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Pharmacokinetics and dose selection of etravirine in HIV-infected children between 6 and 17 years, inclusive

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Abstract

Background

Etravirine (ETR; TMC125) is a NNRTI approved in combination with other antiretrovirals for the treatment of HIV-infected, treatment-experienced adults. Pediatric dosing of ETR has not been established. The primary objective of this Phase I, open-label trial was to determine the weight-based dose of ETR that will achieve exposures in treatment-experienced children comparable to those in adults.

Methods

HIV-1-infected children between 6 and ≤17 years with at least two consecutive viral loads <50 copies/mL on a stable lopinavir with low-dose ritonavir (LPV/r)-containing regimen were enrolled; concomitant NNRTI use was excluded. The trial was conducted in two sequential stages. In both stages, ETR was added for 7 days followed by a morning dose and 12-hour pharmacokinetic (PK) assessment on Day 8. ETR was administered following a meal and dosed 4mg/kg bid in Stage I and 5.2mg/kg bid in Stage II – 25mg and 100mg tablets were used. ETR pharmacokinetics were assessed using noncompartmental analysis; PK parameters were compared to those previously established in HIV-1-infected adults. Safety and tolerability were assessed throughout the study up to 30 days post-dosing.

Results

Twenty-one children were enrolled into each stage (seven children participated in both stages); pharmacokinetics were available in 19 and 20 children in Stages I and II, respectively. The mean (standard deviation [SD]) maximum plasma concentration (C_{max}) in Stage I and II, respectively, was 495ng/mL (453ng/mL) and 757ng/mL (680ng/mL); minimum plasma concentration (C_{min}) was 184ng/mL (151ng/mL) and 294ng/mL (278ng/mL); and area under the plasma concentration-time curve from time of administration to 12 hours after dosing (AUC_{12h}) was 4050ng•h/mL (3602ng•h/mL) and 6141ng•h/mL (5586ng•h/mL). PK parameters in Stage II were more comparable to adults participating in the Phase III DUET-1 and DUET-2 trials (mean [SD] population derived C_{min} was 393ng/mL [391ng/mL] and AUC_{12h} was 5506ng•h/mL [4710ng•h/mL], n=575). All children remained <50 copies/mL on Day 8. No serious adverse events (AEs) occurred during ETR treatment; 14 and nine children in Stage I and II, respectively, reported at least one AE, mostly grade 1 or 2. Two children in Stage I developed a mild (grade 1) or moderate (grade 2) rash; no rash was reported in Stage II.

Conclusions

The proposed dose of ETR in children 6–17 years, inclusive is 5.2mg/kg bid. This dose provides comparable exposure to the adult dose of ETR (200mg bid) and was generally safe and well tolerated. Further PK, safety and tolerability of ETR in this population will be investigated in the Phase II PIANO (**P**ediatric trial with **I**NTELENCE as an **A**ctive **N**NRTI **O**ption) trial.

Introduction

- ETR is a next-generation NNRTI with potent in-vitro activity against both wild-type and NNRTI-resistant HIV-1[1]
- PK characteristics[2]
  - ETR must be administered following a meal
  - substrate and inducer of CYP3A
  - substrate and inhibitor of CYP2C9 and 2C19
  - inhibitor of P-glycoprotein, but not a substrate
  - no relevant effect of mild or moderate hepatic impairment
  - minimal (<1.2%) renal excretion
  - mean terminal elimination half-life of 41 hours
- Two large, randomized, double-blind, placebo-controlled trials, DUET-1 and DUET-2, demonstrated the efficacy and safety of ETR in HIV-infected adults to Week 48[3,4]

Pediatric trial objectives

Primary objectives

- To determine steady-state pharmacokinetics of ETR in treatment-experienced HIV-1-infected children
- To determine dose recommendations of ETR per bodyweight in HIV-1-infected children ≥6 years old and weighing ≥20kg

Secondary objective

- To evaluate short-term safety and tolerability of ETR in HIV-1-infected children

Pediatric trial design

- Open-label trial in two sequential dosing stages

Stage I ETR 4mg/kg bid following a meal

↓

Stage II ETR 5.2mg/kg bid following a meal

- Each stage to enroll 20 HIV-1-infected children on a stable LPV/r-containing regimen with viral load <50 copies/mL
  - 10 children ≥6 to <12 years
  - 10 children ≥12 to ≤17 years
- ETR added to regimen for 7 days with a morning dose on Day 8 followed by 12-hour PK evaluation

ETR dosing and formulation

Stage I (4mg/kg bid)

Weight (kg)	Dose* (mg, bid)
20–24.9	100
25–34.9	125
35–39.9	150
40–44.9	175
≥45	200

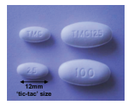
*Based on baseline weight

Stage II (5.2mg/kg bid)

Weight (kg)	Dose* (mg, bid)
20–24.9	125
25–29.9	150
30–34.9	175
≥35	200

*Based on baseline weight

- 25mg tablet currently available only for clinical research use
  - compositionally proportional to 100mg tablet



PK analysis

- Plasma samples for ETR pharmacokinetics were collected over 12 hours on Day 8
  - pre-dose and 1, 2, 3, 4, 6, 8, 10 and 12 hours post-dose
- Plasma concentrations of ETR were determined using a validated LC-MS/MS method
  - lower limit of quantification: 2ng/mL
- PK analyses were performed using WinNonlin Professional (version 5.1; Pharsight Corporation, Mountain View, California, USA)

