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Pharmacokinetics of the next-generation NNRTI etravirine (ETR; TMC125) in HIV-infected children between 6 and 17 years, inclusive

Thomas N Kakuda,[1] Christoph Königs,[2] Cornelia Feiterna-Sperling,[3] Claudio Viscoli,[4] Raffaella Rosso,[4] Rekha Sinha,[5] Ingeborg Peeters,[5] Monika Peeters,[5] Katrien Janssen,[5] Richard MW Hoetelmans,[5] Katia Boven[1]

[1]Tibotec, Inc, Yardley, PA, USA; [2]J W Goethe University, Frankfurt, Germany; [3]Charité Campus Virchow-Klinikum, Berlin, Germany; [4]Azienda Ospedaliera Universitaria San Martino, Genoa, Italy; [5]Tibotec BVBA, Mechelen, Belgium

Thomas N Kakuda, PharmD
Tibotec Inc.
1020 Stony Hill Road
Suite 300
Yardley, PA 19067
USA
Phone: +1 609 730 7528
tkakuda@tibus.jnj.com

Abstract

Background

ETR is a next-generation NNRTI that has demonstrated significant antiviral activity in two large Phase III trials, DUET-1 and 2, conducted in HIV-infected adults with evidence of NNRTI resistance. Pediatric dosing of ETR has not yet been established. The objective of this study is to determine the weight-based dose of ETR that will achieve exposures in children comparable to those in adults.

Methods

HIV-1-infected children between 6 and ≤17 years with at least two consecutive viral loads of <50 copies/mL on a lopinavir/ritonavir (LPV/r)-containing regimen, were enrolled. ETR 4mg/kg bid was added for 7 days followed by a morning dose and 12-hour pharmacokinetic (PK) assessment on Day 8. Both 25 and 100mg tablets were used. ETR PK was assessed using non-compartmental analysis; C_{min} and AUC_{12h} were compared to parameters previously established in adults administered 200mg bid on a LPV/r-containing regimen. Safety and tolerability were assessed throughout the study up to 30 days postdosing.

Results

Seventeen children were enrolled in the study; PK data were available in 16: 10 between the ages of 6 and <12 and six between the ages of ≥12 and ≤17. The mean (standard deviation; SD) C_{max} and C_{min} in 16 children were 555.2 (514.6) ng/mL and 233.2 (237.9) ng/mL, respectively. Mean (SD) AUC_{12h} was evaluable in 15 children and was 4788 (4459) ng•h/mL. Relative to adults, the least square means ratio (90% CI [confidence interval]) for C_{min} and AUC_{12h} was 1.08 (0.69–1.69) and 1.11 (0.76–1.62), respectively. Intersubject PK variability was greater in children compared to adults, primarily as a result of one outlier. The range of exposures observed in children with the outlier removed was similar to that observed in adults. Exposure was not associated with age or body surface area (BSA). No serious adverse events (AEs) occurred;12 children reported at least one AE, mostly grade 1 or 2. Two children developed a rash (grade 1 and grade 2, respectively), both on Day 8 and resolving after 5–6 days; the AUC_{12h} in these children were 7408 and 1826ng•h/mL, respectively.

Introduction

- ETR is a next-generation NNRTI with potent in-vitro activity against both wild-type and NNRTI-resistant HIV-1[1]
- Two ongoing, randomized, double-blind, placebo-controlled, Phase III trials (DUET-1 and DUET-2) demonstrated significant and sustained antiviral efficacy after 48 weeks of treatment with ETR and background regimen including darunavir/ritonavir in treatment-experienced adults with NNRTI resistance. Treatment with ETR was generally safe and well tolerated[2,3]

Study objectives

- Primary objectives
  - to obtain steady-state pharmacokinetics of ETR in treatment-experienced HIV-1-infected children
  - to determine dose recommendations of ETR per kg body weight in HIV-1-infected children age 6–17 years, inclusive, and weighing ≥20kg
- Secondary objective
  - to evaluate short-term safety and tolerability of ETR in HIV-1-infected children

Study design

- Open-label trial in two sequential dosing stages

Stage I ETR 4mg/kg bid following a meal

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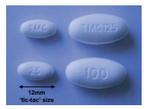
Stage II ETR 5.2mg/kg bid following a meal

- Each stage to enroll 20 HIV-1-infected children on a stable LPV/r-containing regimen and 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

Stage I dosing

Weight (kg)	Dose	Tablets
20–24.9	100mg bid	4 x 25mg bid or 1 x 100mg bid
25–34.9	125mg bid	5 x 25mg bid or 1 x 100mg + 1 x 25mg bid
35–39.9	150mg bid	6 x 25mg bid or 1 x 100mg + 2 x 25mg bid
40–44.9	175mg bid	7 x 25mg bid or 1 x 100mg + 3 x 25mg bid
≥45	200mg bid	8 x 25mg bid or 2 x 100mg bid

