ABSTRACT

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

METHODS

• Methods: Treatment-experienced children on a failing ARV regimen for 8 weeks or 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, and no evidence of phenotypic resistance to ETR at screening were enrolled. Participants were randomized to a weight band: 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-h PK sampling on day 14 (±4 days). Participants with ETR AUC12h <10th percentile of adults (>2350 ng*hr/mL) had Day 14 AUC12h <200ng*hr/mL. For each cohort, % NRTI suppression (defined as the last 2 log10 reductions in the week immediately prior to the last follow-up) was determined. The primary and key secondary endpoints were percentage of participants who passed PK and safety criteria, as well as mean ETR AUC12h in participants who swallowed ETR whole for each age band. Covariates for ETR AUC12h were last-measurable concentration, weight, and weight-to-height ratio. Summary statistics provided descriptive data analysis, and the percentage of participants who passed PK and safety criteria were compared between age bands using the unpaired t-test.

RESULTS

• 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-h PK sampling on day 14 (±4 days). Participants with ETR AUC12h <10th percentile of adults (>2350 ng*hr/mL) had Day 14 AUC12h <200ng*hr/mL. For each cohort, % NRTI suppression (defined as the last 2 log10 reductions in the week immediately prior to the last follow-up) was determined. The primary and key secondary endpoints were percentage of participants who passed PK and safety criteria, as well as mean ETR AUC12h in participants who swallowed ETR whole for each age band. Covariates for ETR AUC12h were last-measurable concentration, weight, and weight-to-height ratio. Summary statistics provided descriptive data analysis, and the percentage of participants who passed PK and safety criteria were compared between age bands using the unpaired t-test.

ACKNOWLEDGEMENTS

• We thank all of the members of the IMPACT P1000 team for their efforts and the outstanding clinical sites for their contributions and commitment to the trial. We owe a considerable debt of gratitude to the children and families who participated in this study.

REFERENCES

[1] IMPAACT P1090 is a Phase I/II study of etravirine (ETR) pharmacokinetics (PK), dosing and safety in treatment-experienced HIV-infected children aged 1 to 6 years in the United States (SA) and Brazil.

BACKGROUND

• Nevirapine and efavirenz, the two most widely used non-nucleoside reverse transcriptase inhibitors (NNRTIs) globally, have a low genetic barrier for the development of resistance mutations.
• Etravirine is an NNRTI that is active against NNRTI-resistant mutants and has a relatively high genetic barrier for resistance development.

STUDY DESIGN

• Participants received ETR for at least 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, age 1 to 6 years at study entry, and no evidence of phenotypic resistance to ETR at screening.
• Clinical and safety data were collected weekly for 14 days, and at day 14, participant tolerating; dose increased to target AUC12h of 2713 to 6783 ng*hr/mL.
• Conclusion: The target geometric mean ETR AUC12h for each cohort is 2713 to 6783 ng*hr/mL (60-150% of adult geometric mean AUC12h from the DUET studies (2713 to 6783 ng*hr/mL)). The CONCLUSIONS

• Children receiving ETR exhibit considerable inter-patient variability in PK. Weight-adjusted ETR dosing achieved predefined AUC12h targets in HIV-infected children receiving an ARV regimen including a PI.
• 33% of participants, all of which were taking ETR tablets dispersed in liquid, had Day 14 (x4) AUC12h<10th percentile of the adult AUC12h (2350 ng*hr/mL).
• Three of 21 participants have discontinued due to virologic reasons. This study is ongoing and additional data, specifically on efficacy and safety, will be presented separately.