Project Brief: IMPAACT 2036 CRAYON STUDY

Full Title of Study/Programme	Phase I/II Study of the Safety, Tolerability, Acceptability, and Pharmacokinetics of Oral and Long-Acting Injectable Cabotegravir and Rilpivirine in Virologically Suppressed Children Living with HIV-1, Two to Less Than 12 Years of Age
Technical Focus Area	Research Pediatric
Rationale	Rationale IMPAACT 2036 is a Phase I/II study to propose the weight-band dosing of oral cabotegravir (CAB)+ oral rilpivirine (RPV) followed by long-acting injectable CAB (CAB LA) + long-acting injectable RPV (RPV LA) and assess the long-acting injectable regimen with and without an oral lead-in period in virologically suppressed children living with HIV-1, two to less than 12 years of age and weighing ≥10 kg and <40 kg. Both the European Medicines Authority (EMA) and United States Food and Drug Administration (FDA) have determined that the CAB LA + RPV LA regimen would not provide a significant therapeutic benefit over existing therapies in children less than two years of age and they will, therefore, not be included in the study population for IMPAACT 2036.The CAB LA and RPV LA formulations provide prolonged drug exposures, resulting from gradual release from the IM injection, that exposes the injected individual to detectable levels of cabotegravir and rilpivirine for up to 52 weeks or longer after an injection. An oral lead-in period of daily oral CAB and RPV prior to injectable administration, with serial safety assessments, can allow identification of any acute toxicity prior to administration of a non-dialysable, non-removable depot injection. A similar oral lead-in period was initially employed in previous trials in adults using these LA formulations. Throughout the course of the clinical development program for CAB LA and RPV LA, including the large Phase 3/3b trials FLAIR, ATLAS and ATLAS-2M, an oral lead-in phase of cabotegravir (30 mg) along with rilpivirine (25mg), administered daily for 30 days, was an integral component of these trials and allowed for a safety assessment before study participants were allowed

	to advance to the LA phase of these studies. As a result, all study participants underwent a onemonth period of oral dosing with CAB/RPV followed by an evaluation of safety labs, and if labs were within normal limits, participants were allowed to transition into LA dosing. PK and safety data are necessary with the oral dosing to support labeling of an appropriate oral dose for children.The oral lead-in period in Cohort 1 will provide uninterrupted study product coverage while awaiting the Week 4 safety laboratory test results, which will determine eligibility for receiving the LA formulations. The safety assessment is done towards the end of the 4-week oral lead-in and, for clarity, has been named the visit 4a. Safety lab results from the 4a study visit will be reviewed and, if appropriate, the next visit will be scheduled as soon as possible to administer the first study injections; this next visit has been named visit 4b. This nomenclature has been adopted to promote consistency across the CAB/RPV studies and allow for clearer interpretation and comparisons. Given a participant population with a history of durable viral load suppression at and prior to study entry, together with a viral load assessment at the 2-week visit, and questionable clinical meaningfulness of a single HIV-1 viral load blip, a repeat HIV-1 viral load assessment is not part of the laboratory assessments done at visit 4a to approve giving the first study injection at visit 4b. A HIV-1 viral load sample is collected at visit 4b to time with the first injections.Rationale for Cohort 2 optional oral lead-in and duration of follow-up .Subsequent findings from adult trials with CAB and RPV demonstrated that the LA formulations can be safely administered without an oral lead-in. This has resulted in regulatory approval to administer CAB LA + RPV LA to adults with or without an optional oral lead-in. The FLAIR 124-week Extension Phase data showed that after 24 weeks of treatment, switching to LA treatment with or without an oral lead-in phase had similar safety, tolerability, and efficacy, supporting future evaluation of the simpler direct-to-injection approach. As a result of the accumulated safety data which has been generated, the safety of oral CAB and RPV during these four weeks of oral lead-in was not significantly different than at any other time during the FLAIR/ATLAS studies. The FDA and EMA have approved CAB LA + RPV LA to be administered with or without oral lead-in for adults based on the results of the 201584 FLAIR study. The FDA has also approved the oral lead-in to be optional for adolescents. The purpose of Cohort 2 is to incorporate giving study participants the choice to decide between starting with an oral lead-in or initiating a direct to injection regimen with CAB LA and RPV LA

