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ETRAVIRINE PHARMACOKINETICS IN TREATMENT-EXPERIENCED CHILDREN AGES 1-<6 YEARS

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ABSTRACT

Background: IMPAACT P1090 is a Phase I/II study of etravirine (ETR) pharmacokinetics (PK), dose-finding, and safety in antiretroviral (ARV) treatment-experienced HIV-infected children 1 to <6 yrs from the U.S., South Africa (SA) and Brazil.

Methods: Treatment-experienced children on a failing ARV regimen for ≥8 wk or on a treatment interruption for ≥4 wk with a history of virologic failure (VF) were enrolled into one of two age cohorts (2-<6 yr; 1-<2 yr). ETR was combined with at least two active ARVs, one of which was a ritonavir-boosted protease inhibitor (PI/r). ETR was dosed by weight-band. Participants 8-<10 kg received 75mg twice daily [bid]; 10-<20 kg, 100mg bid; and 20-<25 kg, 125mg bid. Tablets were swallowed whole or dispersed in liquid. All participants underwent 12-hr PK sampling on day 14 (±4 days). Participants with ETR AUC12h <10th percentile of adults (<2350 ng*hr/mL) had an individual ETR dose increase and repeat PK. For each cohort, PK and safety were confirmed in the first six participants before further enrolling at the same dose. The target geometric mean ETR AUC12h was 2713 to 6783 ng*hr/mL (60-150% of adult AUC12h). Criteria for acceptable safety included no suspected adverse drug reaction resulting in death, life-threatening toxicity, any grade 4 event, or ≥3 participants discontinuing due to grade ≥3 toxicity.

Results: Twenty-one participants (nine each from SA and Brazil, three from U.S.) received ETR weight-band based doses. Demographics, ETR dosing and PK are shown for each cohort in the table. Both cohorts passed pre-determined PK and safety criteria, but seven (33%) children, all taking ETR dispersed, had an AUC12h of <2350 ng*hr/mL and underwent an ETR dose increase. Geometric mean ETR AUC12hr was significantly higher in participants that swallowed the tablet whole vs. dispersed, 10710 ng*hr/mL (n=4) vs. 2841 ng*hr/mL (n=16), respectively (p= <0.0001). After a median (range) follow-up of 62 (9-234) weeks, three (14%) participants (2/3 with day 14 AUC12h <2350 ng*hr/mL) have discontinued due to VF. One participant discontinued due to a treatment-related toxicity (grade 4 lipase).

	Cohort 1 (2-<6 yr), n=15	Cohort 2 (1-<2 yr), n=6
Demographics and ETR Dosing Parameters, median (range)		
Age at intensive PK, yr	4.8 (2.8, 5.9)	1.8 (1.5, 2.03)
Weight, kg	16.1 (12.5, 24.3)	10.4 (8.3, 13.3)
Body Surface Area (BSA), m^2	0.68 (0.55, 0.85)	0.48 (0.42, 0.55)
Dose, mg	100 (100, 125)	87.5 (75, 100)
PK Parameters, geometric means (%CV)		
AUC12h, ng*hr/mL	3823 (95%)	3328 (94%)
Cmax, ng/mL	466 (84%)	390 (89%)
Last measurable concentration (Clast), ng/mL	232 (124%)	225 (99%)
Individual ETR dose increase	5 (33%)	2 (33%)

Conclusions: Weight-band based ETR dosing achieved predefined AUC12h targets in HIV-infected children receiving an ARV regimen including a PI/r, but 33%, all taking dispersed tablets, had AUC12h <10th percentile of the adult AUC12h. To date, ETR is well-tolerated and the rate of VF in these 21 treatment-experienced children is low.

