New treatments and approaches to Tuberculosis

Tuberculosis Symposium – Eastern Europe and Central Asia
RA Ministry of Health and Médecins Sans Frontières

TB trials for new treatment combinations: end TB and PRACTECAL

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Head of the Manson Unit / TB adviser
MSF UK
Overview

• Why do we need Clinical Trials?
• What clinical Trials are planned
• MSF Trial Initiative
  – end TB
  – PRACTECAL
We have new drugs so why do we need Clinical Trials?
New drugs ≠ New regimens

- Still treating with multiple drugs
- Usually still with injectables or intravenous
- Long duration
- Not sure optimal combination
New MDR-TB treatment regimes

- At least one new class
- At least 3 and max 5 effective drugs
- Effective against MDR and XDR strains
- 6 - 9 months
- Oral
- Simple dosing schedule
- Good side effect profile, limited monitoring
- Minimal interaction with antiretrovirals
Good Clinical Practice (GCP) Guidelines

- International ethical and scientific quality standard for designing, conducting, recording and reporting clinical trials that involve the participation of human subjects.
- Lays out the responsibilities of the ethics committees, sponsors and investigators.
Good Clinical Practice (GCP) Guidelines

- Ethical principles: Declaration of Helsinki
- Favourable benefit(s) vs. risk(s)
- Subject’s rights
- Adequate supporting data
- Scientifically sound protocol
- Independent ethics committee oversight
- Medical care by qualified investigator
- Qualified personnel
- Informed consent
- Record-keeping
- Subject confidentiality
- GMP manufacturing of the investigational product
- Quality assurance & monitoring
## Clinical Trial Landscape

<table>
<thead>
<tr>
<th>Trial Name (Funding Source)</th>
<th>Duration Experimental Regimen</th>
<th>Experimental Arms</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>C213 Delamanid Phase 3 Trial (Otsuka)</td>
<td>24 mths</td>
<td>6 mths Dlm + OBR</td>
<td>Completed follow up for primary end point</td>
</tr>
<tr>
<td>Delamanid safety study children</td>
<td>24 mths</td>
<td>6 mths Dlm + OBR (6-17 yr old)</td>
<td>Enrolling</td>
</tr>
<tr>
<td>STREAM I Trial (MRC)</td>
<td>9 mth</td>
<td>Comparison std WHO regimen vs 9 mth modified Bangladesh regimen</td>
<td>85% enrolled</td>
</tr>
<tr>
<td>STREAM II Trial</td>
<td>6-9 mths</td>
<td>Comparison of short bedaquiline-containing regimens against the WHO and Bangladesh regimen</td>
<td>Expected to being enrolling 1Q15</td>
</tr>
</tbody>
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<tr>
<td>PRACTECAL</td>
<td>6 mths</td>
<td>3 regimens with Bdq+Prt+Lzd</td>
<td>Protocol Finalised Expected start Q3 2015</td>
<td></td>
</tr>
<tr>
<td>end TB</td>
<td>9 mths</td>
<td>Novel, no inj, regimens 4-5 drugs with Bdq and/or Dlm</td>
<td>Protocol near finalised</td>
<td></td>
</tr>
<tr>
<td>Bedaquiline/PA-824/PZA (GATB NC-005)</td>
<td>8-week SSCC Study of Bedaquiline plus PA-824 plus PZA</td>
<td>Study of B/PA/Z for drug-susceptible TB; has one arm enrolling patients with MDR-TB that adds Moxifloxacin to B-PA-Z</td>
<td>Expected to begin enrolling in 4Q14</td>
<td></td>
</tr>
<tr>
<td>NiX-TB</td>
<td>6-9 mths</td>
<td>Prt, Lzd, Bdq</td>
<td>Salvage regimen for XDR TB</td>
<td></td>
</tr>
<tr>
<td>PA-824/moxi/PZA (GATB NC-006)</td>
<td>4 or 6 months</td>
<td>Prt/M/Z for DS-TB; 1 arm with MDR-TB (susc. to FQ and Z)</td>
<td>Expected to begin enrolling 4Q14</td>
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<td>Study of Bdq/Prt/Z for DS-TB; 1 arm with MDR-TB adds Mfx</td>
<td>Expected to begin enrolling in 4Q14</td>
</tr>
<tr>
<td>DDI of bedaquiline + delamanid (ACTG A5343)</td>
<td>Safety, Tolerability, &amp; Pharmacokinetics Study</td>
<td>Bedaquiline and delamanid Drug-drug interactions and combined QT effects</td>
<td>Expected to begin enrolling in 1Q15</td>
</tr>
<tr>
<td>NExT Trial</td>
<td>6-9 mths</td>
<td>Injection free regimen containing bedaquiline, linezolid, levofloxacin, ethionamide/high dose INH, and PZA</td>
<td>Open labelled RCT Waiting for MCC approval, expected enrollment at 5 sites in South Africa</td>
</tr>
</tbody>
</table>
MSF MDR-TB Clinical Trial Initiative

