Use of *Cabenuva* in Adolescents and Children with HIV

Summary

- IMPAACT 2017 (MOCHA) is an ongoing phase 1/2 study evaluating *Cabenuva* (long-acting cabotegravir and rilpivirine [CAB + RPV LA]) in HIV-1 infected, virologically suppressed adolescents aged 12 to < 18 years old.[1]
    - Plasma trough concentrations of both CAB and RPV (dosed every-4-weeks [Q4W] and every-8-weeks [Q8W]) were similar to those reported for adults when administered at the same dose.[1-3]
    - Injection site reactions (ISRs) were the most common adverse event reported; 30% and 34% of participants reported at least one ISR at Weeks 24 and 48, respectively. Most were Grade 1 or 2 in severity.[1-3]
    - In Cohort 2, where participants received CAB + RPV LA Q8W as their only antiretroviral therapy (ART), 99% and 100% of participants remained virologically suppressed (HIV-1 RNA < 50 copies/mL) at Weeks 24 and 48, respectively.[2,3]
- IMPAACT 2036 (CRAYON) is a phase 1/2 study evaluating CAB + RPV LA Q4W in HIV-1 infected, virologically suppressed children aged 2 to < 12 years old.[4]
    - An interim analysis at Week 12, in children 20 to 40 kg, reported no new safety concerns and pharmacokinetic results similar to adults and adolescents.
    - All participants maintained virologic suppression through Week 12.
- CAB + RPV LA is only approved in adolescents 12 years or older and ≥ 35 kg; there is no dosage adjustment necessary.[1]
- Important Safety Information can be found in the Prescribing Information and can also be accessed from Our HIV Medicines.

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IMPAACT 2017 (MOCHA)

The pharmacokinetics and safety of CAB LA and RPV LA for the treatment of HIV-1 infection are being assessed in an ongoing phase 1/2 multicenter, open-label, non-comparative study which included virologically suppressed adolescents (aged 12 to < 18 years) weighing at least 35 kg (IMPAACT 2017 [MOCHA]).[1]

Cohort 1[1]

In Cohort 1, participants received an oral lead-in of oral CAB 30 mg once daily, or oral RPV 25 mg once daily, for approximately 1 month. Participants then received standard adult doses of either Q4W or Q8W CAB LA (Cohort 1C) or RPV LA (Cohort 1R) while continuing background antiretroviral therapy (ART).

Data are available from the Week 16 analysis. Thirty adolescents were included in Cohort 1C and 25 in Cohort 1R.

At baseline in Cohort 1C, the median (interquartile range [IQR]) age of participants was 15 years (14, 16), 43% had a baseline weight ≥ 50 kg, 47% were female, and 70% were Black/African American.

At baseline in Cohort 1R, the median (IQR) age of participants was 16 years (15, 17), 60% had a baseline weight ≥ 50 kg, 48% were female, and 84% were Black/African American.

Trough plasma concentrations of CAB and RPV at Week 16 were similar to what has been reported for CAB + RPV LA in adults. The median (range) Week 16 concentrations for Q4W and Q8W CAB LA and RPV LA were 3.11 µg/mL (1.22–6.19), 1.15 µg/mL (< 0.025–5.29), 52.9 ng/mL (31.9–148), and 39.1 ng/mL (27.2–81.3), respectively. These concentrations exceeded the minimum target concentration for this study for both CAB (0.71 µg/mL) and RPV (25 ng/mL).

In adolescents 12 years or older and weighing ≥ 35 kg there is no dosage adjustment necessary.

ISRs were reported in 30% of participants in Cohort 1C (pain) and 36% in Cohort 1R (pain, nodule, swelling, hypoaesthesia). There was 1 permanent discontinuation from the Cohort 1R due to a grade 3 acute allergic reaction (self-limiting urticaria) after the first dose of oral RPV.

Most participants (89%) remained virologically suppressed at each study visit until Week 16. During long-term safety follow up, 2 participants (1 from each cohort) had an HIV-1 RNA ≥ 200 copies/mL at Week 48 which was attributed to suboptimal oral ART intake.

Cohort 2[2]

In Cohort 2, background ART was no longer allowed and participants received both CAB + RPV LA (600 mg/900 mg) Q8W as treatment for HIV-1. The primary outcome was safety, including all adverse events, at Week 24. Forty-four participants rolled over from Cohort 1 and 100 additional participants naïve to CAB + RPV LA were included.

Overall, the median (range) age was 15 years (12–17), 51% were female, and 74% were Black or African American. The median (IQR) weight was 49 kg (44, 55) and CD4 count was 740 (594, 964).

Week 24[2]

At Week 24, 142/144 participants received at least one injection. Overall, 30% of participants reported any ISR and 106 total ISRs were reported; all were Grade 1 (92.5%) or Grade 2 (7.5%). Most resolved within 7 days (92%). The proportion of participants reporting an ISR generally decreased over time after the first injection. No participants withdrew from the study due to an ISR. The most common ISRs reported were pain (30%), swelling (2%), and nodule (1%).

In the evaluable analysis population (n = 139), virologic success (HIV-1 RNA < 50 copies/mL) was reported in 99% (n = 137/139) of participants; the remaining two participants had HIV-1 RNA < 200 copies/mL.

One participant had a positive pregnancy test during the study period and received two injections of CAB + RPV LA prior to discontinuation. The participant delivered a liveborn infant at 39 weeks.

At Week 24 (n = 139), median CAB and RPV trough concentrations were 2.34 µg/mL (90% CI 1.11 to 4.15) and 49.5 ng/mL (90% CI 25.9 to 78.1), respectively. Drug concentrations were similar to those observed in adults from the LATTE-2 and ATLAS-2M studies and were consistent with concentrations at Weeks 8 and 16.

