

IMPAACT 2036

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

CRAYON: Cabotegravir and Rilpivirine Long-Acting Injections in Young ChildreN

**A Study of the International Maternal Pediatric Adolescent
AIDS Clinical Trials Network**

Sponsored by:

National Institute of Allergy and Infectious Diseases

Eunice Kennedy Shriver

National Institute of Child Health and Human Development

National Institute of Mental Health

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PROTOCOL SIGNATURE PAGE

I will conduct this study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable US Food and Drug Administration regulations; standards of the International Council for Harmonisation Guideline for Good Clinical Practice (ICH E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies.

Signature of Investigator of Record

Date

Name of Investigator of Record
(printed)

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ABBREVIATIONS AND ACRONYMS

ADR	Adverse drug reaction
AE	Adverse Event
AESI	AEs of special interest
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine Transaminase
ART	Antiretroviral Therapy
ARV	Antiretroviral
AST	Aspartate Aminotransferase
AUC	Area under the plasma concentration-time curve
BMI	Body Mass Index
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CAB	Cabotegravir
CAB LA	Long-Acting Injectable Cabotegravir
cART	Combination Antiretroviral Therapy
CAR	Current Antiretroviral Regimen
CD4	Cluster of differentiation 4
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	Confidence intervals
CK	Creatine Kinase
CL/F	Apparent total body clearance
CLIA	Clinical Laboratory Improvement Amendments
C _{max}	Maximum concentration
CMC	Clinical Management Committee
COVID-19	Coronavirus disease 2019
CPK	Creatine phosphokinase
CRMS	NIAID Clinical Research Management System
CRPMC	NIAID Clinical Research Products Management Center
C _τ	Trough concentration
CVF	Confirmed Virologic Failure
CYP	cytochrome P450
DAIDS	Division of AIDS
DAIDS RSC	DAIDS Regulatory Support Center
DAIDS PRO	DAIDS Protocol Registration Office
DAERS	DAIDS Adverse Experience Reporting System
DILI	Drug-induced liver injury
DMC	Data Management Center
DTG	Dolutegravir
DT	Dispersible Tablet
EAE	Expedited Adverse Event
EC	Ethics Committee
ECG/EKG	Electrocardiogram

eCRF	Electronic Case Report Form
EFV	Efavirenz
eGFR	Estimated glomerular filtration rate
EIA	Enzyme immunoassay
EMA	European Medicines Agency
ENR	Enrollment
EU	European Union
FDA	Food and Drug Administration
FSTRF	Frontier Science and Technology Research Foundation
FTC	Emtricitabine
GCLP	Good Clinical Laboratory Practice
GCP	Good Clinical Practices
GLP	Good Laboratory Practice
hCG	Human Chorionic Gonadotropin
HDPE	High density polyethylene
HIV-1	Human Immunodeficiency Virus
HPLC/MS/MS	High-performance liquid chromatography and tandem mass spectrometry
HSR	Hypersensitivity reaction
ICF	Informed Consent Form
ICH	International Council on Harmonisation
IDI	In-depth interview(s)
IM	Intramuscular
IMPAACT	International Maternal Pediatric Adolescent AIDS Clinical Trials Network
IND	Investigational New Drug
INSTI	Integrase Strand Transfer Inhibitor
IoR	Investigator of Record
IRB	Institutional review board
ISR	Injection site reaction
ITT-E	Intention to treat-efficacy
LA	Long-acting
LDMS	Laboratory Data Management System
LPC	Laboratory processing chart
LSFU	Long-term Safety and Washout PK Follow-Up
MOCHA	More Options for Children and Adolescents
MOP	Manual of Procedures
NIAID	National Institute of Allergy and Infectious Diseases
NICHD	National Institute of Child Health and Human Development
NIH	National Institutes of Health
NIMH	National Institute of Mental Health
NNRTI	Non-nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitors
NTD	Neural Tube Defect
OHRP	US Office for Human Research Protection
OLI	Oral lead-in
PCR	Polymerase Chain Reaction
PDVF	Protocol defined virologic failure
pH	proton concentration
PI	Protease Inhibitor
PID	Participant Identification Number
PK	Pharmacokinetics
PO	By mouth

