endTB clinical trials

Francis Varaine, MSF endTB Project Leader

GLOBAL CONSULTATION ON TRANSITION TOWARDS NEW AND BETTER TREATMENTS OF DR-TB AND LTBI

Geneva, 14-16 November 2018
endTB trials summary

endTB*

• Rifampicin-resistant and FQ-susceptible pulmonary TB

• Randomized, controlled, open-label, non-inferiority, Phase III trial evaluating the efficacy and safety of shortened treatment regimens containing new and re-purposed drugs for MDR-TB

• Primary endpoint: 73-week favorable outcome

endTB-Q**

• Rifampicin- and FQ-resistant pulmonary TB

* Evaluating Newly approved Drugs for multidrug-resistant TB

** Evaluating Newly Approved Drugs in Combination Regimens for Multidrug-Resistant TB with Fluoroquinolone Resistance (Q)
## Experimental Regimens

<table>
<thead>
<tr>
<th>Experimental Regimens</th>
<th>Bedaquiline</th>
<th>Delamanid</th>
<th>Clofazimine</th>
<th>Linezolid</th>
<th>Quinolone</th>
<th>Pyrazinamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>endTB 1</td>
<td>Bdq</td>
<td></td>
<td></td>
<td>Lzd</td>
<td>Mfx</td>
<td>Z</td>
</tr>
<tr>
<td>endTB 2</td>
<td>Bdq</td>
<td></td>
<td>Cfz</td>
<td>Lzd</td>
<td>Lfx</td>
<td>Z</td>
</tr>
<tr>
<td>endTB 3</td>
<td>Bdq</td>
<td>Dlm</td>
<td></td>
<td>Lzd</td>
<td>Lfx</td>
<td>Z</td>
</tr>
<tr>
<td>endTB 4</td>
<td>Dlm</td>
<td></td>
<td>Cfz</td>
<td>Lzd</td>
<td>Lfx</td>
<td>Z</td>
</tr>
<tr>
<td>endTB 5</td>
<td>Dlm</td>
<td></td>
<td>Cfz</td>
<td></td>
<td>Mfx</td>
<td>Z</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Standard of care control, composed according to WHO Guidelines, including the possible use of DLM or BDQ.

### Sample size: 750

Bayesian adaptive randomization based on efficacy endpoints
## endTB-Q

<table>
<thead>
<tr>
<th></th>
<th>Bedaquiline</th>
<th>Delamanid</th>
<th>Clofazimine</th>
<th>Linezolid</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bdq</td>
<td>Dlm</td>
<td>Cfz</td>
<td>Lzd</td>
<td>6 mths</td>
</tr>
<tr>
<td>2</td>
<td>Bdq</td>
<td>Dlm</td>
<td>Cfz</td>
<td>Lzd</td>
<td>9 mths</td>
</tr>
<tr>
<td>C</td>
<td>Standard of care control per WHO Guidelines</td>
<td></td>
<td></td>
<td></td>
<td>20-24 mths</td>
</tr>
</tbody>
</table>

Sample size: 500  
Fixed randomisation
Primary objective
Assess whether the efficacy of the experimental arms at 73 weeks is non-inferior to that of the control
Objectives

Primary objective
Assess whether the efficacy of the experimental arms at 73 weeks is non-inferior to that of the control

Secondary objectives
Efficacy: Compare to control
• Culture conversion in experimental regimens
• Efficacy of experimental regimens at week 39
• Efficacy of experimental regimen at week 24
• Efficacy of experimental regimens at week 104, including failure & relapse

Safety: Compare to control
• Death, grade 3 or higher AEs and SAEs in experimental arms at 73 and 104 weeks
Pre-screening
RR-TB identified in routine care

Patients are pre-screened and offered simultaneous screening

- Medical history, concomitant medications, physical examination
- Pregnancy test, complete blood count, ALT/AST, bilirubin, albumin, creatinine, electrolyte testing, HIV and hepatitis serology
- ECG
- Molecular test for RIF
- **Molecular test for FQ**

Enrollment in endTB trial

Enroll in endTB
N=750
Meet all eligibility criteria and FQ-susceptible

Not eligible
Do not meet ≥1 eligibility criteria
Unified screening for endTB and endTB-Q clinical trials

Pre-screening
RR-TB identified in routine care

Patients are pre-screened and offered simultaneous screening

- Medical history, concomitant medications, physical examination
- Pregnancy test, complete blood count, ALT/AST, bilirubin, albumin, creatinine, electrolyte testing, HIV and hepatitis serology
- ECG
- Molecular test for RIF
- Molecular test for FQ

endTB Screening
(Single process for both studies)

Enrollment in 2 trials
N=1250

Enroll in endTB
N=750
Meet all eligibility criteria and FQ-susceptible

Enroll in endTB-Q
N=500
Meet all eligibility criteria and FQ-resistant

Not eligible
Do not meet ≥1 eligibility criteria
Trial participation in all arms will last at least until Week 73 and up to Week 104. Study follow-up will end after the scheduled Week 73 for the last participant randomized.
Trial participation in all arms will last at least until Week 73 and up to Week 104. Study follow-up will end after the scheduled Week 73 for the last participant randomized.
### endTB Clinical Trials

**endTB update:**
7 opened sites in 5 countries

<table>
<thead>
<tr>
<th>Country</th>
<th>First Patient Enrolled</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Georgia</td>
<td>22-Feb-2017</td>
<td></td>
</tr>
<tr>
<td>Peru (2→3 sites)</td>
<td>18-Jul-2017</td>
<td></td>
</tr>
<tr>
<td>Kazakhstan (2 sites)</td>
<td>07-Aug-2017</td>
<td></td>
</tr>
<tr>
<td>Lesotho</td>
<td>10-Jan-2018</td>
<td></td>
</tr>
<tr>
<td>South Africa</td>
<td>06-Apr-2018</td>
<td></td>
</tr>
</tbody>
</table>

- **Pakistan**
  - Under preparation – target Feb 2019

- **Potential new sites**
  - KZ (Astana and Karaganda under assessment)
endTB Clinical Trials
endTB update:
7 opened sites in 5 countries
Objective:
12 sites in 6 countries

Georgia
First patient enrolled
22-Feb-2017

Peru (2→3 sites)
First patient enrolled
18-Jul-2017

Kazakhstan (2 sites)
First patient enrolled
07-Aug-2017

Lesotho
First patient enrolled
10-Jan-2018

South Africa
First patient enrolled
06-Apr-2018

Pakistan
Under preparation – target Feb 2019

Potential new sites
KZ (Astana and Karaganda under assessment)

India
Potential sites
To be assessed
Recruitment Update

As of 12 Nov 2018, 173 patients randomized
Adaptive randomization will start after 180 patients are randomized

Around 15 pts /month

Current projection (with new sites) shows completion of enrolment by Q4 2020
Ministries of Health and NTPs:
Georgia, Kazakhstan, Lesotho, Peru, South Africa
Thank you