	(optional oral lead-in) in this component of the study. The FLAIR 124-week Extension Phase data showed that after 24 weeks of treatment, switching to LA treatment with or without an oral lead-in phase had similar safety, tolerability, and efficacy, supporting future evaluation of the simpler directto-injection approach (19). As a result of the accumulated safety data generated, the safety of oral CAB and RPV during these four weeks of oral lead-in was not significantly different than at any other time during the FLAIR/ATLAS studies. Cohort 2a includes an oral lead-in period, while Cohort 2b does not. This decision to dose with or without an oral lead-in will be determined by the study participant, their parent/caregiver, and any consulting healthcare providers, following parental permission and informed assent discussions with the investigator. While Cohort 1 will provide data to support the regulatory approval of CAB/RPV in this population, it is anticipated that Cohort 2 will add to the existing adult data to support the realworld implementation of CAB/RPV where persons living with HIV will be given the choice for an optional oral lead-in. Cohort 2 will include approximately 48 or 44 weeks of follow-up for Cohort 2a and 2b respectively; as Cohort 2a participants will receive the oral study product, their on-study period will be approximately 4-6 weeks longer than Cohort 2b. This follow-up period will allow for an adequate evaluation of safety and PK in the Cohort 2 participant population without unnecessarily extending the overall duration of the study. Both Cohort 2a and Cohort 2b participants will have the same number of injections over the course of study participation. Cohort 2 study objectives reflect the duration of the study treatment, duration of study follow-up, and timing of study visits. Rationale for staggered enrollment in Cohort 1.There is currently a robust database with CAB and RPV, albeit there are few data on participants below 50 kg in weight, though the MOCHA study evaluates CAB+RPV in adolescents weighing at least 35kg. A staggered enrollment is proposed to allow for a safe and gradual introduction of the CAB LA + RPV LA regimen in early childhood. The largest three weight bands, Weight Bands 1(35-<40 kg), 2 (25-34.9 kg), and 3 (20-24.9 kg), will be initially opened for enrollment and a Week 12 interim analysis (minimum n=8 dose-evaluable, with at least 2 dose-evaluable participants in Weight Band 3) will be conducted to evaluate CAB LA + RPV LA in these upper weight-bands before opening enrollment to the remaining two weight-bands, Weight Bands 4 (14-19.9 kg) and 5 (10-13.9 kg).

	As long as no safety concerns are noted, enrollment in the first three weight bands to open will continue while an ongoing assessment of PK is made. The priority population in IMPAACT 2036 (two to less than 12 years old) presents a wide range in physiological parameters including BMI and body weight. It is relatively easy to adjust dosing for oral components based on body weight. However, BMI, body composition, and muscle mass among others, may have a considerable impact on drug absorption from the injection site with the longacting intramuscular route of administration and present some additional challenges when extrapolating to the two to less than 12-year-old population. Changes in absorption from the injection site with LA can significantly alter drug concentrations. Drug absorption from the IM route could, for example, be faster in children than in adults, although the extent may depend on drug formulation, injection volume, injection site etc. Rationale for Cohort 1 interim analyses and the related components of the study design. The first interim analysis will be conducted once a minimum of 8 dose-evaluable participants across Weight Bands, 1, 2, and 3 (with at least 2 participants in Weight Band 3) have completed Week 12. The PK and safety data from this first interim analysis will support the determination of the appropriate frequency and dose of CAB LA + RPV LA for the remaining participants enrolled in Weight Band 1, 2, and 3, and will allow the opening of Weight Bands 4 and 5 for accrual. A second Week 12 interim analysis will be conducted including the safety and PK from participants in Weight Bands 3, 4, and 5 (minimum n=8 dose-evaluable across Weight Bands 3, 4, and 5, with at least 2 dose-evaluable participants in the Weight Band 5) through their Week 12 visit. The PK and safety Cohort 1 interim analyses will support the determination of the appropriate frequency and dose of CAB LA + RPV LA for remaining participants enrolled in the study. The proposed single-arm study design is consistent with and responsive to HIV-1 pediatric regulatory guidance from the EU and US, which allows extrapolation of adult efficacy data. The Week 24 safety assessment time point will serve as the primary endpoint for the study. However, safety, acceptability, PK and antiviral activity will continue to be assessed through Week 72 with related study endpoints at Weeks 24, 48 and 72. These data will provide important information on the short term and long term, (through 72 weeks) use of this two-drug injectable ART in children. Rationale for allowing different administration methods for CAB DT and RPV 2.5 mg tablets in Cohort 2a