- 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
  - predose and 1, 2, 3, 4, 6, 8, 10 and 12 hours postdose
- Plasma concentrations of ETR were determined using a validated liquid chromatographic-tandem mass spectrometric method
  - lower limit of quantification: 2ng/mL
- PK analyses were performed using WinNonlin Professional (version 5.1; Pharsight Corporation, Mountain View, California, USA)

Interim statistical analysis

- PK parameter analysis
  - mean AUC_{12h} and mean C_{min} vs that obtained in HIV-1-infected treatment-experienced adults (80–125% CI)[4]
    - HIV-1-infected adults administered ETR 200mg bid on a stable LPV/r-containing regimen
- Safety analysis
  - AEs and laboratory abnormalities overall per age group
  - severity and relatedness of AEs to ETR
  - cardiovascular safety evaluation and physical examination

AUC_{12h} = area under the curve from time of administration to 12 hours after dosing
C_{min} = minimum plasma concentration

Baseline demographics

- 16 patients (eight male and eight female) completed Stage I
  - 10 patients ≥6 to <12 years
  - six patients ≥12 to ≤17 years
  - race/ethnicity
    - Caucasian: 11
    - Black: three
    - Hispanic: one
    - other: one

	Mean (SD)	Range
Weight (kg)	36.8 (15.2)	20–65
Height (cm)	142 (18.6)	120–180
BSA (m^2)	1.2 (0.3)	0.8–1.7

PK parameters in adults and children

Mean ± SD, t_{max}: median (range)	200mg bid adults (reference)[4]	4mg/kg bid children (test)
n	27	16*
C_{0h}, ng/mL	235.9 ± 163.1	263.8 ± 255.1
C_{min}, ng/mL	184.7 ± 128.1	233.2 ± 237.9
C_{max}, ng/mL	451.3 ± 232.3	555.2 ± 514.6
t_{max}, h	4.0 (2.0–8.0)	4.0 (3.0–8.0)
AUC_{12h}, ng•h/mL	3713 ± 2069	4788 ± 4459

*n=15 for AUC_{12h}

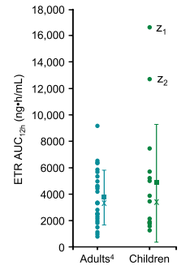
t_{max} = time to reach the maximum plasma concentration; C_{0h} = predose plasma concentration; C_{max} = maximum plasma concentration

PK comparisons between adults and children

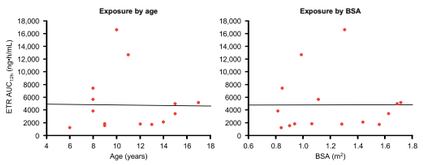
Least squares mean ratio (90% CI), %	Test (children) vs reference (adults)
n	16* vs 27
C_{min}	108.3 (69.49–168.8)
AUC_{12h}	110.8 (75.90–161.9)

*n=15 for test AUC_{12h}

- Similar median AUC_{12h} values (x): 3333 (adults) vs 3420 (children) ng•h/mL
- Comparable mean AUC_{12h} values (■): 3713 (adults) vs 4788 (children) ng•h/mL
- Comparable range of exposures
  - two apparent outliers in pediatric study increases overall variability
  - critical z = 2.55 for n=15
    - z_1 = 2.63 (outlier)
    - z_2 = 1.77 (not an outlier)



AUC_{12h} by age or BSA



- Exposure (AUC_{12h}) appears independent of age or BSA thus weight-based dosing of ETR is appropriate

Safety results

- Safety
  - two patients (12%) developed rash on treatment
    - grade 1 rash in 8-year-old male on Day 8 resolved after 5 days; AUC_{12h} = 7408ng•h/mL
    - grade 2 maculopapular rash in 9-year-old male on Day 8 resolved after 6 days; AUC_{12h} = 1826ng•h/mL
  - no other clinically relevant AEs or treatment-emergent laboratory abnormalities
  - no serious AEs or deaths were reported
  - no patients prematurely discontinued the trial

Conclusions

- ETR administered at 4mg/kg bid following a meal provides comparable exposure in children (age 6–17, inclusive) to 200mg bid in adults
- ETR was generally safe and well tolerated
  - two patients developed a transient rash of mild-to-moderate severity
  - no apparent association with ETR exposure (AUC_{12h})
- Given the general concern for under dosing of antiretrovirals in children[5,6] and lack of safety signal during Stage I, Stage II of this trial with a 30% higher dose (5.2mg/kg bid) was started and recruitment is ongoing
- A Phase II trial to further determine pharmacokinetics, safety and efficacy in treatment-experienced children will begin after final dose selection

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