POP PK	Population PK
PoR	Pharmacist of Record
Q4W	Study drug administration every 4 weeks
Q8W	Study drug administration every 8 weeks
QTc	Corrected Q-T interval
RNA	Ribonucleic Acid
RPV	Rilpivirine
RPV LA	Long-acting injectable rilpivirine
RSC	DAIDS Regulatory Support Center
SAE	Serious Adverse Event
SC	Subcutaneous
SD	Standard deviation
SDMC	Statistical and Data Management Center
SES	Study Enrollment System
SID	Study Identification Number
SMC	Study Monitoring Committee
SMR	Sexual Maturity Rating
SOC	System Organ Class
SOP	Standard Operating Procedure
SUSAR	Suspected, Unexpected Serious Adverse Reactions
TAF	Tenofovir alafenamide
TDF	Tenofovir disoproxil fumarate
T _{max}	Time of maximum concentration
TQT	Thorough QT
ULN	Upper Limit of Normal
US	United States of America
VL	Viral load
VQA	Virology Quality Assurance Program
WHO	World Health Organization

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IMPAACT 2036

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

SCHEMA

Purpose: 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) in children living with HIV-1, and to describe participant choice and experience with the regimen with or without an oral lead-in period.

Design: Phase I/II, multicenter, open-label, non-comparative study

Study Population: Children living with HIV-1, two years to less than 12 years of age and weighing ≥ 10 kg and < 40 kg, who are virologically suppressed on stable antiretroviral therapy and their parents/caregivers.

Sample Size: Up to 90 children in total, across Cohort 1 and Cohort 2, as follows:

- **Cohort 1:** Up to 70 children will be enrolled to achieve at least 50 evaluable participants. Additional evaluable targets per weight band and across weight bands are provided below.

Weight Bands (minimum accrual per weight band)		Total Minimum Accrual Across Weight Bands
1.	35-<40 kg (min n=6)	Minimum of n =18 across Weight Band 1 and 2
2.	25-34.9 kg (min n=6)	
3.	20-24.9 kg (min n=6)	Minimum of n=32 across Weight Band 3,4, and 5
4.	14-19.9 kg (min n=6)	
5.	10-13.9 kg (min n=10)	

- **Cohort 2:** 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). The maximum allowed enrollments to Cohort 2 depends upon the total number of children enrolled to Cohort 1 (see above). 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.

Approximately 90 parents/caregivers of child participants will also be enrolled across both cohorts to complete behavioral assessments. Approximately 30 enrolled parents/caregivers will be selected by the protocol team to also complete a qualitative in-depth interview.

Study Treatment: Cohort 1: Once daily oral CAB + oral RPV through the Week 4b visit, followed by intramuscular injection doses of CAB LA + RPV LA every four weeks (Q4W dosing regimen) or every eight weeks (Q8W dosing regimen) through the Week 72 visit. Dosing regimen modifications (including dose and frequency) for each weight band will occur as needed based on ongoing reviews of safety and pharmacokinetics (PK) data within the study or from other ongoing studies of the study drugs in pediatric populations.

Cohort 2: Participants will have the option of joining Cohort 2a or Cohort 2b as follows:

- Cohort 2a: Once daily doses of oral CAB + oral RPV through the Week 4b visit, followed by Q4W or Q8W intramuscular injection doses of CAB LA + RPV LA through Week 48.
- Cohort 2b: Q4W or Q8W intramuscular injection doses of CAB LA + RPV LA through Week 44.

Study Duration: Approximately three and a half years in total, from the time of the first participant enrollment. Accrual into Cohort 1 is expected to require approximately 12 months. Accrual into Cohort 2 will continue for a maximum of six months. Participants will be followed approximately 18 months on study product in Cohort 1 and approximately 12 months in Cohort 2.

Participants who meet criteria will be followed for approximately one year off study product for long-term safety and washout PK follow-up (LSFU).

