IMPAACT 2005 Update

Ethel D. Weld, MD

IMPAACT Annual Meeting

May 30, 2017

IMPAACT
International Maternal Pediatric
Adolescent AIDS Clinical Trials Network

IMPAACT 2005:

A Phase I/II Open-label, Single-Arm Study to Evaluate the PK, Safety, and Tolerability of Delamanid (DLM) in Combination with Optimized Multidrug Background Regimen (OBR) for Multidrug-Resistant Tuberculosis (MDR-TB) in Children with MDR-TB with and without HIV

IMPAACT

International Maternal Pediatric Adolescent AIDS Clinical Trials Network

IMPAACT 2005 Milestones

- **Protocol Version 1.0 achieved!**
- IND: FDA comments on protocol received; team response submitted
- SMP created and finalized
- CTA w/ Otsuka finalized and fully executed
- Population PK Analysis Plan drafted, reviewed, finalizing
- LPC created
- MOP in preparation
- EC/IRB/DRA submissions pending
- Site Activation Checklist Finalized

IMPAACT 2005 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

IMPAACT 2005 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

IMPAACT 2005 Feasibility & Sites

- Otsuka to provide study drug; pediatric formulation now available. Otsuka provided raw PK data & PK model to Uppsala
- DLM registered in Europe and several other countries; ?NDA submission date
- DLM & DM-6705 metabolite assays under development at UCT
- Pharmacometrics Collaborators: Mats Karlsson & Elin Svensson (Uppsala University)
- Industry Collaborators: Lawrence Geiter; Suresh Mallikaarjun; & Jeffrey Hafkin (Otsuka)

IMPAACT Sites with Capacity, Expertise & Interest:

- Stellenbosch University Desmond Tutu TB Center: Cape Town, South Africa
- Gabarone & Molepolole: Botswana
- Soweto: JHB, South Africa
- BJ Medical College Pune, India
- Kilimanjaro Christian Medical Center: Moshi, Tanzania

Additional DAIDS-supported, non-IMPAACT sites with Capacity, Expertise & Interest:

- Sizwe Tropical Diseases Hospital: JHB, South Africa
- PHRU Matlosana: Klerksdorp, South Africa

IMPAACT 2005 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

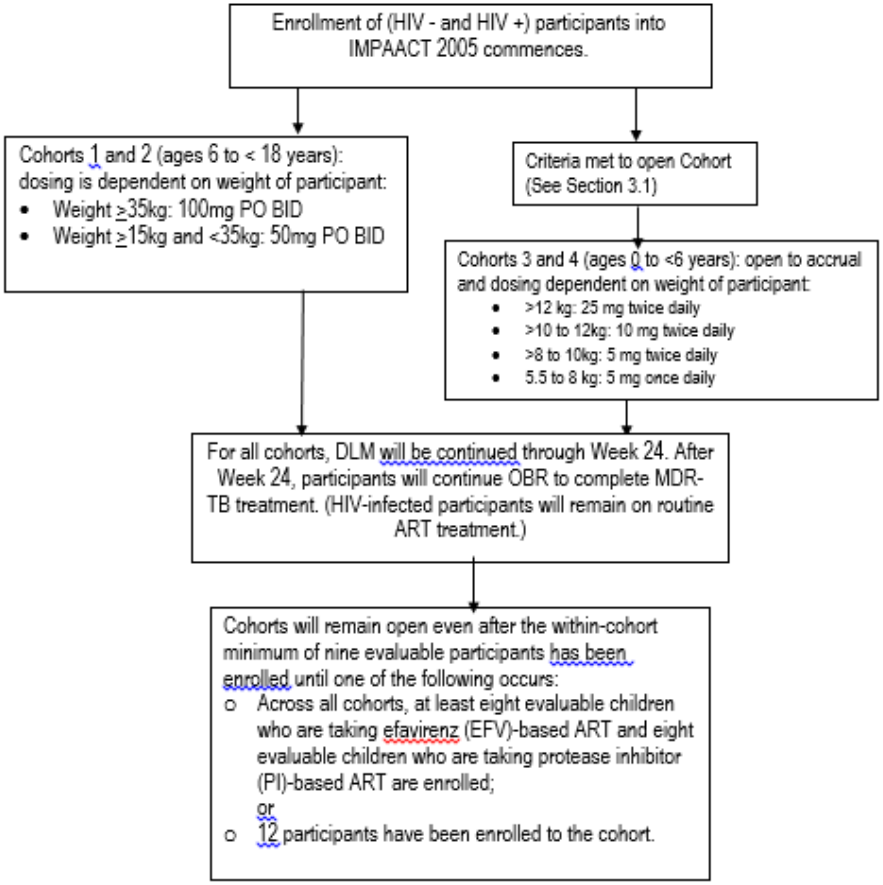
Duration: 24 weeks on study treatment, follow-up through 96 weeks

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

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

Interim Analysis

- Timing: Week 8 PK and safety data are available for 6 participants with HIV-infection taking LPV/r.
- Purpose:
  - **to assess interaction between DLM and LPV/r**
- Rationale: LPV/r increases DLM/DM-6705 concentrations in adults, which could potentially result in increases in QT interval
- Will include all available PK and safety data for all participants at the time of the interim analysis.

PK targets:

- median observed DLM $AUC_{0\text{-}24h}$ at Day 56 above the 25th %ile and below the 95th%ile of the adult DLM $AUC_{0\text{-}24h}$ distribution at Day 56
  - Dose increase if low

Day 56	Delamanid		DM-6705	
Trial 204 (Adults)	Cmax ng/mL	$AUC_{0\text{-}24h}$ ng*h/mL	Cmax ng/mL	$AUC_{0\text{-}24h}$ ng*h/mL
Median	391	7654	143	2990
5th Percentile	176	3571	55	1177
25th Percentile	289.0	**5698**	96.3	2004
75th Percentile	493.8	9873	203	**4145**
95th Percentile	730	**13205**	269	5628

(yellow highlighted area–target range)

- median observed DM-6705 $AUC_{0\text{-}24h}$ at Day 56 below the 75th%ile of the adult DM-6705 $AUC_{0\text{-}24h}$ distribution at Day 56
  - Dose decrease if high

IMPAACT
International Maternal Pediatric
Adolescent AIDS Clinical Trials Network

Acknowledgements

Kelly Dooley
Tony Garcia-Prats
Grace Montepiedra
Elin Svensson
Anneke Hesseling
Kathryn Lypen
Jackie Mountcastle
Diane Costello
Anne-Marie Demers
Patrick Jean-Philippe
Betsy Smith

Overall support for the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network was provided by the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH) under Award Numbers UM1AI068632 (IMPAACT LOC), UM1AI068616 (IMPAACT SDMC) and UM1AI106716 (IMPAACT LC), with co-funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and the National Institute of Mental Health (NIMH). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Thank You!

Photo: Jason Beaubien/NPR

IMPAACT
International Maternal Pediatric
Adolescent AIDS Clinical Trials Network