TB innovation for tomorrow.

Updates in the Development of Delamanid, OPC-167832, and Otsuka’s LAM Biomarker

Dr Jeffrey Hafkin

TB innovation for tomorrow.
Registrations

- **Approved**: EU, Japan, South Korea, Hong Kong
- **Submitted**: China, Indonesia, the Philippines, Turkey
- **In preparation**: South Africa, India, Peru, Vietnam, Russia

**Global Drug Facility** (launched Feb 2016)

- Available to all countries eligible for Global Fund TB financing
- 1350 treatment courses delivered in 2016

**Expanded Access Programs in Preparation**

- Launching:
  - South Africa
- In Preparation:
  - India
  - Indonesia and Vietnam

**Compassionate Use**

- >145 cases approved from 15 countries

TARGET: HIGH BURDEN COUNTRIES AND CLINICAL TRIAL SITES
FighTBacK: Responsible Access to Delamanid

>2,100 treatment courses supplied for patients in ~45 countries
## FighTBack: Early Outcomes with Delamanid Treatment

<table>
<thead>
<tr>
<th>Setting</th>
<th>2 Month Culture Status</th>
<th>6 Month Culture Status</th>
<th>QTcF&gt;500ms or Change&gt;60ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Japan</td>
<td>25/28 (89.3%)</td>
<td>20/20 (100%)</td>
<td>0/28 (0%)</td>
</tr>
<tr>
<td>Korea</td>
<td>20/21 (95.2%)</td>
<td>5/5 (100%)</td>
<td>N/A</td>
</tr>
<tr>
<td>Latvia</td>
<td>N/A</td>
<td>26/29 (89.7%)</td>
<td>N/A</td>
</tr>
<tr>
<td>Estonia</td>
<td>N/A</td>
<td>6/10 (60.0%)</td>
<td>N/A</td>
</tr>
<tr>
<td>PIH – endTB</td>
<td>N/A</td>
<td>N/A</td>
<td>0/14 (0%)</td>
</tr>
<tr>
<td>MSF – endTB, CU, other</td>
<td>18/27 (66.7%)</td>
<td>24/27 (88.9%)</td>
<td>8/210 (3.8%)</td>
</tr>
<tr>
<td>Compassionate Use</td>
<td>N/A</td>
<td>53/66 (80%)</td>
<td>3/78 (3.8%)</td>
</tr>
</tbody>
</table>

### Notes
- Patients are MDR-TB, preXDR-TB, and XDR-TB for each setting
- Culture Status defined as at least last culture result after 2 and 6 months of delamanid treatment, respectively
- Culture Status includes culture positive and culture negative patients at baseline
- Culture Status includes patients completing 2 and 6 months of delamanid treatment, respectively
- QTcF data provided for any patient receiving delamanid
- Data reported for MSF also included in Compassionate Use data
- Data provided in aggregate for each Setting

### Data Acknowledgements:
- **Japan** = Fukujuji Hospital, Osaka Prefectural Medical Center for Respiratory and Allergic Diseases, National Hospital Organization (NHO) Higashinagoya National Hospital, NHO Kinki-Chuo Chest Medical Center and NHO Ibarakihigashi National Hospital; **Korea** = Pusan National University Hospital, Masan National TB Hospital, Pusan National University Yangsan Hospital, Chonbuk National University Hospital, Ulsan University Hospital, Severance Hospital; **Latvia** = L. Kuska; **Estonia** = M. Danilovits; **PIH** = C. Mitnick; **MSF** = F. Varaine
Delamanid Pediatric Development: Trials 232/233

- **Current Tablet Formulation**
  - Group 1: Adolescents 12 to 17 years
    - (100 mg BID; n=6)
  - Group 2: Children 6 to 11 years
    - (50 mg BID; n=6)

- **Pediatric formulation**
  - Group 3: Children 3 to 5 years
    - (25 mg BID; n=12)
  - Group 4: Newborns and infants 0 to 2 years
    - (>10kg, 10mg BID)
    - (>8 – 10kg, 5mg BID)  (n=12)
    - (5.5 – 8Kg, 5mg QD)

- Overall target sample size = 36 children
Guidelines: delamanid may be added to the WHO-recommended longer regimen in children and adolescents (6 – 17 years) with multidrug- or rifampicin-resistant TB (MDR/RR-TB) who are not eligible for the shorter MDR-TB regimen, under specific conditions:

1. Proper patient inclusion
2. Adherence to the principles of designing a WHO-recommended longer MDR-TB regimen
3. Close monitoring of patients
4. Active TB drug safety monitoring and management
5. Informed decision-making process ensured

