Background: Current antiretroviral (ARV) treatment options for children co-infected with TB and HIV are limited. RIF induces UDP-glucuronosyltransferase activity accelerating the clearance of raltegravir (RAL). In adults, doubling the RAL dose partially overcame this PK interaction with no safety concerns. We sought to determine the optimal and safe dose of RAL when administered with RIF-containing anti-TB therapy in HIV-infected children.

Methods: P1101 is a dose finding study for RAL for HIV-infected children receiving RIF-containing anti-TB therapy for at least one week, with three age cohorts: Cohort 1: 2 to <6 years; Cohort 2: 6 to <12 years of age and Cohort 3: 4 weeks to <2 years (enrolling). Results from Cohort 1 are presented here. Each cohort requires n=12 evaluable participants for pharmacokinetics and safety assessments.

At enrollment, participants start 3 ARVs, including chewable RAL formulation at 12 mg/kg/dose twice daily (twice the recommended pediatric dose). Intensive RAL PK sampling is done 1 week after ARV therapy is initiated and then a 4th ARV is added. Clinical and lab assessments are routinely completed. RAL is stopped at TB treatment completion and children are followed for additional 3 mos. PK targets are a geometric mean (GM) AUC(0-24) of 14.45 µM*h and GM Cmax ≥ 75 ng/mL. Here we report the results from Cohort 1.

Results: Among 12 children, 7 (58%) were male, median age 3 years (IQR 2.5); baseline log10 RNA median 4.31 (IQR 4.42-5.42); median CD4 count 552 cells/µL (IQR 390-1185); median CD4 percent 15% (IQR 9-24). PK at Week 1 showed GM AUC(0-24) of 28.8 µM*h (50%); the GM Cmax was 229 nm (76%); 1/2 (8% with 95% CI 0%-34%) had a grade 3 elevation of ALT at Week 4 deemed possibly related to RAL. RAL/ART were temporarily withheld for 21 days and then restarted, with no subsequent recurrence. While RAL was held temporarily, this child did not achieve virologic success (>1 log10 drop from baseline at Week 8 or HIV RNA ≤400 copies/mL). 1/12 (92%) were virologically suppressed by Week 8, with 95% CI (62%, 100%). For n=12 at Week 8, median log10 RNA change from baseline was -3.16 (IQR -3.75 to -2.55); median CD4 change from baseline was 101 cells/µL (-70 to 230); median CD4 percent change from baseline was 6.1% (IQR 1.9-7.7).

Conclusions: A 12 mg/kg dose twice daily of the oral chewable formulation of RAL safely achieved PK targets in HIV-infected children 2 to <6 years with TB.

Abstract (as submitted)

• IMPAACT P1101 is a Phase III dose finding study for RAL for HIV-infected children receiving RIF-containing anti-TB therapy for at least one week.

• The 3 age cohorts include: Cohort 1: 2 to <6 years (closed); Cohort 2: 6 to <12 years of age (closed) and Cohort 3: 4 weeks to <2 years (enrolling). Results from Cohort 1 are presented here.

• Each cohort requires n=12 evaluable participants for pharmacokinetics and safety assessments.

• At enrollment, participants start 3 ARVs, including chewable RAL formulation at 12 mg/kg/dose twice daily (twice the recommended pediatric dose).

• Intensive RAL PK sampling is done 1 week after ARV therapy is initiated and then a 4th ARV is added. Clinical and laboratory assessments are routinely completed. RAL is stopped at TB treatment completion and children are followed for additional 3 mos. PK targets are geometric mean (GM) AUC(0-24) of 6-20 mg*h (14.45 µM) and GM Cmax ≥33 ng/mL. (275 nm).

• Virologic Success is defined as achieving at least 1 log10 copies/mL drop from baseline, or HIV RNA ≤ 400 copies/mL at Week 8.

• To determine the pharmacokinetics and appropriate dose of RAL when administered with RIF-containing anti-TB therapy in HIV/TB co-infected infants and children that generates PK parameters generally comparable to those seen in HIV-infected infants and children in the absence of RIF.

• To determine safety and tolerance of RAL-containing ART when administered with RIF-containing anti-TB therapy in HIV/TB co-infected children and infants.

Methods

• IMPAACT P1101 is a Phase III dose finding study for RAL for HIV-infected children receiving RIF-containing anti-TB therapy for at least one week.

• The 3 age cohorts include: Cohort 1: 2 to <6 years (closed); Cohort 2: 6 to <12 years of age (closed) and Cohort 3: 4 weeks to <2 years (enrolling). Results from Cohort 1 are presented here.

• Each cohort requires n=12 evaluable participants for pharmacokinetics and safety assessments.

• At enrollment, participants start 3 ARVs, including chewable RAL formulation at 12 mg/kg/dose twice daily (twice the recommended pediatric dose).

• Intensive RAL PK sampling is done 1 week after ARV therapy is initiated and then a 4th ARV is added (standard of care with TB treatment is added, usually efavirenz (EFV) or lopinavir/ritonavir (LPV/r)).

• Clinical and laboratory assessments are routinely completed.

• RAL is stopped at TB treatment completion and participants are followed for an additional 3 months.

• PK targets are geometric mean (GM) AUC(0-24) of 6-20 mg*h (14.45 µM) and GM Cmax ≥33 ng/mL (275 nm).

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Baseline Characteristics

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<table>
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Conclusions

• The burden of tuberculosis (TB) among HIV-infected adults and children is high in many resource-limited settings (RLS).

• Antiretroviral options for children co-infected with TB are limited because of drug interactions, especially with rifampicin-containing (RIF) TB regimens.

• Pediatric clinical trials for new drugs usually exclude TB co-infected children making it difficult to determine drug efficacy and safety in these co-infected children.

• RIF induces UDP-glucuronosyltransferase activity accelerating the clearance of raltegravir (RAL).

• In adults, doubling the RAL dose partially overcame this PK interaction with no safety concerns.

• We sought to determine the optimal and safe dose of RAL when administered with RIF-containing anti-TB therapy in HIV-infected children.

Safety Results

• Only one out of n=12 had an adverse event (AE) deemed at least possibly related to RAL.

• Participant: 3 year old male.

• At Week 4: Grade 3 AST and Grade 3 ALT elevations, assessed by the site and Protocol Team.

• Week 5: RAL and other ARVs were temporarily held for 2 weeks, then resumed RAL+ARVs, until the end of the study.

References