Primary Objectives: Cohort 1

- 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: Cohort 1

- To assess the safety of CAB + RPV (oral and injectable) through Weeks 48 and 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)
- 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)

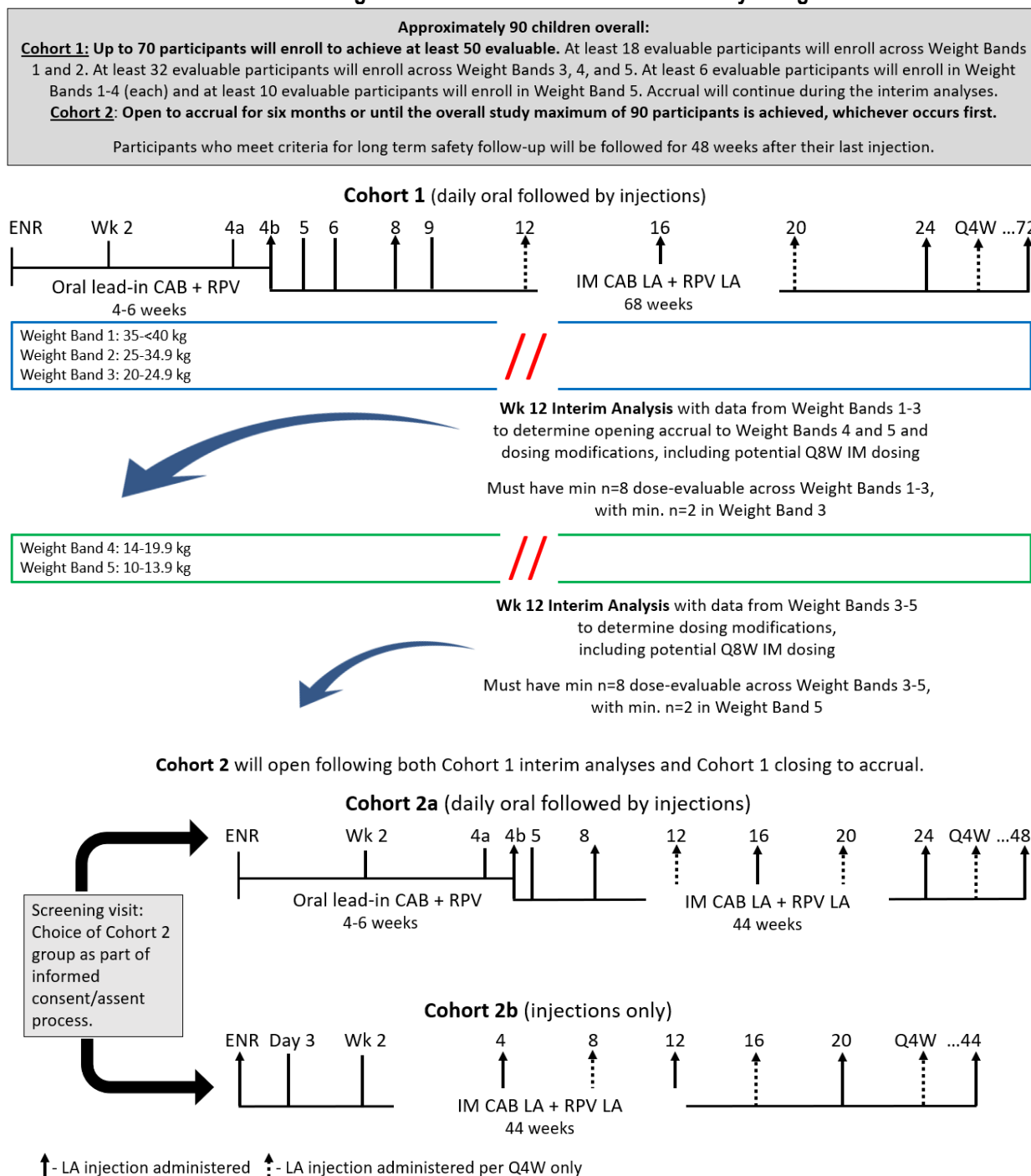
Other Objectives: Cohort 1 and Cohort 2

- To characterize long-term safety and washout PK through 48 weeks after permanent discontinuation of injectable CAB LA + RPV LA
- To characterize PK of CAB + RPV oral formulations when dispersed in liquid vs. directly ingested (Weight Bands 3, 4 and 5)

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Figure 1. IMPAACT 2036 Overview of Study Design



1 INTRODUCTION

1.1 Background

Decades of antiretroviral therapy (ART) advances have led to simplified treatment regimens for people living with human immunodeficiency virus (HIV-1). Viral suppression in adults is frequently achieved through close adherence to once daily, single-tablet ART regimens. However, the rates of viral suppression in children are lower when compared to those in adults. The lack of simple paediatric formulations and potent regimens in children contribute to difficulties in adherence and lower suppression rates. ART safety profiles have gradually improved, allowing for the inclusion of well-tolerated medications with infrequent adverse effects in treatment regimens. Despite ART advances for older populations, young children have access to a fewer simplified HIV-1 regimens. The same hurdles that contribute to suboptimal paediatric ART adherence have also led to the deferment of paediatric clinical trials for medications already approved in adults, compounding the obstacles faced by children living with HIV-1 (1). The use of long-acting (LA) injectable ART may circumvent many of these hurdles.