Delamanid is currently approved in the EU, Japan, Korea, and Hong Kong for use in adult patients only.
<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Study title</th>
<th>Started</th>
</tr>
</thead>
<tbody>
<tr>
<td>Korea CDC</td>
<td>MDR-END: Treatment Shortening of MDR-TB Using Existing and New Drugs</td>
<td>✓</td>
</tr>
<tr>
<td>US NIH</td>
<td>A5300B/PHOENIx: Protecting households on exposure to newly diagnosed index MDR-TB patients</td>
<td></td>
</tr>
<tr>
<td>US NIH</td>
<td>ACTG 5343: Evaluating the safety, tolerability, and pharmacokinetics of bedaquiline and delamanid, alone and in combination, for Drug-Resistant Pulmonary Tuberculosis</td>
<td>✓</td>
</tr>
<tr>
<td>US NIH</td>
<td>IMPAACT 2005: DLM for MDR/HIV paediatric patients w/o injectable</td>
<td></td>
</tr>
<tr>
<td>US NIH</td>
<td>ACTG 5356: Linezolid dose ranging in combination with DLM</td>
<td></td>
</tr>
<tr>
<td>US NIH</td>
<td>DMID/VTEU: Standard regimen vs. DLM plus injectable-free regimen for MDR-TB</td>
<td></td>
</tr>
<tr>
<td>UNITAID/MSF/PIH</td>
<td>endTB: OBR vs. 5 different 6-month treatment shortening, injectable-free regimens</td>
<td>✓</td>
</tr>
<tr>
<td>USAID</td>
<td>Evaluate six-month regimen (DLM + BDQ + LZD) for patients with drug resistance to isoniazid, rifampicin and a quinolone.</td>
<td></td>
</tr>
</tbody>
</table>
FighTBack: Introduction to OPC-167832

- OPC-167832 is a 3,4-dihydrocarbostyril derivative
- Otsuka has experience and success with carbostyril compounds
Mechanism of Action of OPC-167832

- Inhibition of decaprenylphosphoryl-β-D-ribose 2’-oxidase (DprE1), an enzyme involved in the cell wall biosynthesis

In-vitro Pharmacology of OPC-167832

- MIC for Mycobacterium tuberculosis (MTB): 0.00024 to 0.002 μg/mL
- Frequency of spontaneous resistance: 2.60 × 10⁻⁹ to 1.52 × 10⁻⁷ for MTB H37Rv at 16 × MIC
- Bactericidal against growing and intracellular bacilli
In-vivo Efficacy Pharmacology

In mouse model of chronic TB:

- OPC-167832 shows potent antimycobacterial activity
  - Effective dose 1.25 mg/kg
  - OPC-167832 plus delamanid, in combination with other anti-TB drugs, more effective than standard regimens for DS/MDR-TB
  - Results suggest OPC-167832/DLM regimens have potential to shorten treatment period and improve treatment outcomes
Development of a New TB treatment Regimen with OPC-167832 + Delamanid

- Develop regimen containing:
  OPC-167832 + delamanid
  
  plus

  1 to 2 recently developed anti-TB drugs

- Goals:
  
  • Target active TB patients regardless of baseline susceptibility (i.e. universal/pan-TB regimen)
  
  • Improve safety profile
  
  • Shorten TB treatment
  
  • Remove need for an injectable agents (all oral regimen)
Next Steps in Development Process

- Single ascending dose study for OPC-167832
  - Completed evaluation of 5/6 doses; final dose being evaluated
  - No significant safety signals thus far; PK data are linear

- Multiple ascending dose and EBA studies to follow

- Regimen selection guided by:
  - Hollow fiber model studies in collaboration with CPTR
  - Marmoset model studies in collaboration with NIH
  - Mouse models in Otsuka labs

- Planning grant for development of Integrated Product Development Plan awarded by Bill and Melinda Gates Foundation
High Unmet Need for Real-Time Assessment of Efficacy in TB Drug Development Trials

Field requires a tool that:

- Assesses early bactericidal activity (EBA) and sputum culture conversion in real-time, allowing for quick decision making (i.e. adaptive designs)
- Reduces cost associated with delayed results
- Not affected by contamination or drug carry-over effect
- Can be easily utilized in any laboratories suitable for clinical trials
Quantification of Bacterial Load by LAM-ELISA Assay

- New immunoassay developed to measure sputum lipoarabinomannan (LAM), a major MTB cell wall component
  - Specific for MTB and some slow growing mycobacterium strains
  - No cross-reactivity with oral bacteria
  - Sensitivity close to solid culture (\(~70 – 120\) cfu/mL)
  - Strong correlation between sputum LAM and cfu counts/TTD during treatment
  - Not affected by contamination or drug carry-over
Sputum LAM and MGIT Culture Trend Together in DS-TB patients (n=36) on HRZE treatment

Otsuka Data, unpublished
LAM: Next Steps

- Currently seeking Qualification of LAM as an Innovative Drug Development Method/Tool via FDA/EMA (in collaboration with CPTR)
  - Clinical Path Innovation Meeting – 3 March 2017

- Further clinical studies:
  - Participating in NexGen EBA Study (CFU, MGIT TTD)
  - Planning additional studies to evaluate LAM in various TB populations against range of drugs/regimens

- Further preclinical studies
  - Assess degradation of LAM during treatment to confirm dead bacilli not detected by antibodies
  - Identification of LAM epitopes that are the antibody binding side(s)
Thank you!