BACKGROUND

- Nevirapine and efavirenz, the two most widely used non-nucleoside reverse transcriptase inhibitors (NNRTI) globally, have a low genetic barrier for the development of resistance mutations.
- Nevirapine use to prevent mother to child and breastfeeding-associated transmission of HIV has led to NNRTI resistance in children.
- Alternative ARV options with activity against NNRTI-resistant virus are needed.
- Etravirine (ETR) is an NNRTI with regulatory approval for use in treatment-experienced adults and children > 6 years.
- P1090 is a Phase I/II, multicenter, open-label study designed to determine the pharmacokinetic (PK) profile, optimal dosage, safety and tolerability of ETR in treatment experienced HIV-infected children ages 1 to < 6 years old.

STUDY DESIGN

- Participants received ETR with at least two other active antiretroviral (ARV) agents including a ritonavir-boosted protease inhibitor (PI/r)
- Two cohorts were evaluated based on age
  - Cohorts opened sequentially once PK and safety were confirmed
    - → Cohort 1 – Children ages 2 - < 6 years old
    - → Cohort 2 – Children ages 1-< 2 years old

METHODS

ELIGIBILITY CRITERIA

- ARV experienced children on a failing regimen containing at least 3 ARVs for 8 weeks OR treatment experienced on a treatment interruption of at least 4 weeks with history of virologic failure
- Ability to swallow ETR whole or dispersed in appropriate liquid
- HIV-1 RNA > 1,000 copies/mL
- Ages 1 to < 6 years at study entry
- No evidence of phenotypic resistance to ETR at screening

DOSING

- Weight-band dosing
  - Participants 8 -<10kg received 75mg twice daily
  - Participants 10-<20kg received 100mg twice daily
  - Participants 20-<25kg received 125mg twice daily
    - Tablets were 25mg (scored) or 100mg; swallowed whole or dispersed in 5mL of water and further diluted (if desired) to 30mL with water, mineral water, orange juice, milk, or formula

PK ASSESSMENTS

- Intensive PK visits conducted on day 14 (±4)
  - ETR area under the concentration-time curve from 0 to 12 hours (AUC12h) determined from samples obtained at pre-dose, and 1, 2, 4, 6, 9 and 12 hours post-observed dose.
- INDIVIDUAL DOSE ADJUSTMENTS. Based on exposures in DUET studies
  - AUC12h >2350ng*hr/mL (10^{th} percentile AUC12h in adults) and tolerating - no dose adjustment necessary
  - AUC12h <2350 ng*hr/mL and participant tolerating; dose increased to target AUC12h of 2864 ng*hr/mL (20^{th} percentile AUC12h in adults)
    - Max dose following first low AUC12h is 200mg twice daily (adult dosing)
    - If second dose adjustment is required due to AUC12h <2350 ng*hr/mL dose can be increased above 200mg BID
  - AUC12h <2350 ng*hr/mL and participant NOT tolerating (e.g. Grade 3 or greater toxicity) subject will discontinue study
  - AUC12h >4380ng*hr/mL (median adult AUC12h in DUET) and participant NOT tolerating (e.g. Grade 3 toxicity) dose will be adjusted targeting an AUC of 4380ng*h/mL. If no dose reduction possible participant will discontinue study
- COHORT. The target geometric mean ETR AUC12h for each cohort is between 60% and 150% of the adult geometric mean ETR AUC12h from the DUET studies (between 2713 and 6783 ng*hr/mL)

DATA ANALYSIS

- ETR PK parameters presented are from intensive PK studies performed on day 14 (±4) prior to any PK-directed dose adjustments
- All PK data was log transformed to reduce the skew
- ETR AUC12h was determined using non-compartmental methods in Excel and dosing recommendation reported in real-time to study sites.
- Cmax, Tmax, and Clast were determined visually.
- CL/F was determined using non-compartmental methods in Phoenix (version 64, model 200-202, extravascular input).
- Log-transformed ETR AUC12h was compared between those receiving ETR tablets swallowed whole vs. dispersed using an unpaired t-test.

