8/19)</td>
</tr>
<tr>
<td>2BZR/2BR</td>
<td>56%</td>
<td>(10/18)</td>
<td>28%</td>
<td>(5/18)</td>
</tr>
<tr>
<td>2BZH/2BH</td>
<td>68%</td>
<td>(13/19)</td>
<td>72%</td>
<td>(13/18)</td>
</tr>
</tbody>
</table>

Combos of BZ plus R or H are treatment-shortening, R > H

Swiss mice, IV infection: Ibrahim et al, AJRCCM (2009); 180:553

BZR > RMZ > RHZ
BZH ≥ RMZ > RHZ

\(^1 p \leq 0.005\) vs. BZ

Adding a rifamycin to BZ gives impressive increase in activity
Regimen components—rationale

Drug #4: What are best options? Which rifamycin?

Rifapentine and rifampin reduce bedaquiline concentrations (would need 1000 QD for 2 weeks, then 1000 TIW)

Rifabutin does not meaningfully reduce BDQ exposures

Healan 2018 AAC

Svensson 2015 JAC
Linkages to other treatment-shortening studies in DS-TB

• PANACEA 2 STAGE STUDY (Phase 2B SUDOCU, then 4-mo 2C):
  • High-dose rifampin with or without high-dose PZA
  • **Bedaquiline/Delamanid/Moxifloxacin + Sutezolid (U)** (dose finding for U, then including that dose in 2C)

• TBA SimpliciTB (Phase 2/3): **Bedaquiline/moxi/pretomanid/PZA**
  • 4 BPaMZ

• BMRC TRUNCATE-TB (Phase 3): Multiple drugs
  • 2 HR$^{35}$ZELinezolid (extend to 3 mos for persistent + sx/smear)
  • 2 HR$^{35}$ZEClofaz
  • 2 HP$^{1200}$ZLinezolidLevoflox
  • 2 HBZELevofolex
Adaptive design – to consider:
DprE1 inhibitors- completely new drug class

| **DprE1 inhibitor** - Inhibits decaprenyl-phosphoribose epimerase (DprE1) involved in cell wall arabinan biosynthesis |
|---------------------------------|-------------------------------------------------|----------------------------------------------------------------------------------------------------------|
| **OPC-167832** | Otsuka Pharmaceutical Development & Commercialization, Inc. | Activity against replicating and dormant intracellular bacilli; Active in acute and chronic murine models; No antagonism with other TB drugs; Additive effect with Dlm exceeding RHZE; NCT03678688 (1-2, enrolling) |
| **BTZ043** | University of Munich, Hans-Knöll Institute, Jena, German Center for Infection Research (DZIF) | Superior to INH at 2 months in mice (6 month pending) No antagonism with existing drugs, apparent synergy in vivo with Bdq-Rif Low level CYP450 interaction; NCT03590600 (1, enrolling) |
| **Macozinone, PBTZ169** | IM4TB-Innovative Medicines for Tuberculosis, Bill & Melinda Gates Foundation, Nearmedic Plus LLC | Highly active against replicating bacteria; No antagonism with RHZE, synergy in vitro with Bdq, Cfz, Dlm, sutezolid Prior formulation with good tolerability, bactericidal activity against DS TB at 640mg; NCT03776500 (1, pending) |
| **TBA-7371** | TB Alliance | Efficacy in vitro and in mice Phase 1 trial complete on food effect, optimal dose, DDI, PK, PD as single dose or multiple doses; NCT03199339 (1, complete; 2, pending) |
The Design
Study design: CRUSH-TB

Rationale: Optimization of new and existing drugs to make a complete regimen, considering properties needed to shorten treatment duration plus safety, for a public health purpose.

Design: Phase IIIC, randomized, open-label, ≥3-arm trial assessing the safety and efficacy of 4-month BZM-based regimens compared to 6-month standard of care among adult patients with drug-sensitive pulmonary TB.

<table>
<thead>
<tr>
<th>Arm</th>
<th>Weeks 0-8</th>
<th>Weeks 9-17</th>
<th>Weeks 18-26</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BMZ+Rb</td>
<td>BMRb</td>
<td>--</td>
</tr>
<tr>
<td>2</td>
<td>BMZ+D</td>
<td>BMD</td>
<td>--</td>
</tr>
<tr>
<td>3 (standard Rx)</td>
<td>HRZE</td>
<td>HR</td>
<td>HR</td>
</tr>
</tbody>
</table>

Rb=rifabutin; M=moxifloxacin; B=bedaquiline; D=delamanid; H=isoniazid; E=ethambutol; Z=pyrazinamide; R=rifampicin

Duration: Until last participant reaches 12 months of follow-up

Sample size: 90/arm
Inclusion/Exclusion Criteria

**Inclusion**
- Pulmonary TB without concurrent CNS or bone involvement
- Age 12 and older
- AFB smear-positive (at least 1+) or GeneXpert positive (medium/high)
- If HIV+, CD4 at least 100 cells/mm³