Normal childhood weight gain requires periodic changes in weight-based ART dosing, making it difficult to produce a single fixed-dose combination formulation containing multiple antiretroviral medications whose doses can be adjusted as a child grows. In addition, young children also have difficulty swallowing tablets, requiring the creation of specific drug formulations (i.e., liquids, dispersible tablets) aimed at this relatively small group of patients, further delaying access to new medications.

LA injectable ART can alleviate many of the challenges children living with HIV-1 face. Improving treatment adherence rates will allow these patients to achieve sustained viral suppression. Cabotegravir (CAB) and rilpivirine (RPV) are the first LA injectable ARTs approved for the treatment of HIV-1. CAB is a potent integrase strand transfer inhibitor (INSTI) with attributes allowing formulation and delivery as a LA parenteral product. RPV, also formulated as a LA product, is a diaryl pyrimidine derivative and a potent non-nucleoside reverse transcriptase inhibitor (NNRTI) with in vitro activity against wild type HIV-1 and select NNRTI-resistant mutants. The combination of CAB LA plus RPV LA has an acceptable safety profile and is well-tolerated and efficacious as a dual injectable ART among adults and (by extrapolation) adolescents living with HIV-1 (2-7).

This study aims to build on the experience to date with CAB LA + RPV LA in adults and adolescents living with HIV-1. Prior studies have established the dosing, safety, tolerability, and pharmacokinetics of oral and CAB LA + RPV LA in adults. These studies have also demonstrated that CAB LA + RPV LA can be safely initiated with or without an oral lead-in. In the present study, we will propose the weight-band dosing and assess the safety, tolerability and pharmacokinetics (PK) of oral CAB + oral RPV followed by injectable CAB LA + RPV LA in virologically suppressed children living with HIV-1, aged two to less than 12 years old. We will also establish if virologically suppressed children living with HIV-1 remain suppressed upon the two-drug intramuscular (IM) regimen of CAB LA + RPV LA.

1.2 Prior Research

1.2.1 Cabotegravir

Cabotegravir (CAB) is an INSTI with in vitro activity against HIV-1. CAB 30-mg once daily (oral tablet) is approved in multiple countries and regions for the short-term treatment of HIV-1 in adults who are virologically stable and suppressed (plasma viral load (VL) <50 HIV-1 RNA copies/mL) in

combination with oral RPV. This indication for oral CAB is limited to use as either an oral lead-in prior to CAB LA + RPV LA or oral bridging therapy for planned missed CAB LA + RPV LA injections. The CAB oral tablet and a parenteral long-acting formulation of CAB (CAB LA) have been approved for use in combination with oral RPV and RPV LA in a number of countries as a dual regimen to treat HIV-1 in virologically stable and suppressed adults (HIV-1 RNA <50 copies/mL).

Summary of Cabotegravir Drug Metabolism and Pharmacokinetics (DMPK):

CAB is rapidly absorbed following oral administration of the micronized tablet formulation, with median T_{max} observed two to three hours post-dose in the fasted state. CAB LA is a 200 mg/mL nanosuspension that has been administered as an IM and a subcutaneous (SQ) injection of single doses of 100 to 800 mg and repeat doses from 200 to 800 mg. CAB LA exhibits absorption-limited (flip-flop) kinetics, and CAB has been detected in plasma up to 52 weeks or longer after administration of repeat IM injections of CAB LA.

Following administration in humans, CAB is primarily eliminated through metabolism by UGT1A1, with minimal cytochrome P450 (CYP)-mediated metabolism. Renal elimination of unchanged CAB represents less than 1% of the total dose administered. CAB is the predominant circulating compound in plasma, representing >90% of plasma total radiocarbon. Fifty-eight percent of the total oral dose is excreted as unchanged CAB in the faeces, and 26.8% of the total oral dose is excreted in the urine, primarily as a glucuronide metabolite (8).

