


FIGHTBACK

CPTR – 2017
Washington D.C

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


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Otsuka

TB innovation for tomorrow.

FighTBack: Responsible Access to Delamanid

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

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

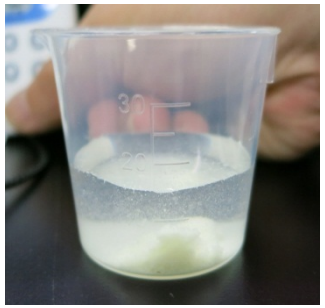
Notes

- 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
  - Enrollment Completed
    - Group 1: Adolescents 12 to 17 years
      - (100 mg BID; n=6)
    - Group 2: Children 6 to 11 years
      - (50 mg BID; n=6)

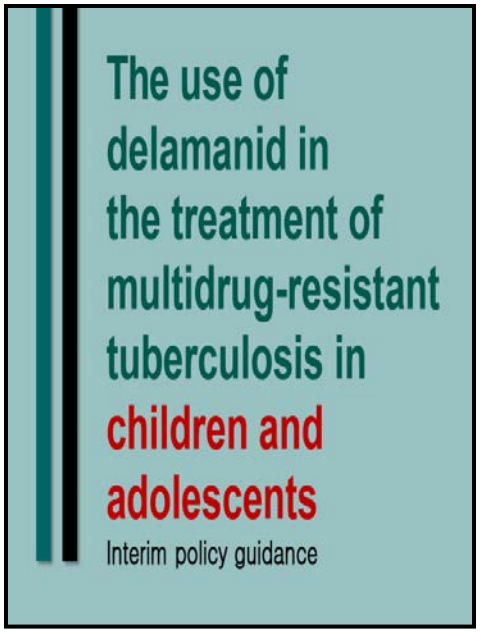


- Pediatric formulation
  - Enrollment Completed
    - Group 3: Children 3 to 5 years
      - (25 mg BID; n=12)
  - Enrollment Starting
    - Group 4: Newborns and infants 0 to 2 years
      - (>10kg, 10mg BID)
      - (>8 – 10kg, 5mg BID) (n=12)
      - (5.5 – 8Kg, 5mg QD)

- Overall target sample size = 36 children

Additional WHO Guidance on Delamanid (Oct 2016)

- 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.

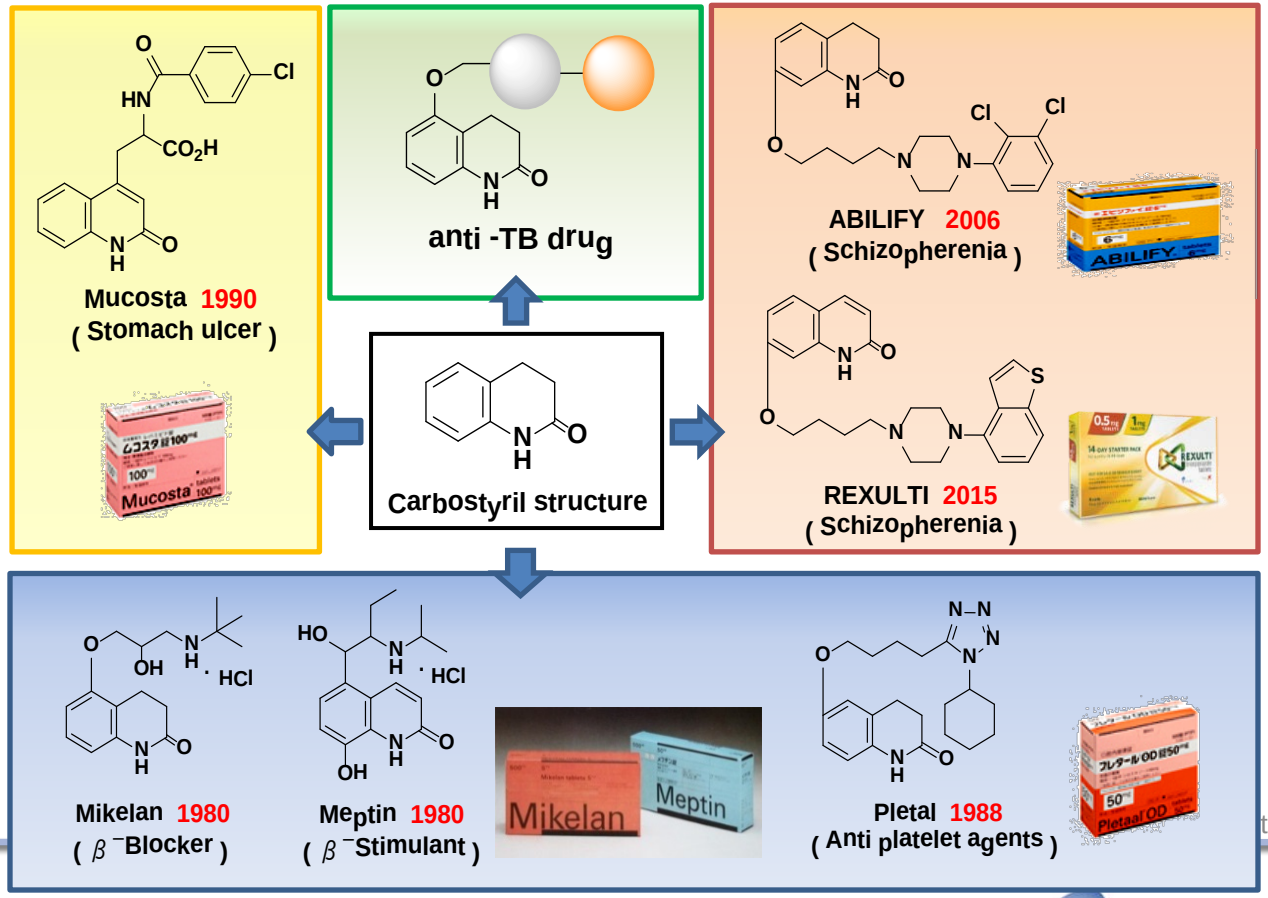
FighTBack: Collaborative Capacity Building/Optimized Patient Management