LC-MS/MS = liquid chromatography-mass spectrometry/mass spectrometry

Statistical analysis

PK analysis

- LSM and 90% CI of AUC_{12h} and C_{min} in children compared to HIV-1-infected treatment-experienced adults[5]
  - HIV-1-infected adults administering ETR 200mg bid on a stable LPV/r-containing regimen
  - post-hoc comparison to pooled DUET PK parameters[6]

Safety analysis objective

- AEs and laboratory abnormalities
- Severity and relatedness of AEs to ETR

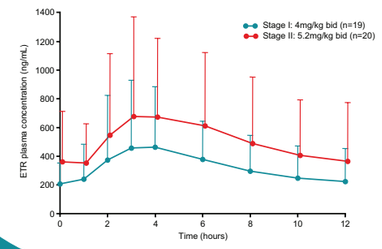
LSM = least square mean; CI = confidence interval

Baseline demographics and subject disposition

	Stage I	Stage II
Sex, male/female	13/8	8/13
Median (range) age, years	12 (6–17)	10 (7–17)
Median (range) weight, kg	39 (20–65)	38 (22–63)
Race, n (%)		
Caucasian	13 (61.9)	10 (47.6)
Black	5 (23.8)	9 (42.9)
Hispanic	1 (4.8)	2 (9.5)
Other	2 (9.5)	0 (0)
Mode of HIV transmission, n (%)		
Mother-to-child transmission	20 (95.2)	21 (100)
Other	1 (4.8)	–
Dropout due to AE, n (%)	1 (4.8)*	0
Evaluable pharmacokinetics	19‡	20§

*Subject had grade 3 creatinine at baseline visit and was withdrawn per protocol; ‡One subject removed from analysis due to administration of the wrong dose; §One subject removed from analysis due to coadministration of a disallowed medication (efavirenz)

Plasma concentration-time profile of ETR by stage



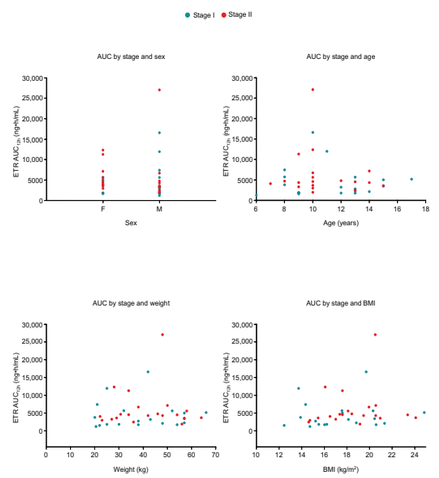
ETR PK parameters

	Stage I 4mg/kg bid	Stage II 5.2mg/kg bid	Adult reference: TMC125-C228[5]	Adult reference: Pooled DUET[6]
n	19	20	27	575
t_{max}	4 (2–8)	4 (2–6)	4 (2–8)	–
C_{max}	495±453	757±680	451±232	–
C_{min}	184±151	294±278	185±128	393±391
LSM (90% CI)*	0.99 (67–145)	1.58 (109–228)	–	–
AUC_{12h}	4050±3602	6141±5586	3713±2069	5506±4710
LSM (90% CI)*	1.02 (73–142)	1.58 (116–215)	–	–

*Protocol-specified comparison (HIV-1-infected adults administering ETR 200mg bid on a stable LPV/r-containing regimen)

t_{max} = time-to-reach the maximum plasma concentration

AUC_{12h} by trial stage and sex, age, weight or BMI



BMI = body mass index

HIV disease surrogate markers

- All subjects had a viral load <50 HIV-1 RNA copies/mL at screening, baseline and after 8 days of ETR treatment
- Small changes in CD4+ and CD8+ cell counts and percentages were observed after 8 days of ETR treatment

	Stage I	Stage II
CD4 absolute, cells/mm³	–22	–54
% change	–0.7	+0.5
CD8 absolute, cells/mm³	+14	–9
% change	+1.4	+0.9

Safety

- ETR was generally safe and well tolerated
- The majority of AEs were grade 1 or 2
- Most commonly reported AEs were rhinitis and headache
- Mild-to-moderate rash was seen in two subjects on Day 8 in Stage I
  - resolved spontaneously after a few days
  - there were no subjects with rash in Stage II
- No discontinuation or serious AEs occurred during the treatment period
- ETR was not associated with any clinically relevant laboratory abnormalities

Conclusions

- ETR administered at 4mg/kg and 5.2mg/kg bid following a meal provides comparable exposure in HIV-infected children (aged 6–17 years, inclusive) to 200mg bid in HIV-infected adults
- ETR was generally safe and well tolerated
  - two subjects developed a transient rash of mild-to-moderate severity during Stage I
    - no apparent association of rash with ETR exposure (AUC_{12h})
- Given the general concern for underdosing of antiretrovirals in children[7–9] and lack of any safety signal during Stage II, the selected target dose of ETR in children aged 6–17 years inclusive, is 5.2mg/kg bid
- A Phase II trial (TMC125-C213; PIANO) to further determine pharmacokinetics, safety and efficacy over 48 weeks in treatment-experienced children is ongoing

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