	Some children may prefer to swallow the pediatric formulation tablets (CAB DTs and RPV 2.5 mg tabs) whole. This is an option used for other pediatric formulation tablets (e.g., dolutegravir dispersible tablets SmPC at Tivicay, INN-dolutegravir [europa.eu]) To possibly expand the options of taking the CAB and RPV pediatric formulation tablets, the option to take the tablets swallowed whole with drinking water (direct-to-mouth) will be explored in this study in Cohort 2a and preliminary analysis of the differences of exposure between the routes of administration will be conducted when data emerges. Rationale for social-behavioral assessments, including qualitative in-depth interviews In the FDA's 2017 guidance document on patient-focused drug development, patient experience data is recommended as critical to "robust, meaningful, sufficiently representative patient input to inform medical product development and regulatory decision making". In the context of this study, the first to evaluate a long-acting injectable regimen for the treatment of HIV-1 in young children,assessments of acceptability (e.g., preferences, likability, satisfaction, costs/benefits and recommendations) and tolerability can provide much needed context for better understanding experiences with the treatment regimen. Furthermore, given the young age of the participant population in this study, collecting acceptability and tolerability from participants alone may not be sufficient or even possible in some cases; as the primary decision-makers around HIV-1 treatment options for their children, the experiences of parents/caregivers of child participants are essential to understand as well. This study will use a mixed-methods approach to gather participant experience data that includes brief staff-collected questionnaires for parents/caregivers of all participants and for participants who meet age eligibility requirements specified. Semi-structured in-depth interviews (IDIs) with a subset of enrolled parents/caregivers to expand upon the themes explored in the questionnaires. For Cohort 2, qualitative IDIs will also include an exploration of how and why the decision to join Cohort 2a or Cohort 2b was made. Qualitative work is important in populations where experience is limited and there is reason to believe that interests and behaviors could be different than previously studied populations (i.e., adult/adolescents vs. children). In this case, there is a lack of qualitative data on the topic of a long-acting injectable, repeat dose medicine in young children. The caregiver will have tremendous influence on the healthcare of the child, so understanding their interests and the driving force behind their behaviors is key. Such data will also provide nuance to the validity and relevance of the questions asked in the quantitative questionnaires. In addition, by

	incorporating both quantitative and qualitative components in a single study, we can integrate (mix) findings to address inherent limitations in each of the methodologies when used in isolation
Primary Objectives	Primary Objectives: Cohort 1 The primary objectives of this cohort are to: To describe the repeat-dose pharmacokinetics of CAB + RPV (oral and injectable) through Week 24 To assess the safety of the oral lead-in of CAB + RPV, and the safety of CAB + RPV (oral and injectable) through Week 24
Secondary Objectives	**2 Secondary Objectives: Cohort 1** The secondary objectives of this cohort are to: To assess the safety of CAB + RPV (oral and injectable) through Week 48 and through Week 72 To describe the repeat-dose pharmacokinetics of injectable CAB LA + RPV LA through Weeks 48 and 72 To assess the maintenance of viral suppression of CAB + RPV (oral and injectable) through Weeks 24, 48, and 72 To evaluate the tolerability and acceptability of injectable CAB LA + RPV LA through Weeks 24, 48, and 72 To describe HIV-1 genotypes and phenotypes for children who experience virologic failure during study treatment To assess immunologic activity of CAB + RPV (oral and injectable) through Weeks 24, 48, and 72 **Secondary Objectives: Cohort 2** To describe tolerability and acceptability of 48 weeks of CAB + RPV (oral and injectable) and 44 weeks of CAB LA + RPV LA (injectable only) IMPAACT 2036, Version 1.0 Page 35 of 226 22 September 2022 To describe the safety and repeat-dose pharmacokinetics of 48 weeks of CAB + RPV (oral and injectable) or 44 weeks of CAB LA + RPV LA (injectable only) To describe the maintenance of viral suppression and immunologic activity of 48 weeks of