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

FighTBack: Introduction to OPC-167832

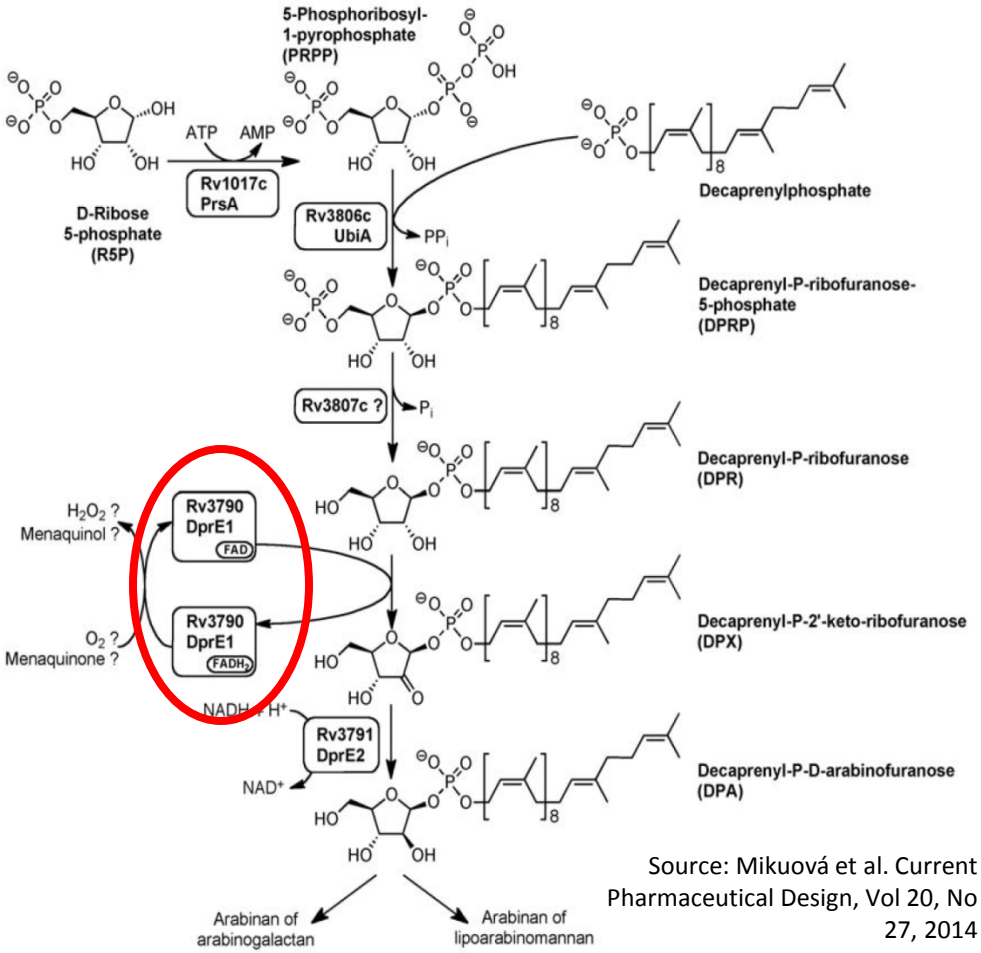
- OPC-167832 is a 3,4-dihydrocarbostyril derivative

