Safety and pharmacokinetics of long-acting cabotegravir and rilpivirine in young children 10 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 <12 years of age living with HIV-1. Here, we present the interim safety and PK data from IMPAACT 2036 (CRAYON), including the first data from children <20 kg.

METHODS

Children living with HIV-1 who were on stable antiretroviral therapy (cART) and virologically suppressed (viral load <50 copies/mL) were enrolled into weight-band (WB): WB1 (35-<40 kg), WB2 (25-<35 kg), WB3 (20-<25 kg), WB4 (14<20 kg) and WB5 (10-<14 kg). Participants were recruited from sites in the United States of America, Brazil, Botswana, South Africa and Thailand. After discontinuing background cART, participants received once daily PO CAB + RPV as intact or pediatric dispersible tablets for 4 weeks, followed by CAB-LA+RPV-LA IM injections every 4 weeks (Q4W) as per WB dosing (**Table 1**). PK samples were drawn at W2 (to assess PO dosing) and W4, 5, 6, 8, 9, 12 and every injection visit up to W72 (to assess LA dosing). All adverse events (AEs) were reported, including post-injection reactions to RPV-LA, which may include respiratory symptoms, agitation, sweating, oral numbness, blood-pressure changes, and pain, which usually start to improve within minutes of the injection. All available data up to the 2nd interim analysis on the 16th July 2025 are presented here.

Table 1. Weight band 4 and 5 dosing for PO CAB+RPV and IM CAB-LA + RPV-LA **

Weight Band	Daily Oral Dose (Oral lead-in)	Initial IM Injection	Subsequent IM Injection every four weeks
Weight Band 4 14 -<20 kg	10 mg CAB + 12.5 mg RPV	300 mg (1.5ml) CAB-LA + 450 mg (1.5ml) RPV-LA	200 mg (1ml) CAB-LA + 300 mg (1ml) RPV-LA
Weight Band 5 10 -<14 kg	Administered as two 5 mg CAB tablet + five 2.5 mg RPV tablet		

** Dosing for Weight bands 1, 2, and 3 have been presented previously (M Archary, CROI, 2025). For WB1, the initial IM injection was 600mg CAB-LA + 900mg RPV-LA followed by 400mg CAB-LA + 600mg RPV-LA every 4 weeks. For WB 2/3, the initial IM injection was 300mg CAB-LA + 600mg RPV-LA, followed by 200mg CAB-LA + 450mg RPV-LA every 4 weeks.

Long-acting Cabotegravir and Rilpivirine after an oral lead-in used in children 10 to <40 kg demonstrated no new or unexpected safety concerns and the weight-band dosing achieved drug exposures comparable to adults and adolescents

Monthly injections of long–acting Cabotegravir and Rilpivirine can be used safely to treat young children with HIV

Figure 1. Predose CAB (A) and RPV (B) concentrations after IM CAB-LA and RPV-LA: CRAYON/IMPAACT 2036

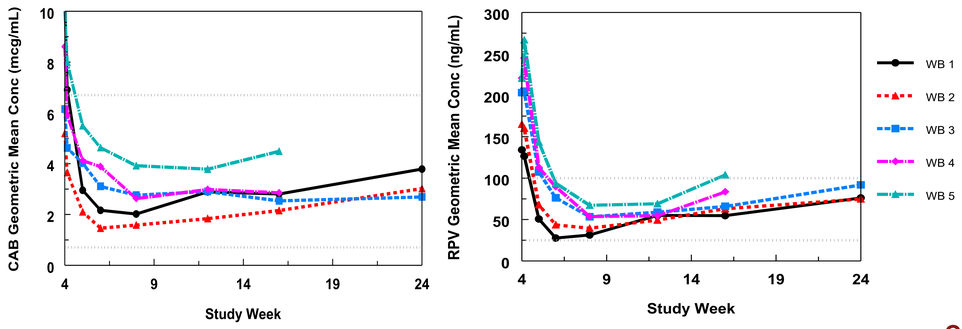

Figure 1 describes the median concentrations by weight-band of IM CAB-LA **(A)** and IM RPV-LA **(B)** and the protocol-defined PK acceptable criteria (minimum and maximum median pre-dose concentrations (…….) evaluated at W12)

RESULTS

61 participants were enrolled (8 in WB1, 18 in WB2, 13 in WB3, 9 in WB4 and 13 in WB5). The median (min, max) age and body weight at entry were 8 years of age (2, 11) and 22 kg (10.8, 39.3); 54% were female; 23% were Asian, 62% were Black.

Median (Q1, Q3) time on study was 57 weeks (28, 70). Three participants prematurely discontinued due to withdrawal of consent (n=2) and virological failure on PO CAB+RPV with a peak viral load of 573 copies/ml (n=1). All other participants remained virally suppressed during the study period.

51 participants contributed to the PK analysis (**Figure 1**). WB1-3 PK have been previously reported (M Archary, CROI, 2025). In 18 WB4-5 participants, the median (Q1, Q3) AUCs during oral lead-in were 166.0 (133.5, 219.6) mcg*h/mL for CAB-PO and 3856 (2533,4407) ng*h/mL for RPV-PO. Median (Q1, Q3) pre-dose concentrations at W12 (n=13) were 3.49 (2.67, 4.72) mcg/mL for CAB-LA and 61.3 (49.4, 68.5) ng/mL for RPV-LA. These values met protocol-defined targets for both drugs by PO (median W2 AUC between 38 and 277 mcg*h/ml for CAB and 1250 and 4166 ng*h/mL for RPV) and IM (median W12 trough 0.71-6.7 mcg/mL for CAB and 25-100 ng/mL for RPV) routes.

While on study, 6 (10%) children experienced ≥ Grade 3 adverse event (AE), all of which resolved. One ≥ Grade 3 AE was drug-related (Grade 3 post-injection reaction). Two additional children had a Grade 2 post-injection reactions. All 3 participants continued the study treatment. Injection site pain in 28 children (46%) was the most frequent AE. All injection site reactions (ISRs) are shown in **Table 2**. No AEs led to treatment discontinuation.

Table 2. Number of participants with Injection site (IS) reactions

Adverse Event	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Total n (%)
IS pain	24 (39.3)	4 (6.6)	0	28 (45.9)
IS swelling	7 (11.5)	1 (1.6)	0	8 (13.1)
IS erythema	3 (4.9)	0	0	3 (4.9)
IS induration	2 (3.3)	1 (1.6)	0	3 (4.9)
IS nodule	2 (3.3)	0	0	2 (3.3)
IS pruritus	2 (3.3)	0	0	2 (3.3)
IS haematoma	1 (1.6)	0	0	1 (1.6)

CONCLUSIONS

Administration of PO CAB+RPV for 4 weeks, followed by IM CAB-LA+RPV-LA Q4W in children weighing 10-<40 kg from the CRAYON study, achieved CAB and RPV plasma concentrations and exposure in line with expectations based on adolescent and adult populations. No new or unanticipated safety concerns were identified. Grade 1 or 2 injection site pain was the most common AE.

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