1.2.2 Rilpivirine

Rilpivirine (RPV) is an NNRTI with in vitro activity against wild type and select NNRTI-resistant HIV-1. RPV 25-mg once daily (oral tablet) has already been approved to treat HIV-1 infection in ART-naïve patients 12 years of age and older in multiple countries and regions. A RPV (dose 25 mg) has also been approved as part of once-daily single-tablet oral regimens as FTC/RPV/TDF, FTC/RPV/tenofovir alafenamide [TAF] and DTG/RPV (9).

A parenteral long-acting RPV (RPV LA) formulation (200mg/mL) has been approved for use in combination with CAB LA in the US, the EU and multiple countries/regions. Oral RPV in combination with oral CAB is also approved in multiple countries and regions, for the short-term treatment of HIV-1 in adults who are virologically stable and suppressed (plasma viral load (VL) <50 HIV-1 RNA copies/mL), as an oral lead-in for the injectable regimen or to replace missed injections.

Oral RPV 25-mg once daily has been approved as a component of combination therapy to treat HIV-1 among adolescents (≥ 12 years old). The 48-week results of an adolescent cohort (n=36) demonstrated that treatment with RPV 25-mg once daily, combined with an investigator-selected background regimen, is efficacious, generally safe and well-tolerated in adolescents of ≥ 12 to <18 years of age (10). The Week 240 long-term data in the adolescents who continued treatment in the post-Week 48 treatment extension period also demonstrated efficacy, and no new safety findings were identified; there were no relevant differences from the safety profile in adults living with HIV-1 treated with a RPV-based regimen (8).

Summary of Rilpivirine Drug Metabolism and Pharmacokinetics (DMPK):

RPV LA has been administered IM to healthy adults and adults living with HIV-1 at 300 mg to 1200 mg. After IM injection of RPV LA, RPV is slowly absorbed from the injection site, exhibiting flip-flop pharmacokinetics with an apparent half-life of 200 days in adults (11).

RPV is primarily metabolised, via CYP3A, and eliminated by the liver. No dose adjustment is required in patients with mild or moderate hepatic impairment (9). Oral RPV must be taken with a

meal for optimal absorption (9). Exposure to oral RPV can be affected by modulators of CYP3A4-enzyme activity and drugs that increase gastric pH. Drugs that induce CYP3A4 activity can reduce RPV exposure and should not be co-administered. Drugs that inhibit CYP3A4 activity can increase RPV exposure but do not require dose adjustments (9). Renal elimination of RPV is negligible. Therefore, no dose adjustment of RPV is required in patients with renal impairment (9).

1.2.3 Clinical trial experience using cabotegravir plus rilpivirine as a dual antiretroviral therapy regimen in adults

Phase III/IIIb studies including ATLAS (2), ATLAS-2M, and FLAIR (6), and Phase IIb studies, including LATTE (4) and LATTE-2 (5), have been conducted with oral CAB and/or IM CAB LA plus oral RPV and/or IM RPV LA. Phase III/IIIb studies including ATLAS (2), ATLAS-2M, and FLAIR (6), and Phase IIb studies, including LATTE (4) and LATTE-2 (5), have been conducted with oral CAB and/or IM CAB LA plus oral RPV and/or IM RPV LA.

FLAIR Trial

In the FLAIR Trial (6), data indicate that CAB LA + RPV LA effectively maintain the suppression of plasma HIV-1 RNA (<50 c/mL) following induction of viral suppression with oral dolutegravir-abacavir-lamivudine in HIV-1 ART naive adults and is non-inferior to continued oral dolutegravir-abacavir-lamivudine at Week 48. Overall, in the intent to treat – efficacy (ITT-E) population, 2.1% of participants in the CAB + RPV group and 2.5% of participants in the dolutegravir-abacavir-lamivudine group met the ‘virologic failure’ primary efficacy endpoint of plasma HIV-1 RNA >50 c/mL at Week 48.

The FLAIR 96-week results reaffirm the 48-week results, showing LA CAB and RPV continued to be non-inferior compared with continuing a standard care regimen in adults with HIV-1 for the maintenance of viral suppression. These results support the durability of long-acting CAB and RPV, over an almost 2-year-long period, as a therapeutic option for virally suppressed adults with HIV-1.

The FLAIR 124-week Extension Phase results show 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. The week 124 results for participants randomly assigned originally at study baseline to the long-acting therapy show LA CAB plus RPV remains a durable maintenance therapy with a favorable safety profile.