- 2 MDR TB clinical trials
  - end TB
  - PRACTECAL
- Novel short course regimens without injectables
- Using new and repurposed drugs
TB Trial Initiative

- PRACTECAL

University College of London

Uzbekistan national institute of Tuberculosis

- end TB
PRACTECAL Trial overview

- Adults with pulmonary MDR and XDR-TB
- Open label, 4 parallel arms, randomised and controlled
- Multicentre, phase II-III trial
- Adaptive 2 stage design with a seamless transition
PRACTECAL Trial overview

- Adults with pulmonary MDR and XDR-TB
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PRACTECAL Trial overview

- Adults with pulmonary MDR and XDR-TB
- Open label, 4 parallel arms, randomised and controlled
- Multicentre, phase II-III trial
- Adaptive 2 stage design with a seamless transition
PRACTECAL Trial Arms

• Intervention arms:
  1. Bedaquiline + PA-824 + linezolid + moxifloxacin
  2. Bedaquiline + PA-824 + linezolid + clofazimine
  3. Bedaquiline + PA-824 + linezolid

• Control arm: Locally accepted standard of care which is consistent with the WHO recommendations for the treatment of M/XDR-TB
Summary end TB trial: Regimen optimization

• Phase III pragmatic, open-label, multicentric trial in 2 parts
  – Part I: test different 36-week regimens with 1 new drug (Bdq or Dlm) in patients with MDR, sensitive to FQs
  – Part 2: test different regimens combining 2 new drugs (Bdq AND Dlm) in patients with MDR, including FQ resistant patients

• Part I will be implemented while awaiting results of DDI study

• Randomization in this study will be adapted to outcome: bad outcomes on a regimen will result in decreased randomization to that regimen allowing the trial to progress quicker
### end TB: Experimental 9-month Regimens (Part I)

<table>
<thead>
<tr>
<th>#</th>
<th>Bdq</th>
<th>Dlm</th>
<th>Cfz</th>
<th>Lzd</th>
<th>FQ</th>
<th>Z</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Bdq</td>
<td></td>
<td>Lzd</td>
<td></td>
<td>Mfx</td>
<td>Z</td>
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<tr>
<td>2</td>
<td>Bdq</td>
<td></td>
<td>Cfz</td>
<td>Lzd</td>
<td></td>
<td>Z</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>Dlm</td>
<td>Lzd</td>
<td></td>
<td>Mfx</td>
<td>Z</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>Dlm</td>
<td>Cfz</td>
<td>Lzd</td>
<td>Lfx</td>
<td>Z</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>Dlm</td>
<td>Cfz</td>
<td></td>
<td>Lfx</td>
<td>Z</td>
</tr>
</tbody>
</table>

Bdq=bedaquiline, Dlm=delamanid, Cfz=clofazamine, Lzd=linezolid, FQ=fluoroquinolone, Z=pyrazinamide
Expected outputs MSF TB Trial Initiative (end TB and PRACTECAL)

- Short, safe and effective regimens that can be used in treating both MDR and XDR – TB
- The effect on safety and efficacy of adding Mfx or Cfz to a back bone of B+Pa+Lzd
- Cardiac specific safety of the new drugs (Bdq, Dlm, Prt) in combinations
- Tolerability of the new regimens
- Pharmacokinetic data of the new drugs when administered in combination regimen
Conclusions

• Important that we don’t just have new drugs but also research to inform better combinations and potential shorter duration

• Several new MDR TB drug combination trials starting or about to start

• MSF and partners have started an MDR TB Trial Initiative – 2 trials

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