Tuberculosis in 2017: Searching for new solutions in the face of new challenges

6th TB Symposium – Ministry of Health of the Republic of Belarus, Republican Scientific and Practical Center for Pulmonology and Tuberculosis, and Médecins Sans Frontières

1-2 March, 2017, MINSK, BELARUS

endTB clinical trial – Q study

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Co – Principal Investigator, MSF
endTB-Q: a trial for fluoroquinolone-resistant MDR-TB

Background and Justification
Treatment outcomes: MDR- to XDR-TB

WHO (N=69763)
- MDR-TB: 64%
- XDR-TB: 29%

Bonnet (N=1433)
- MDR-TB: 60%
- Pre-XDR Fq: 33%
- XDR-TB: 27%

Kim (N=1407)
- MDR-TB: 48%
- Pre-XDR Fq: 36%
- XDR-TB: 29%

1WHO Global report 2015; 2Bonnet et al, IJTLD 2016; 3Kim et al, AJRCCM 2010
Treatment outcomes: XDR-TB

• Meta-analysis showed treatment success between 43% and 19% depending on additional resistance (“simple XDR”, 2 SLI, group 4, E, Z)

• In two studies assessing the follow-up of XDR-TB patients in South Africa, the mortality rate was 64% within two years\(^2\) and 73% within five years from the end of treatment\(^3\)

• Moreover, incurable XDR-TB cases are often discharged in the community, leading to continuous transmission of the disease\(^4\)

Current MDR/XDR-TB treatment

- Long (18-24 months)
- Toxic
- Poorly effective
- Complex
- Expensive
- Impossible to scale-up
- Largely based on expert opinion and very low quality of evidence
Advent of Bedaquiline and Delamanid: Breakthrough drugs offer new hope but...

- Adding new drugs to today’s regimens won’t solve the problems of complexity, toxicity, length and cost
- There is no evidence on how best to use these drugs
- Risk of scarce or chaotic use. Neither is an acceptable alternative
- **Urgent need and unique opportunity for regimen development research**
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• Expand access to new TB drugs according to WHO guidance (15 countries, 2600 patients)

• Perform a clinical trial with novel regimens for FQ-susceptible MDR-TB that include bedaquiline and/or delamanid (5 countries, 750 participants) – endTB trial

• Produce evidence on new TB drugs to inform policy and clinical decision making.
endTB-Q
(Evaluating Newly approved Drugs for multidrug-resistant-TB with fluoroQuinolone resistance)

Trial Design and Objectives
Trial Summary

- Rifampicin- and FQ-resistant pulmonary TB
- Randomized, controlled, open-label, non-inferiority, Phase III trial evaluating the efficacy and safety of a shortened treatment regimen containing newly approved and re-purposed drugs for MDR/XDR-TB
- Two experimental arms of 26 and 39 weeks of treatment vs. conventional, 20-24 month control
- 500 randomized participants
- Primary endpoint: 73-week favorable outcome
New, Repurposed Drugs with Limited Population Exposure

- Bedaquiline and Delamanid
- Linezolid (Lzd)
  - Meta-analyses
  - Improved conversion in XDR-TB trial
  - Toxicity concerns (600mg→300mg)

- Clofazimine
  - Active in acute and chronic mouse models
  - Observational studies support contribution in MDR & XDR
  - Inapparent EBA
  - Improved success in MDR-TB trial

1. Lee et al. 2012  2. Tang et al. 2015
# Treatment Arms

<table>
<thead>
<tr>
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<th>Treatment regimen</th>
<th>Duration</th>
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<tr>
<td><strong>E1</strong></td>
<td>Bdq</td>
<td>Dlm</td>
</tr>
<tr>
<td><strong>E2</strong></td>
<td>Bdq</td>
<td>Dlm</td>
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<td><strong>C</strong></td>
<td>Standard of care control per WHO Guidelines: may include Dlm, or Bdq, or both</td>
<td>20 to 24 months</td>
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Bdq=bedaquiline, Dlm=delamanid, Cfz=clofazimine, Lzd=linezolid
Objectives

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

- Secondary efficacy: Compare to control
  - Culture conversion in experimental regimens
  - Efficacy of experimental regimens at 26 and 39 weeks
  - Efficacy of experimental regimens at 130 weeks, including failure & relapse

- Secondary safety: Compare to control
  - At 73 and 130 weeks: death; grade 3 or higher AEs, SAEs, QTc prolongation in experimental arms

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Patient Inclusion and Statistical Considerations

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Study Population: Inclusion

- Pulmonary TB, RIF-resistant (x 2) & FQ-resistant, by validated rapid molecular test;
- ≥ 15 years of age;
- Negative pregnancy test & willingness (for ♀ & ♂) to use appropriate contraception;
- Informed consent by participant (& guardian);
- Intends to remain accessible to study
Assumptions, sample size and study populations

- \( \Delta = 12\% \)
- Control Response = 72\%
- Response non-inferior experimental arm = 75\%
- 80\% power
- ITT: all randomized participants with \( \geq 1 \) dose
- mITT: ITT, culture positive, confirmed RR-R/FQ-R
- PP: mITT without deviation that affects endpoint assessment

\[ N = 500 \]

80\% power to show the non-inferiority of at least one experimental arm against the control in both mITT and PP analyses

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endTB-Q

Sites and Timeline
Potential trial Sites
## Timeline

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Acknowledgements

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- Institute of Tropical Medicine
- Global TB CAB
- MSF MDR-TB Clinical Trial Scientific Advisory Committee