IMPAACT 2005 Update

Ethel Weld

Tony Garcia-Prats

Kelly Dooley

IMPAACT Annual Meeting: TBSC

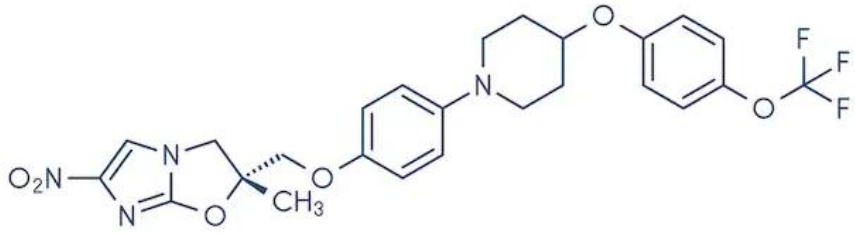
June 18, 2018, Washington, D.C.

IMPAACT
International Maternal Pediatric
Adolescent AIDS Clinical Trials Network

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-irreversible 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_{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

[Diacon AH et al. Lancet. 2012;380(9846):986-93; Gupta R, et al. NEJM 2015;373(3):291-2; Gler MT, et al. NEJM 2012;366(23):2151-60.]

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 $\geq$ 500 ms

Secondary Endpoints

- Covariate effects on population PK model
- Grade $\geq$2 AE, QTcF $\geq$ 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

IMPAACT 2005 Participating Sites	Activation Date
Tanzania	
5118 KCMC	15 June 2018
Botswana	
12701 Gaborone	Expected July 2018
12702 Molepolole	Expected July 2018
South Africa	
31790 DTTC	Expected August 2018
31929 Sizwe	Expected August 2018
31976 PHRU Matlosana	Expected August 2018
India	
31441 BJMC	Expected September 2018

The Team!

thank you

Study schema

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