Week 48[3]

Overall, 140 participants completed the Week 48 visit. Drug-related adverse events were reported in 37% (53/144) of participants, none of which were serious adverse events. Adverse events Grade 3 or higher occurred in 2 participants (injection site pain and abscess [n =1] and injection site abscess [n = 1]); both participants continued on treatment. One participant was reported to experience an anaphylaxis reaction and discontinued treatment; the Clinical Management Committee conducted an independent assessment and determined this was consistent with a post-injection reaction rather than anaphylaxis.

Thirty-four percent (48/142) of participants reported experiencing at least one injection site reaction (ISR). Most ISRs were Grade 1 (90%) and 89% resolved within 7 days.

Median (Q1–Q3) plasma concentrations (pre-dose) for CAB LA and RPV LA were 2.77 µg/mL (1.99–3.55) and 67.9 ng/mL (52.8–82.4), respectively. These concentrations were similar to concentrations observed in adults and were above the protein-adjusted IC_{90} for each medication.

At Week 48, 140 participants had a viral load assessment; all patients were virologically suppressed (HIV-1 RNA < 50 copies/mL). According to the FDA Snapshot analysis, 97% of participants had virologic success. No confirmed virologic failures occurred (2 consecutive HIV-1 RNA levels ≥ 200 copies/mL).

All participants who responded to the Preference Questionnaire (n = 140) preferred LA injections to daily oral therapy.

IMPAACT 2036 (CRAYON)

IMPAACT 2036 (CRAYON) is a phase 1/2, multicenter, open-label, non-comparative study to evaluate the safety, tolerability, acceptability, and pharmacokinetics of oral CAB + RPV and CAB + RPV LA in children 2 to < 12 years of age living with HIV-1.[4] Interim data at Week 12 in children 20 to < 40 kg were presented.

Children living with HIV who were virologically suppressed (HIV-1 RNA < 50 copies/mL) were enrolled into three different weight-bands (WB).[4] Background ART was discontinued and participants received oral CAB + RPV for 4 weeks, followed by CAB + RPV LA Q4W; dosing was based on the WB (Table 1).

Table 1. Weight Band Dosing for Oral and IM CAB + RPV

Weight Band	Daily Oral Dose (oral lead-in)	Initial IM Injection	Subsequent IM injection Q4W
Weight Band 1 (35 to < 40 kg)	30 mg CAB (one 30-mg CAB tab) + 25 mg RPV (one 25-mg RPV tab)	600 mg CAB LA + 900 mg RPV LA	400 mg CAB LA + 600 mg RPV LA
Weight Band 2 (25 to 34.9 kg)	10 mg CAB (two 5-mg CAB DT) + 25 mg RPV (one 25-mg RPV tab)	300 mg CAB LA + 600 mg RPV LA	200 mg CAB LA + 450 mg RPV LA
Weight Band 3 (20 to 24.9 kg)	10 mg CAB (two 5-mg CAB DT) + 15 mg RPV (six 2.5-mg RPV tabs)	300 mg CAB LA + 600 mg RPV LA	200 mg CAB LA + 450 mg RPV LA

CAB = cabotegravir; DT = dispersible tablet; IM = intramuscular; LA = long-acting; Q4W = every 4 weeks; RPV = rilpivirine; Tab = tablet

PK samples were obtained at Weeks 2 (to assess oral dosing), 4, 5, 6, 8, 9, and 12.[4]

Overall, 35 participants were enrolled (WB1, n = 8; WB2, n = 16; WB3, n = 11); one participant in WB3 prematurely discontinued the study due to "needle anxiety."[4]

The interim safety analysis included participants who completed treatment through Week 12 (n = 20 children).[4] Median (IQR) age and weight were 10 (8, 10.5) years and 26.2 (22.2, 29.9) kg, respectively. Most were female (60%) and Black/African American (75%).

Any adverse event was reported in 40% (n = 8) of participants through Week 12; no AEs were Grade 4 or 5.[4] The most common AEs included: injection site pain (n = 3), headache (n =3), pyrexia (n = 2), oropharyngeal pain (n = 2), and cough (n = 2); all were Grade 1. Thirteen ISRs were reported (by 3 participants), including Grade 1 injection site pain (n = 12) and swelling (n = 1). One participant had two Grade 3 AEs (elevated creatine phosphokinase and decreased neutrophil count), both of which resolved.

Through Week 12, all participants maintained virologic suppression.[4]

The PK analysis included 34 participants, 24 of which completed Week 12.[4] For both the oral and IM routes, the protocol-defined targets were met. During the oral lead-in, median (IQR) area under the cure (AUC) values for oral CAB and RPV were 109 (86, 130) mcg*h/mL and 3086 (2351, 4440) ng*h/mL, respectively. Median (IQR) pre-dose concentrations at Week 12 (n = 24) during the injection phase for CAB LA and RPV LA were 2.16 (1.44, 3.43) mcg/mL and 52 (43, 66) ng/mL, respectively. These values met the protocol-defined targets for both routes of administration and that drug exposure was similar to what has been reported previously for adults and adolescents.

This information is scientific and non-promotional in nature and is not intended for further distribution.

The described use of this product has not been approved by the FDA; therefore, no conclusions should be drawn about the safety or efficacy of this product. This information is not intended to offer recommendations for using this product in a manner inconsistent with its approved labeling. Please consult the applicable Prescribing Information. For ViiV Healthcare to monitor the safety of our products, we encourage healthcare professionals to report adverse events or suspected overdoses to the company at 877-844-8872.

Selection of references follows principles of evidence-based medicine and, therefore, references may not be all inclusive.

REFERENCES

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