IMPAAACT 2005 Update

Ethel Weld
Tony Garcia-Prats
Kelly Dooley

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IMPAACT 2005: A Phase I/II Open-label, Single-Arm Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of Delamanid in Combination with Optimized Multidrug Background Regimen (OBR) for Multidrug-Resistant Tuberculosis (MDR-TB) in HIV-infected and HIV-uninfected Children with MDR-TB
Background & Rationale: Delamanid

• The drug
  • Nitroimidazole class, mycobacterial cell wall synthesis inhibitor
  • Bactericidal, with potent sterilizing activity
  • First-in-class for MDR-TB; EMA approved; WHO guidance

• Microbiologic efficacy in adults
  • RCT: DLM vs. placebo + OBR
  • N=481 adults (4 HIV+) with PTB
  • DLM 100mg BID vs 200mg BID vs placebo (2 mos on Rx + 1 mo F/U)
  • Higher 2-month culture conversion \(45.4\%\ vs. \ 29.6\%; \ p=0.008\) with DLM c/w placebo

• Safety and long-term outcomes in adults
  • F/U 24-mo Observational Study in Adults
  • lower mortality in those who received >6 months vs. < 2 months of DLM \(1.0\%\ vs 8.3\%; \ p<0.001\)
  • 74.5\% vs 55\% favorable outcomes \(p<0.001\)
  • QT prolongation but no clinical SAEs

• Critical Need for Safe and Effective Injectable-Sparing Treatment Regimens for MDR-TB in Children
Rationale for Injectable-sparing Regimen in Children

Injectables commonly cause severe, often-reversible toxicities
- **Ototoxicity**
  - ≥ 25% of children, often irreversible
  - Significantly affects neurocognitive development, psychosocial functioning, school performance [Seddon JA et al Thorax 2014;69(5):458-64]
- Programmatic challenge
- Profound source of **physical and emotional suffering** for children and caregivers

The contribution of injectables to standard MDR-TB treatment efficacy is unclear
- **In vitro**—amikacin weakly bactericidal; kanamycin bacteriostatic [Sanders WE et al Tubercle 1982;63(3):201-8.]
- **EBA**—Amikacin 5-15mg/kg/day has **no early bactericidal activity** [Donald PR et al IJTLD 2001;5(6):533-8; Jindani A et al Am Rev Resp Dis 1980;121(6):939-49.]

Clinical outcomes:
- **Adults:** Large, Individual Patient Data Meta-analysis including 9153 pts, the use of kanamycin, amikacin, or capreomycin vs. no injectable was NOT associated with a successful treatment outcome [Ahuja SD et al PloS Med 2012;9(8):e1001300.]
- **Children:** IPD meta-analysis of 842 children: 119 children were treated **without injectables** and **71.9% with culture-confirmed MDR-TB** had a successful outcome.

Adding new drug with proven sterilizing activity to MDR-TB regimen should improve outcomes significantly
- Example of bedaquiline (high cure rates in patients with TB resistant to injectables (pre-XDR and XDR TB) [Njeka IJTLD 2015]
- Example of another nitroimidazole, pretomanid (high potency in combination with moxifloxacin, pyrazinamide)

Children typically have paucibacillary disease, so generally are easier to treat than adults
Delamanid Pharmacokinetics & Safety

**Adult PK highlights**
- $T_{\text{max}} = 4$ hours; $T_{1/2}$ is 30-38 hours; metabolites (including DM-6705) 150-600 hours
- Increased bioavailability with food & with separating dose from companion drugs; non-linear bioavailability
- No significant DDI with key ARV
- Effects of HIV infection on absorption unknown

**Adult safety**
- QT prolongation (maximum 15 ms) , no other cardiac toxicity
- Maximal QT effect at 8 weeks, associated with DM-6705 exposures