ATLAS Trial

In the ATLAS Trial (2), data indicate that CAB + RPV effectively maintain the suppression of plasma HIV-1 RNA (<50 c/mL) and was non-inferior to cART at Week 48 among already virally suppressed participants. Study participants were randomised to once-daily oral lead-in CAB + RPV followed by Q4W injections of CAB LA + RPV LA versus continuation of their baseline oral ART regimen (CAR). Overall, in the ITT-E population, 1.6% of participants in the CAB + RPV group and 1.0% of participants in the CAR group met the ‘virologic failure’ primary efficacy endpoint of plasma HIV-1 RNA >50 c/mL at Week 48.

ATLAS-2M

In ATLAS-2M (3), the data indicate that every two-month (Q8 Week) dosing with CAB + RPV is effective in maintaining the suppression of plasma HIV-1 RNA (<50 c/mL) and non-inferior to monthly (Q4 Week) CAB + RPV at Week 48. In the ITT-E population, 1.7% of participants in the CAB + RPV Q8W group and 1.0% of participants in the CAB + RPV Q4W group met the primary efficacy endpoint plasma HIV-1 RNA > 50 c/mL at Week 48(3).

LA cabotegravir and rilpivirine dosed every 8 weeks had non-inferior efficacy compared with that of every 4 weeks through the 96-week analysis, with both regimens maintaining high levels of virological suppression. These results show the durable safety, efficacy, and acceptability of dosing LA CAB and RPV monthly and every 2 months as maintenance therapy for people living with HIV-1(12).

LATTE Trial (Study LAI116482)

In the LATTE trial (4), participants were randomised in a partially blinded fashion to either one of three different doses of oral CAB or to efavirenz, in addition to a dual NRTI. At Week 24, virally suppressed participants in the CAB group were transitioned to the same oral CAB (10, 30 or 60mg) + oral RPV (25 mg) dose, efavirenz participants remained on the same regimen. At Week 96, 79% (CAB 10 mg group), 85% (CAB 30 mg group), 93% (CAB 60 mg group) and 83% (EFV 600 mg group) of participants maintained virologic suppression (HIV-1 RNA <50 c/mL). The study was unblinded at this timepoint, with efavirenz participants considered to have completed the study. CAB participants switched to the Sponsor's selected regimen of open label CAB 30 mg + RPV 25mg. At Week 312, 52% (31/60; CAB 10 mg arm), 52% (31/60; CAB 30 mg arm) and 70% (43/61; CAB 60 mg arm) of participants randomized to oral CAB dosing maintained virologic suppression (HIV-1 <50 c/mL). The LATTE trial provided the rationale for the selected CAB oral dose of 30 mg for adults and was supportive of the efficacy and durability of the dual CAB + RPV regimen.

LATTE-2 Trial (Study 200056)

In LATTE-2 (5), participants were randomised to CAB LA + RPV LA Q4W vs Q8W vs continued oral CAB + dual NRTI treatment. At Week 160, 83% of participants receiving CAB LA + RPV LA Q4W dosing and 90% Q8W dosing maintained virologic suppression (HIV-1 RNA <50 c/mL). The difference in virologic success was primarily due to non-virologic reasons. Of the 44 participants in the oral treatment group who opted to switch to CAB LA + RPV LA (Q4W or Q8W) at Week 100 (beginning of the Extension phase), 100% (Q4W) and 97% (Q8W) maintained virologic suppression (HIV-1 RNA <50 c/mL) at Week 160.

1.2.4 Clinical trial experience using cabotegravir plus rilpivirine as a dual antiretroviral therapy regimen in adolescents

IMPAACT 2017, also known as More Options for Children and Adolescents (MOCHA), is an ongoing Phase I/II, multi-center, open-label, non-comparative study to confirm the dose and evaluate the safety, tolerability, acceptability, and PK of oral CAB, long-acting injectable CAB (CAB LA), and long-acting injectable RPV (RPV LA) in adolescents aged 12 to less than 18 years, living with HIV who are virologically suppressed, and weighing at least 35 kg. CAB LA + RPV LA is approved for treating virologically suppressed adolescents living with HIV who are 12 years of age or older and weighing over 35kgs by the US Food and Drug Administration (FDA) based on data from adult and MOCHA studies.