- 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



Source: Mikuová et al. Current Pharmaceutical Design, Vol 20, No 27, 2014

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

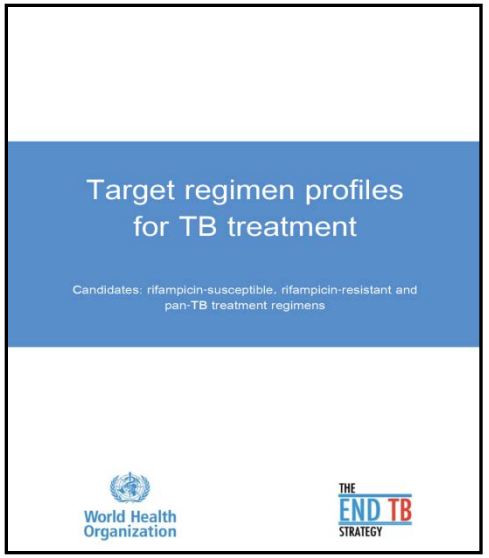
- Develop regimen containing:

  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

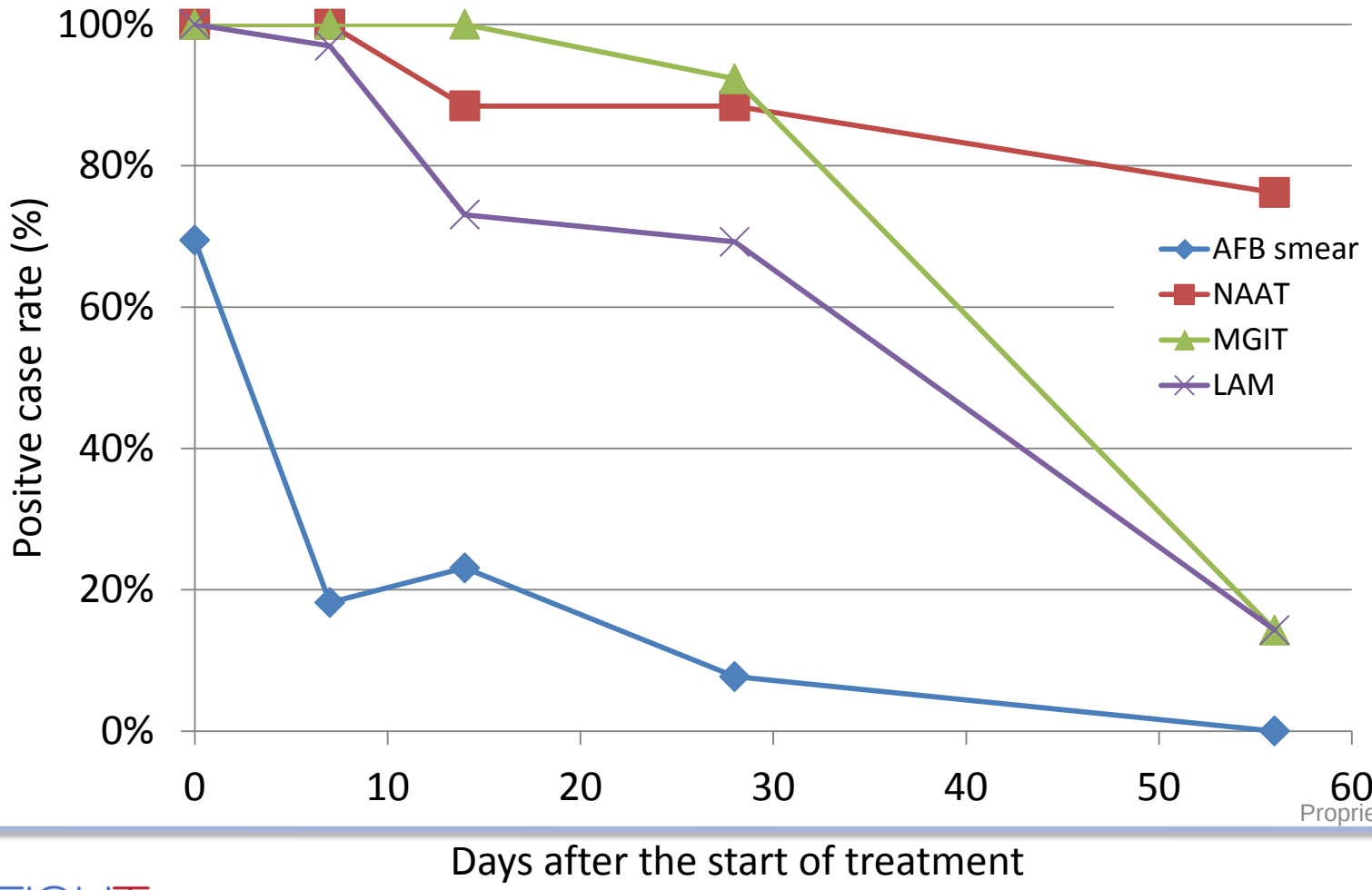
High Unmet Need for Real-Time Assessment of Efficacy in TB Drug Development Trials

- 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



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!