**Pediatric PK & safety**: (Otsuka Trials 232 (14 days) and 233 (24 weeks))
- In small pediatric trial of children with MDR-TB without HIV infection:
  - Ages 0-17 (n=31): exposures similar to those seen in adults (exception: Group 4)
  - Drug safe and well-tolerated in children (*no QT prolongation*).
- Delamanid Pediatric Formulation (DPF) developed and available
  - bioequivalence study completed: 125mg DPF is bioequivalent to 100mg adult formulation DLM

Objectives

In HIV-infected and HIV-uninfected children treated for MDR-TB with OBR

**Primary Objectives**

- Evaluate the PK of DLM, at doses most likely to achieve exposures similar to those achieved in adults with 100mg twice-daily
- Safety of DLM over treatment period (24 weeks)

**Secondary Objectives**

- Effects of HIV co-infection and/or co-treatment, dose, age contributions on PK variability
- Acceptability/ tolerability of DLM
- Long-term safety (72 weeks following treatment initiation)
- TB treatment outcomes

**Exploratory Objectives**

- HIV treatment outcomes; TB treatment outcomes, safety and tolerability of injectable-sparing, delamanid-containing regimens in the treatment of MDR-TB; PK-QT relationships; longitudinal biomarkers of TB treatment responses in children
Endpoints

Primary Endpoints

- **PK**: population PK model and simulation results
- **Safety**: Over 24 weeks--Grade 3 or 4 AE, permanent study drug discontinuation due to AE, QTcF ≥ 500 ms

Secondary Endpoints

- Covariate effects on population PK model
- Grade ≥2 AE, QTcF ≥ 500 ms, or ΔQTcF >60ms, over 72 weeks
- Drug discontinuation for reasons other than toxicity
- Acceptability questionnaire responses, by week 24
- Bacteriological cure, probable cure, death, treatment failure
Study Design

**Design:** Phase I/II open label, single-arm study with modified age de-escalation approach

- Cohort 1: ages 12 to <18 years: adult formulation
- Cohort 2: ages 6 to <12 years: adult formulation
- Cohort 3: ages 3 to <6 years: pediatric formulation
- Cohort 4: ages 0 to <3 years: pediatric formulation

**Regimen:**

- Cohorts 1 & 2: 100 mg BID for >35 kg; 50 mg BID for 15-35 kg
- Cohorts 3 & 4: open to accrual and dosing dependent on weight of participant:
  - >12 kg: 25 mg twice daily
  - >10 to 12kg: 10 mg twice daily
  - >8 to 10kg: 5 mg twice daily
  - 5.5 to 8 kg: 5 mg once daily

**Duration:** 24 weeks on study treatment, follow-up through 96 weeks

**Population:** Children with confirmed or probable MDR-TB (including XDR), with or without HIV co-infection

**PK sampling:** 14 samples per child, over 28 weeks; 504 total observations (semi-intensive & sparse)

*participants will also receive optimized background treatment, ART as appropriate
Safety Assessment & Monitoring

• Risks
  • QT prolongation--ECGs each study visit while on drug, 4 weeks after drug discontinuation; ECGs read centrally

• Toxicity management
  • Specific management guidelines for ECG-determined or clinical cardiac toxicity, liver toxicity
  • Guidance for management of known toxicities related to companion drugs

• Monitoring
  • Protocol team, in real time
  • SMC—Meetings annually and as-needed; if pre-specified AEs occur
IMPAACT 2005 Milestones & Updates

• MOP, LPC, CRFs finalized
• January 2018: Study opened to accrual
• February 2018: Regional study-specific start-up training held in Cape Town, South Africa
• 15 June 2018: First site (KCMC, Tanzania) activated!
• June/July 2018: First enrollment expected!!
Sites & Activation Timeline

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The Team!
Semi-intensive PK: Weeks 1, 2, 8
Sparse PK: Weeks 4, 12, 16, 24, 28

Minimum of 9 participants/cohort (6HIV+, 3HIV-)
Minimum of 8 children taking EFV
Minimum of 8 children taking PI