**Exclusion**
- >5 days of TB treatment in past 6 months
- Resistance to INH, RIF, or fluoroquinolones
- Pregnancy
- QT prolongation
- Unacceptable baseline labs
- History of aortic dissection/aneurysm
Endpoints

• **Primary**
  • Time to sustained sputum culture conversion in liquid media

• **Secondary**
  • Safety (proportion of grade 3-5 AEs by arm)
  • Tolerability (all-cause discontinuation by arm)
  • Alternative microbiologic endpoints (e.g. solid media, 8-week culture conversion)
  • Pharmacodynamic analyses
  • Long-term efficacy outcome (phase 2C outcome)
Procedural Highlights

- Randomization stratified by site (African/not African) and cavity (Y/N)
- 7/7 dosing with 5/7 DOT and SAT doses on weekends
- Intensive PK sampling in convenience sample, sparse PK sampling in all
- Serial microbiologic and safety monitoring, including ECG
- Follow-up until last participant is 12 months post treatment completion
  - Provides extra information on delayed relapse while keeping the trial short
Key Issues Debated and +/- Decided

- Dosing schedule for bedaquiline (200 QD x 8 weeks, then 100 QD)
- Dosing schedule for delamanid (200mg QD) (with food)
- Flat vs. weight-based dosing for pyrazinamide (1500 ≤50kg, 2000>50kg)
- Duration of pyrazinamide (2 months)
- Biomarkers: sputum LAM
- Media type/standardization (solid YES and not standardized; liquid YES)

To sort still:
- resistance testing for bedaquiline and delamanid
- Logistics of ECG evaluations
- CDA → CTA
Preclinical link

(Stay tuned– Nuermberger lab to test different combinations in different mouse models....)
CRUSH Summary

• Phase 2C trial, 3+ arms, 90/arm
• Estimated 18 months to enroll, additional 12 months of followup after last participant=total trial duration ~30 months
• Will complement efforts by other groups, elucidating some key questions (e.g. additional activity of rifamycin plus bedaquiline, activity of delamanid vs. pretomanid in regimen)
• BZM backbone
  • BZ is most potent two-drug regimen in mice; B with sterilizing activity better than rifamycins; BZM backbone performed extremely well in human trials (NC-005); drug with good bactericidal activity in the regimen (M); Oral, once daily, few side effects, all drugs taken by hundreds of patients with good safety profile; Compatible with first-line ART regimen (dolutegravir) without dose adjustment
• With 4th drug to shore things up, give best shot at exceptional activity (rifabutin, delamanid, maybe a DprE1 inhibitor added via adaptive design)
• PhC format will provide concrete guidance on likelihood of success in phase 3, facilitating planning of “next trial”; concurrent preclinical work for translational links
Thanks again-- CRUSH TB Protocol Team Members

- Jason Stout, MD, MHS
- Kelly Dooley, MD, PhD
- Charles Bark, MD
- Debra Benator, MD
- Joseph Burzynski, MD
- Eduardo Gotuzzo, MD
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- Marie Theunissen
- Wendy Carr, PhD
- Jessica Ricaldi, MD, PhD
- Nigel Scott, MS
- Katya Kurbatova, MD, PhD, MPH

Microbiology, pharmacology, pediatrics, community, clinicians, biomarkers, drugs, international/US, young/old
Extra slides
Most promising (currently-available) backbone for treatment shortening: rationale for BZM

• BZ is most potent two-drug regimen in mouse model; B with sterilizing activity better than rifamycins
• BZM backbone performed extremely well in human trials (NC-005)
• We need to have a drug with good bactericidal activity in the regimen (M)
• Oral, once daily, few side effects, taken by hundreds of patients with good safety profile, well-tolerated
• Compatible with first-line ART regimen (dolutegravir) used in US and increasingly globally, without dose adjustment
4th drug (to add activity, prevent resistance)- on-the-shelf possibilities to demonstrate JZM shortening safely

- **BZM+rifamycin**
  - Highest potency in animal models, this regimen has 4 drugs with sterilizing activity
  - Proof of concept with rifabutin (and if the rifamycin is *needed* to shorten therapy, then can consider Rifapentine (P) with B dose adjustment because of DDI)
  - Effective for INH-mono-resistant TB (present in ≥10% of isolates globally)

- **BZM+delamanid**
  - JZM alone may or may not be adequate to shorten treatment
  - Nitroimidazoles add some activity to BZM regimen, very active in necrotic lesions
  - DLM has nice safety profile, is registered in several settings
  - Rifamycin- and isoniazid-sparing
  - Regimen could be used in INH-resistant TB (and MDR TB where PZA is active)
  - Comparison can be made to similar regimens in SimpliciTB (BZMPa) and PanACEA (BDSM) trials
    --Is Z needed? Is Pa = D, or is Pa better?

S=sutezolid, M=moxifloxacin, B=bedaquiline, Pa=pretomanid, D=delamanid