Safety and pharmacokinetics of long-acting cabotegravir and rilpivirine in children 20 to <40 kg

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BACKGROUND

Long-acting cabotegravir (CAB-LA) plus long-acting rilpivirine (RPV-LA) are approved for maintenance of viral suppression in adults and adolescents ≥35 kg with HIV-1 infection. IMPAACT 2036 (CRAYON) is a Phase I/II, multi-center, open-label, non-comparative study to evaluate safety, tolerability, acceptability, and pharmacokinetics (PK) of oral (PO) CAB+RPV and intramuscular (IM) CAB-LA+RPV-LA in children 2 to less than 12 years living with HIV-1. Here we present the first report of CAB-LA+RPV-LA in children 20-<40 kg from the interim analysis Week (W)12 data.

METHODS

Virologically suppressed (viral load <50 copies/mL) children living with HIV-1 on stable combination antiretroviral therapy (cART) were enrolled into weight-band (WB) 1 (35-<40 kg), 2 (25-34.9 kg) or 3 (20-24.9 kg). Participants were recruited from sites in the United States of America, Brazil, Botswana, South Africa and Thailand. After discontinuing background cART, participants received PO CAB+RPV for 4 weeks, followed by CAB-LA+RPV-LA IM injections every 4 weeks (Q4W) starting at W4 as per WB dosing (**Table**). PK samples were drawn at W2 (to assess PO dosing) and W4, 5, 6, 8, 9, and 12 (to assess LA dosing).

Table. Weight band dosing for PO and IM CAB + RPV

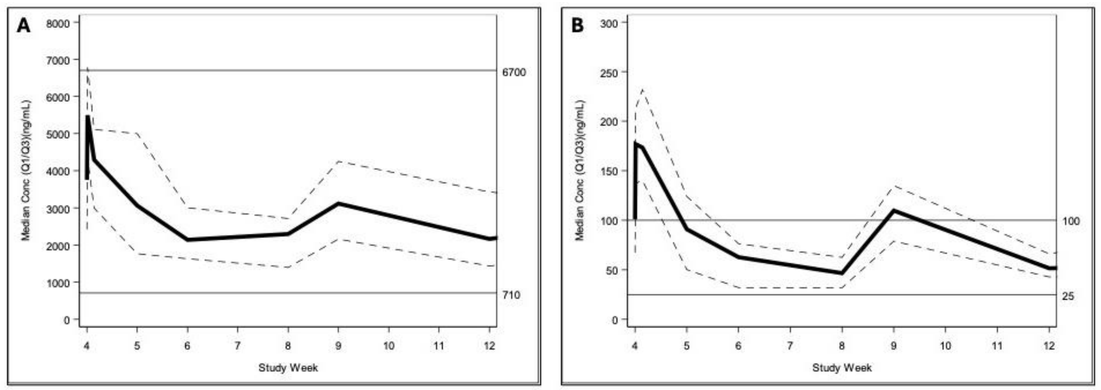
Weight Band	Daily Oral Dose (Oral lead-in)	Initial IMI Injection	Subsequent IMI Injection every four weeks
Weight Band 1 35-<40 kg	30mg CAB + 25mg RPV •• Administered as one 30mg CAB tablet + one 25mg RPV tablet	600mg CAB LA + 900mg RPV LA	400mg CAB LA + 600mg RPV LA
Weight Band 2 25-34.9 kg	10mg CAB + 25mg RPV •• Administered as two 5mg CAB DT + one 25mg RPV tablet	300mg CAB LA + 600mg RPV LA	200mg CAB LA + 450mg RPV LA
Weight Band 3 20-24.9 kg	10mg CAB + 15mg RPV •• Administered as two 5mg CAB DT + six 2.5mg RPV tablets	300mg CAB LA + 600mg RPV LA	200mg CAB LA + 450mg RPV LA

RESULTS

35 participants were enrolled: 8 in WB 1, 16 in WB 2, and 11 in WB 3; one WB 3 participant prematurely discontinued the study drug due to needle anxiety.

Long-acting Cabotegravir and Rilpivirine after an oral lead-in used in children 20 to <40 kg demonstrated no new or unanticipated safety concerns and achieved similar drug exposures to adults and adolescents

Figure 1. Pharmacokinetic evaluation of IM CAB-LA (**A**) and IM RPV-LA (**B**): **CRAYON/IMPAACT 2036**



Legend: median concentration (——) and 25th, 75th percentile (-----) of IM CAB-LA (**A**) and IM RPV-LA (**B**) and the protocol-defined PK acceptable criteria (minimum and maximum median pre-dose concentrations (——) evaluated at W12)

The safety analysis set included 20 children who completed treatment through W12 before the safety interim analysis freeze date. The median (Q1, Q3) age and weight were 10 years (8, 10.5) and 26.2 kg (22.2, 29.9); 60% were female; 25% were Asian, 75% were Black or African American.

Eight (40%) children had any adverse event (AE) through W12 with no Grade 4 or 5 AEs. Frequent AEs included injection site pain (n = 3, all Grade 1), headache (n = 3, all Grade 1), pyrexia (n = 2, all Grade 1), oropharyngeal pain (n = 2, all Grade 1) and cough (n = 2), all Grade 1. Three participants reported a total of 13 injection site reactions (ISRs) across their study visits. The most common AE was Grade 1 Injection site pain (n = 12) with one Grade 1 injection site swelling. One child (5%) had two Grade 3 AEs (elevated creatine phosphokinase and decreased neutrophil count) which resolved. All participants maintained virologic suppression through W12.

34 participants contributed to the PK analysis, with 24 completing W12 before the PK interim analysis freeze date. The median (25th, 75th percentile) AUCs during the oral lead-in were, for CAB-PO:109 (86,130) mcg*h/mL (n = 34) and RPV-PO: 3086 (2351-4440) ng*h/mL. The median (25th, 75th percentile) pre-dose concentrations at Week 12 (n = 24) were 2.16 (1.44,3.43) mcg/mL for CAB-LA and 52 (43,66) ng/mL for RPV-LAas shown in **Figure 1**. These values met protocol-defined targets for both drugs by PO and IM routes.

CONCLUSIONS

Administration of PO CAB+RPV followed by Q4W IM CAB-LA+RPV-LA in children 20-<40 kg through 12 weeks of treatment achieved exposure concentrations comparable to adolescents and adults receiving this regimen. No new or unanticipated safety concerns were identified.

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