Preliminary data from the MOCHA study are described below. At the time of the analysis, a total of 23 participants were enrolled: eight participants having received oral CAB followed by CAB LA (Cohort 1C), and fifteen participants having received oral RPV followed by RPV LA (Cohort 1R). There were two premature treatment discontinuations: one due to urticaria, assessed to be an acute allergic reaction related to study product following first RPV dose, and one due to excessive pain with needle insertion (13).

Acceptability among 21 virologically suppressed adolescents enrolled in the MOCHA trial was generally favorable(14). The desire to avoid taking daily pills and difficulty taking daily pills was the major (76.2%) reason for enrolling into the study. Eleven adolescents and 11 caregivers underwent

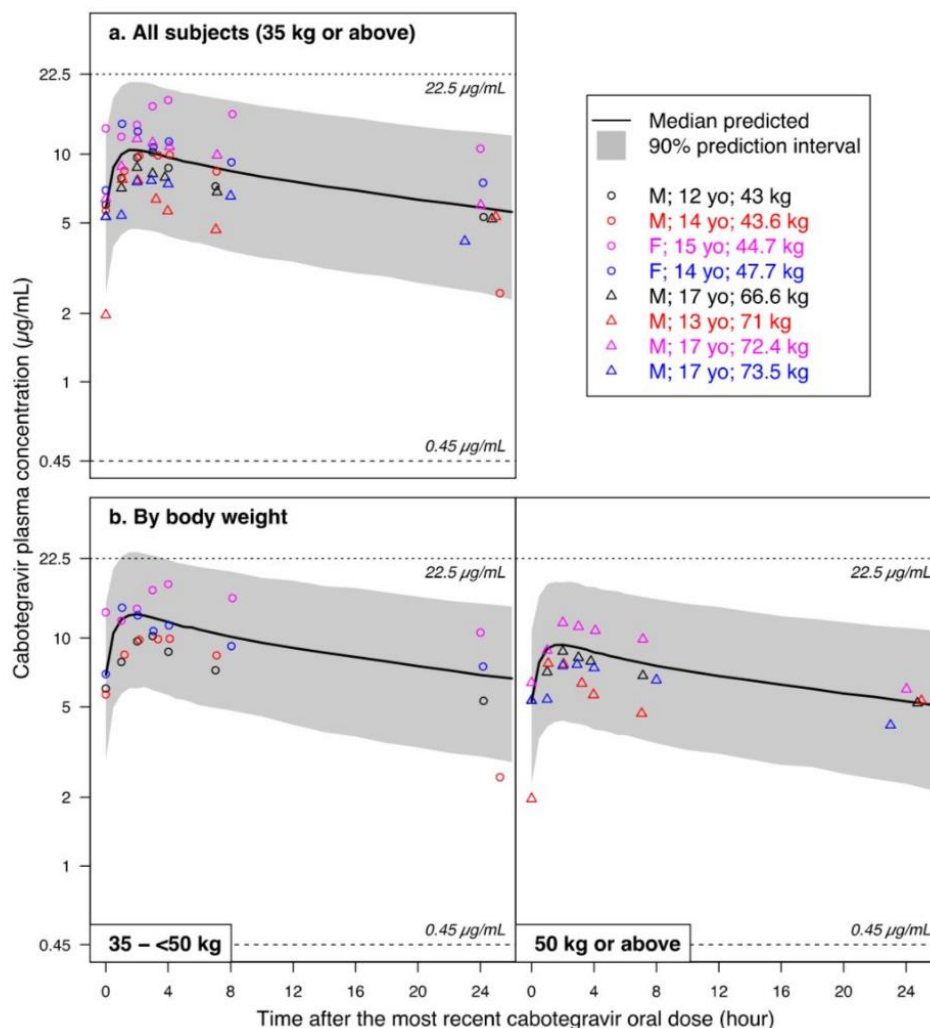
in-depth interviews. The themes reported from the interviews reiterated the difficulty with daily pills and expressed concerns with maintaining long-term adherence to routine injection schedules.

