IMPAACT 2014: Phase I/II Study of the Pharmacokinetics, Safety, and Tolerability of Doravirine (MK-1439) and Doravirine/ Lamivudine/Tenofovir Disoproxil Fumarate (MK-1439a) in HIV-1-infected Children and Adolescents

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IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Background summary

- MK-1439 (DOR) is a novel NNRTI with once daily dosing
- Active against WT and NNRTI-resistant HIV
- Phase 2 studies in adults showed similar efficacy between DOR and EFV when combined with TDF/FTC
- Fewer CNS adverse events in the DOR-treated participants

Background summary

- Non-inferiority of DOR + 2 NRTIs compared to DRV/r + 2 NRTIs in ART-naïve adults (HIV RNA <50 c/ml - 83% DOR arm vs 80% DRV/r arm at 48 wks)
- MK-1439A is an FDC with DOR (100mg)/TDF (300mg)/LMV(300mg) – the TDF and LMV are new generics
- A pediatric granule formulation of DOR and DOR/3TC/TDF has been developed

Background summary

- The 100 mg QD dose in children and adolescents ≥35 kg is projected to achieve drug levels similar to those achieved in adults at the 100 mg QD dose
- First study to evaluate MK-1439 (DOR) and MK-1439A (DOR/TDF/LMV) for labeling in the pediatric population
- Will provide PK data to inform the development of DOR and DOR/3TC/TDF in younger children

Rationale for development of DOR in children

- Potential first line agent:
  - Once daily
  - Improved toxicity - less rash, fewer CNS events
  - Can be taken with and without food
  - No mutagenicity or teratogenicity in pre-clinical studies
  - DOR is not an inducer or inhibitor of CYP3A - fewer drug interactions
  - No decreased efficacy at high viral loads
  - Wide therapeutic margin

Rationale for development of DOR in children

- Potential as a second-line agent:
  - in-vitro inhibition of viruses with K103N, Y181C and G190A as well as the double mutant K103N and Y181C at drug levels which are readily achieved. Cmin of 100mg dose is >10 fold higher than IC_{50} of mutant viruses
  - DOR may be a better switch option than NVP or EFV for young children previously exposed to NVP and now suppressed on lopinavir/r

Schema

Purpose: To evaluate the pharmacokinetics, safety, and tolerability of doravirine (DOR) and of doravirine/lamivudine/tenofovir disoproxil fumarate (DOR/3TC/TDF) in HIV-1-infected children and adolescents

Design: Phase I/II, multi-site, open-label, non-comparative pharmacokinetics (PK) and safety study

Population: HIV-1-infected children and adolescents less than 18 years of age who weigh at least 35 kg. Cohort 1 and 2 will enroll sequentially:

Cohort 1: Virologically suppressed on a combination of dolutegravir (DTG) or raltegravir (RAL) plus two nucleoside reverse transcriptase inhibitors (NRTIs)

Cohort 2: Antiretroviral treatment naïve or virologically suppressed

Sample Size: Cohort 1: Up to 20 participants to achieve 12 evaluable

Cohort 2: Up to 45 participants to achieve 40 evaluable

Study design

- Participants will enroll in 2 sequential cohorts
  - Cohort 1 – single-dose of 100 mg DOR added to suppressive regimen (2NRTIs + INST) with intensive PKs. Follow-up visit at 2 weeks.
  - Cohort 2 – ART-naïve (or suppressed on a first-line regimen) adolescents of the weight determined by Cohort 1 will receive DOR/3TC/TDF (100/300/300) for 96 weeks. A subset will get iPK and all will have sparse PK.
  - Participants from both cohorts can choose either the tablet or granule formulation

Study design

- Cohort 1 - PKs will be done in small batches until 12 participants have evaluable PK and safety data
  - 4 participants 35 -≤ 45kg and 2 ≤ 11 yrs
- Cohort 2 will enroll for participants of the weight determined through Cohort 1
  - 5 participants 35 -≤ 45kg (if this weight group is approved)
  - First 10 participants will have iPK for 3TC and TDF and all will get sparse PK for DOR through week 48
  - Followed until week 96 for safety and efficacy

Primary Objectives: Cohort 1

- Evaluate the single-dose pharmacokinetics of DOR in HIV-1-infected children and adolescents receiving DOR when added to a stable ART regimen with one integrase inhibitor (InSTI) plus two NRTIs, using intensive PK sampling at Entry
- Evaluate the safety and tolerability of a single-dose of DOR in HIV-1-infected children and adolescents when added to a stable ART regimen with one InSTI plus two NRTIs at Week 2.

Primary Objective: Cohort 2

- Evaluate the 24-week safety and tolerability of DOR/3TC/TDF in HIV-1-infected children and adolescents.

Secondary Objectives: Cohort 2

- Safety of DOR/3TC/TDF at Weeks 48 and 96
- Pharmacokinetics of DOR, 3TC, and tenofovir using intensive and semi-intensive PK at Week 1, and sparse PK through Week 48
- Virologic efficacy of DOR/3TC/TDF at Weeks 24, 48 and 96
- Immunologic response from baseline to Weeks 24, 48 and 96
- HIV-1 genotype and phenotype in participants experiencing virologic failure
- Acceptability and palatability of DOR/3TC/TDF

Key inclusion criteria

- Age < 18 years
- Weight ≥ 35 kg
- Suppressed on INST-based ART (Cohort 1)
- ART-naïve or virologically suppressed on first-line regimen (Cohort 2)
- GFR ≥ 60 mL/min at entry
- Grade 2 or lower creatinine, proteinuria, glycosuria (Cohort 2)
- Not pregnant and on appropriate birth control

Key exclusion criteria

- Detectable Hep C RNA
- Decompensated liver disease
- Active tuberculosis

Implementation Timeline