	CAB + RPV (oral and injectable) or 44 weeks of CAB LA + RPV LA (injectable only) To describe HIV-1 genotypes and phenotypes for children who experience virologic failure during 48 weeks of CAB + RPV (oral and injectable) or during 44 weeks of CAB LA + RPV LA (injectable only)
Primary Endpoint/Outcome	• PO dosing: Wk. 2 AUC, CL/F, Cmax, Tmax, and pre10.2.1.1 -dose concentrations (C0) • LA dosing (starting at Week 4b): Wk. 5 concentrations (C5WK), Wk. 12 concentrations (C12WK), trough concentrations (Ct) prior to IM doses through Wk. 24 and accumulation ratio (Wk. 24:Wk. 8).
Secondary Endpoint/Outcome	**<u>COHORT 1</u>** • LA dosing: Ct prior to IM doses at Wk. 48 and Wk. 72 and accumulation 10.2.2.1 ratios (Wk. 48:Wk. 8 and Wk. 72:Wk. 8). **<u>COHORT 2</u>** Cohort 2a LA dosing: Ct prior to IM doses through Wk. 24 and Wk. 48 and accumulation ratios (Wk. 24:Wk. 8 and Wk. 48:Wk. 8). Cohort 2b LA dosing: Ct prior to IM doses through Wk. 20 and Wk. 44 and accumulation ratios (Wk. 20:Wk. 4 and Wk. 44:Wk. 4).
Study Design	This is a Phase I/II, multicenter, open-label, non-comparative study to evaluate the safety, tolerability, acceptability, and PK of oral CAB and oral RPV followed by long-acting injectable CAB (CAB LA) and long-acting injectable RPV (RPV LA) to propose the weight-band dosing in virologically suppressed children living with HIV-1 aged two to less than 12 years. The study will also assess the long-acting injectable regimen with and without an oral lead-in period in the same study population. This study will be conducted among up to 90 children weighing ≥10 kgs and <40 kgs, who are virologically suppressed on stable ART. Approximately 90 parents/caregivers of child participants will also enroll to complete tolerability and acceptability assessments. In-depth qualitative interviews with a subset of enrolled parents/caregivers will also be conducted. Unless otherwise noted, the term 'participant' will refer to the children enrolled in the study. Participants and caregivers will be enrolled at selected study sites. The study will include two discrete cohorts.