RESULTS

Table 1. Baseline Demographics

	Cohort 1 (2-<6 yr), n=15	Cohort 2 (1-<2 yr), n=6
Sex, n (%)		
• Female	7 (47)	3 (50)
• Male	8 (53)	3 (50)
Race, n (%)		
• Black or Black African	8 (53)	4 (67)
• Hispanic	7 (47)	2 (33)
Country, n (%)		
• South Africa	6 (40)	3 (50)
• Brazil	7 (47)	2 (33)
• United States	2 (13)	1 (17)
Age at intensive PK, yr; Median (Range)	4.8 (2.8, 5.9)	1.8 (1.5, 2.03)
Weight, kg Median (Range)	16.1 (12.5, 24.3)	10.4 (8.3, 13.3)
Body Surface Area (BSA), m^2 Median (Range)	0.68 (0.55, 0.85)	0.48 (0.42, 0.55)
Dose, mg Median (Range)	100 (100, 125)	87.5 (75, 100)
Administration at Intensive PK Visit, n(%)		
• Dispersed	11 (73)	5 (83)
• Swallowed whole	3 (20)	1 (17)
• Combination	1 (7)	0 (0)
Concomitant Protease Inhibitor, n(%)		
• Ritonavir-boosted lopinavir	8 (53)	6 (100)
• Ritonavir-boosted darunavir	6 (40)	0 (0)
• Ritonavir-boosted atazanavir	1 (7)	0 (0)
Baseline Viral Load Median (Range)	22431 (338-2445733)	25792 (1732-1040824)
Baseline CD4+ Cell Count Median (Range)	268 (179-2936)	1492 (388-2629)

Table 2. Geometric Mean (%CV) Pharmacokinetic Parameters

	Cohort 1 (2-<6 yr), n=15	Cohort 2 (1-<2 yr), n=6
AUC12h, ng*hr/mL	3823 (95%)	3328 (94%)
Cmax, ng/mL	466 (84%)	390 (89%)
Last measurable concentration (Clast), ng/mL	232 (124%)	225 (99%)
Tmax, h	4.5 (42%)	2 (75%)
CL/F, L/hr/m^2	41.13 (86%)	53.67 (83%)
Individual ETR dose increase required (AUC < 2350 ng*hr/mL)	5 (33%)	2 (33%)

Figure 1. Concentration Time Curves by Cohort

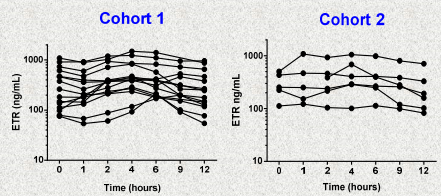

Figure 2. ETR AUC by Dosage Form

Geometric Mean AUC12h in participants who swallowed ETR whole was 10721 ng*hr/mL vs. 2841 ng*hr/mL in those receiving dispersed ETR (p<0.0001)

Table 3. Participant Discontinuations Due to Lack of Virologic Response

Cohort	ETR AUC at Day 14 (ng*hr/mL)	Reason for Discontinuation	Weeks at Study Discontinuation
2	3956	≤2 log10 reduction in HIV-1 RNA at week 48	60
2	1148*	≤1 log10 reduction in HIV-1 RNA from baseline at week 12	16
1	2241*	≤2 log10 reduction in HIV-1 RNA at week 24	24

*Participants had PK-guided ETR dose increases due to AUC12h < 2350 ng*hr/mL. Following ETR dose increase, AUC12h > 2350 ng*hr/mL.

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CONCLUSIONS

- Children receiving ETR exhibit considerable inter-patient variability in PK.
- Weight-band based ETR dosing achieved predefined AUC12h targets in HIV-infected children receiving an ARV regimen including a PI/r.
- 33% of participants, all of which were taking ETR tablets dispersed in liquid, had Day 14 (±4) AUC12h <10th percentile of the adult AUC12h (2350 ng*hr/mL).
- Three of 21 participants have discontinued to date for virologic reasons.
- This study is ongoing and additional data, specifically on efficacy and safety, will be presented separately.

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