	Cohort 1 will open to accrual first. In Cohort 1, participants will be enrolled across five weights bands as follows: Weight Band 1 (35-<40kg), Weight Band 2 (25-34.9kg), Weight Band 3 (20-24.9kg), Weight Band 4 (14-19.9kg), and Weight Band 5 (10-13.9kg). At least 50 evaluable participants will be enrolled in Cohort 1. At least 18 evaluable participants will enroll across Weight Bands 1 and 2 and at least 32 evaluable participants will enroll across Weight Bands 3, 4, and 5. Additionally, at least 6 evaluable participants will be enrolled in each of the four highest weight bands (Weight Bands 1, 2, 3, and 4). At least 10 evaluable participants will be enrolled in the lowest weight band (Weight Band 5). Two interim analyses will be conducted in Cohort 1, as further described in Section 3.2, to assess whether any dosing regimen modifications are indicated per weight band. If a dose modification is indicated following the results of either interim analysis, accrual into the relevant weight band(s) will be paused pending the outcome of an SMC review. The first interim analysis will also determine the opening of Weight Bands 4 and 5 to accrual. Once Weight Bands 4 and 5 are opened, accrual will continue until all sample size targets within and across weight bands are met and the overall Cohort 1 sample size target is reached. The protocol team will routinely review accrual progress and provide guidance to ensure accrual targets are met. Additional details will also be provided in the study-specific MOP. At least the first 8 participants across Weight Bands 1 and 2 and the first 8 participants across Weight Bands 3, 4, and 5 will follow the Rich Sampling Schedule for PK evaluations. Once proposed dosing regimens have been evaluated in each weight band and data are sufficient for the PK parameter estimates for both oral and injectable dosing, the protocol team will issue a Memorandum of Operational Instruction switching all participants (currently enrolled and newly enrolling) from the Rich Samling Schedule to the Limited Sampling Schedule. Once enrolled into Cohort 1, participants in each weight band will move through two steps of study participation. In Step 1 (i.e., at study entry), participants will switch from their pre-study ART regimen to daily oral formulations of CAB + RPV for at least four weeks and up to a maximum of six weeks. Week 4a visit will transition to Step 2 and receive injectable CAB LA + RPV LA through Week 72. Participants who prematurely and permanently discontinue oral CAB + RPV or do not meet eligibility criteria for the injection phase will exit the study 28 days after their last oral study product

	dosing. In Step 2, participants will receive injectable CAB LA + RPV LA. Two IM injections, a single injection of CAB LA and a single injection of RPV LA, will be administered at the Week 4b (Step 2 Entry) visit, at the Week 8 visit, and then continuing every four weeks or every eight weeks thereafter, depending on the recommendation of the Week 12 interim analyses. Once Cohort 1 has completed accrual (defined as having enrolled either 50 evaluable participants, or a maximum of 70 participants overall) and the results of both interim analyses are available and acceptable, Cohort 2 will open to accrual. Cohort 2 will have a planned accrual period of six months, during which up to 20-40 children may enroll (across both Cohort 2a and Cohort 2b, described below). Participants may enroll into either Cohort 2a or 2b, with a minimum accrual target of 4 participants in each. While distribution across weight bands is desirable, there are no weight band requirements for Cohort 2. Should the overall study sample size maximum (approximately 90 children enrolled across all cohorts) not be reached within the six month accrual period for Cohort 2, then Cohort 2 will close to accrual either when the six-month accrual period is completed, or upon reaching the minimum accrual target, whichever is later. Cohort 2 will consist of two groups, Cohort 2a and Cohort 2b, which will allow participants to choose between a regimen that includes an oral lead-in and one that does not. Participants enrolled in Cohort 2a will progress through two steps of study participation, as described above for Cohort 1. Cohort 2a participants will receive oral CAB + oral RPV (Step 1) through the Week 4b visit, followed by intramuscular injection doses of CAB LA + RPV LA from Week 4b (Step 2 entry) through Week 48, based upon the relevant weight band dosing regimens recommended at the time. Participants enrolled to Cohort 2b will skip the oral lead-in phase and receive both CAB LA + RPV LA upon entry into the study and continuing through Week 44, based upon the relevant weight-band dosing regimens recommended at the time. The decision to join Cohort 2a or Cohort 2b will be made by the potential study participant and/orthe parent/legal guardian in consultation with the IoR or designee and other healthcare providers, as applicable. This choice will be made as part of the parental permission and informed assent process and must be confirmed prior to study entry; participants may not change their Cohort 2a or Cohort 2b group selection after enrollment. Participants who will be followed for an additional 48 weeks on an adjusted follow-up schedule to assess long-term safety and washout PK of the study products,

	referred to as the LSFU visit schedule. This includes participants who prematurely permanently discontinue study product during the injection phase, participants who discontinue oral or injectable study product due to pregnancy, and participants who complete the injectable study product regimen, but do not wish to continue the CAB LA + RPV LA regimen outside of the study. Dose-finding and Evaluability: Cohort 1 Cohort 1 will include a dose-finding phase to assess whether any dosing regimen modifications are indicated per weight band; this phase culminates in two separate interim analyses, as described below. Separate terms will be used in the study to describe the participants who will contribute to the dose-finding phase (dose-evaluable) and the participants contributing the accrual targets (evaluable): • Dose-evaluable – The term dose-evaluable refers to participants who will be included in the Week 12 dose-finding interim analyses. Dose-evaluable is defined as participants having been treated on the dose being evaluated, and having either completed all treatment through Cohort 1 Week 12 visit or having experienced any of the following: • study drug-related Grade 3+ events (excluding injection-site adverse events), OR study drug-related SAE, OR • permanently discontinued from treatment due to study drug-related toxicities (regardless of grade) during the dose-finding period.Participants who receive oral bridging within the first 12 weeks of their study participation will not be considered dose-evaluable. • Evaluable – Evaluable participants will be defined as having either (1) completed all treatment through Cohort 1 Week 24, or (2) having experienced any of the following: • study drug-related Grade 3+ events (excluding injection-site adverse events), OR • study drug-related SAE, OR • permanently discontinued from treatment due to study drug-related toxicities (regardless of grade) during these weeks of treatment. The two interim analyses will be conducted separately: • The first interim analysis will be based on Weight Bands 1, 2, and 3 to determine whether criteria have been met to open Weight Bands 4 and 5 to accrual, and to determine if any dosing regimen modifications are indicated. It will be conducted once a minimum of 8 dose-evaluable participants have completed the Week 12 visit, with at

least 2 dose-evaluable participants enrolled in Weight Band 3 (20-24.9 kg).

- The second interim analysis will be based on Weight Bands from 3, 4, and 5 to determine if any dosing regimen modifications are indicated. It will be conducted once a minimum of 8 doseevaluable participants across Weight Bands 3, 4, and 5 have completed the week 12 visit(including any participants in Weight Band 3 who contributed data to the first interim analysis), with at least 2 dose-evaluable participants enrolled in Weight Band 5 (10-13.9 kg).

All available PK, safety, viral load, tolerability, and other relevant data will be reviewed by the CMC.

Note that dose modifications will not result in additional interim analyses. If a dose modification is indicated in either cohort, accrual will be paused in the relevant weight band(s) until an SMC review is convened, and the proposed dose modification is approved .Once accrual is reopened, newly enrolling participants will begin on the modified dose.

Transition from Step 1 to Step 2: Cohort 1 and Cohort 2a

Eligibility for each Cohort 1 and Cohort 2a participant will be assessed prior to entry into Step 2 and receipt of injectable CAB LA + RPV LA . The Week 4b visit serves as the Step 2 Entry visit. This visit should be scheduled to occur as soon as possible after Week 4a laboratory test results are available to minimize the time between the Week 4a visit and initiation of the injectable study products. Clinical assessments conducted at the Week 4b visit, and prior to administering the first injection, will also be used to confirm Step 2 eligibility.

Study visits during Step 2 will be scheduled based on the actual Week 4b visit completion date when the first CAB LA + RPV LA injections are administered.

Qualitative Evaluation Design

Qualitative in-depth interviews (IDIs) with a subset of enrolled parents/caregivers will be conducted to complement the quantitative data collected and allow for a mixed-methods approach to evaluate nuanced aspects of acceptability and tolerability, contributing to the secondary objectives of the study. Approximately 30 parents/caregivers will be purposively selected across up to 6 sites for participation in a semi-structured qualitative IDI at Week 24 for Cohort 1 and Cohort 2a and Week 20 for Cohort 2b. Interviews must be completed within the specified interview window but may be conducted as part of a regular study visit or as a stand-alone visit, per site discretion and parent/caregiver preferences. Approximately 18 IDIs will be allocated to Cohort 1 and an additional 12 to Cohort 2. Additional details regarding the qualitative component, including purposive

	selection criteria and qualitative accrual targets, will be provided in the IMPAACT 2036 study-specific MOP. Sites selected for the qualitative component will outline procedures for conducting the qualitative component in an IMPAACT 2036 study-specific SOP. Study staff members at each participating qualitative site will conduct the IDIs allocated for their site based on cohort-specific qualitative interview guides that will be developed by the protocol team with input from site staff. Interviews will be conducted in the preferred language of the parent/caregiver, audio-recorded, and then transcribed and translated to English (as needed) for analysis
Study Arms	**<u>Weight Band 135-<40 kg</u>** initial injections (Wk 4b): 600mg CAB LA + 900mg RPV LA Subsequent injections (following Wk 4b), every four weeks: 400mg CAB LA + 600mg RPV LA. **<u>Weight Band 225-34.9 kg</u>** Initial injections (Wk 4b): 300mg CAB LA + 600mg RPV LA Subsequent injections (following Wk 4b), every four weeks: 200mg CAB LA + 450mg RPV LA **<u>Weight Band 320-24.9 kg</u>** Initial injections (Wk 4b): 300mg CAB LA + 600mg RPV LA Subsequent injections (following Wk 4b), every four weeks: 200mg CAB LA + 450mg RPV LA **<u>Weight Band 414-19.9 kg and Weight Band 510-13.9 kg</u>** Initial injections (Wk 4b): 300mg CAB LA + 450mg RPV LA Subsequent injections (following Wk 4b), every four weeks: 200mg CAB LA + 300mg RPV LA
Study Population	STUDY POPULATION This study will be conducted with up to 90 children living with HIV-1 and their parents/caregivers. Children will be selected according to the criteria in Sections 4.1-Section 4.4. Parent/caregiver eligibility criteria are outlined in Section 4.5 and Section 4.6. The study-specific approach to

	recruitment, screening, and enrollment is described in Sections 4.8 and 4.9.
Follow-up/Duration	Approximately three and half years in total from the time of the first participant enrollment.
Study/Programme Sites	• Wits RHI Shandukani Research Centre (SRC) • St. Jude Children's Research Hospital CRS • Soweto IMPAACT • Emory University School of Medicine NICHD CRS • Umlazi Clinical Research Site • SOM Federal University Minas Gerais Brazil NICHD CRS • PHPT-Chiangrai Prachanukroh Hospital NICHD CRS • Wits RHI Shandukani Research Centre CRS • Chiang Mai University HIV Treatment CRS • Siriraj Hospital CRS • Instituto de Puericultura e Pediatria Martagao Gesteira Clinical Research Site • Gaborone CRS • Molepolole CRS
Intervention	Hypothesis • Oral CAB + RPV and injectable CAB LA + RPV LA will achieve pharmacokinetic targets in children living with HIV-1, two to less than 12 years of age. • Oral CAB + RPV and injectable CAB LA + RPV LA will exhibit acceptable safety profiles in children living with HIV-1, two to less than 12 years of age.
Operations	Study Specific
Investigators	• Prof Lee Fairlie, Principal Investigator • Dr Faeezah Patel • Dr Elizea Horne • Dr Mrinmayee Dhar • Dr Jeanne Coetzee • Tiffany Deborah Seef
Other Partners & Collaborators	• None
Sponsors/Donors	IMPAACT 2036
Publications/Key Presentations to Date	None as yet
Progress Update as of Mar 2026	Screened: 7 Screen failed: 1 Virological Failure:1 Enrolled: 5 Participants Rolled over to TMC/CARLA: 2 Participants actively on study: 3

Frequency of Donor Narrative Report	3 Monthly
Overall Study/Project Contact	Dr Hermien Gous, Prof Lee Fairlie
Briefing Owner and Date	Rorisang Komane Mar 2026