Preliminary PK data from MOCHA found that CAB LA and RPV LA when given individually, in conjunction with background ART, achieve PK targets in the enrolled adolescents living with HIV(13). The Cohort 1C median CAB (oral and IM) PK parameters were within the desired median PK target ranges: Cohort 1C Week 2 Oral median (range) CAB $AUC_{0-\infty}$: 160 (94.3-325) mcg*h/mL (target median 46-277 mcg*h/mL), Week 16 IM median (range) CAB trough: 3.11 (1.22-6.19) mcg/mL (target median 0.71-6.7 mcg/mL). Similarly, the Cohort 1R median RPV PK parameter was within the desired median PK target range: Week 16 IM median (range) RPV trough: 52.9 (31.9-148) ng/mL (target for median 25-100 ng/mL).

Adult CAB and RPV LA Population (POP) PK models were developed utilising exposure data from adult clinical studies with efficacious dosing regimens having an acceptable safety profile with Q4W and Q8W injections. Simulations were conducted with these models, also considering any potential age and weight-related impact on PK, to recommend appropriate doses in adolescents that achieve comparable exposures to those seen in adults. Additionally, PK data from the first 16 participants enrolled to MOCHA were compared against *a priori* population PK model predictions and agreed with the predicted exposure range and were within thresholds, as displayed in [Figure 2](#), [Figure 3](#), and [Figure 4](#) for CAB and RPV. CAB and RPV exposures at other regimens (e.g., Q8W) in adolescent participants can also be predicted with these models, and based on the results from the model predictions, the MOCHA study has been updated to administer the Q8W regiment to all new participants. These models will inform the selection of the initial weight-band dosing regimens used in the CRAYON study.

Figure 2. Observed preliminary IMPAACT 2017 Cohort 1C CAB concentrations in adolescents stratified by weight and age compared to model-predicted concentrations based on POP PK analyses from adult studies

Note: The plots represent the CAB systemic exposure: solid line and shaded band reflect the population pharmacokinetic model predictions (median and 90% interval) in the adults; the dots represent the observed individual adolescent data from MOCHA. The dashed lines represent the maximum observed geometric mean exposure from the TQT study at (22.5 mcg/mL) at supratherapeutic doses following 150 mg q12h x 3 and the target 5th percentile of the observed CAB trough concentration (0.45 mcg/mL) following the initiation injection in Phase 3 studies.



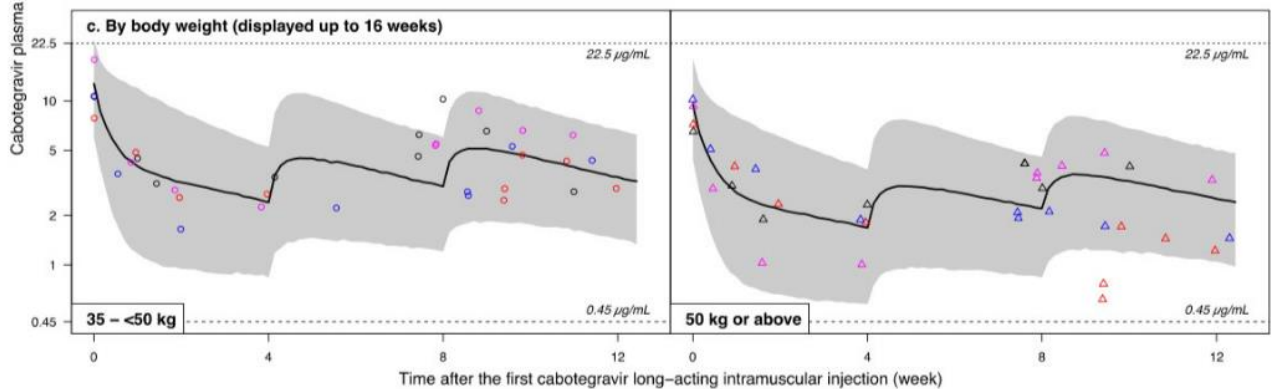
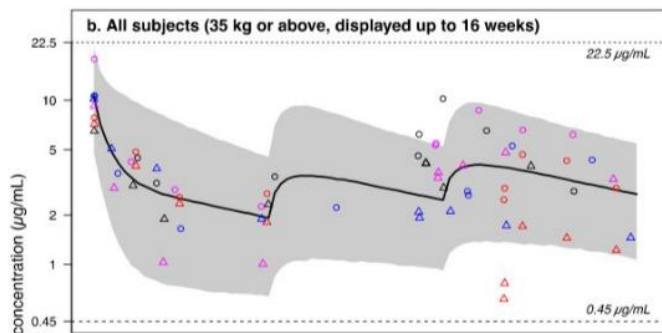
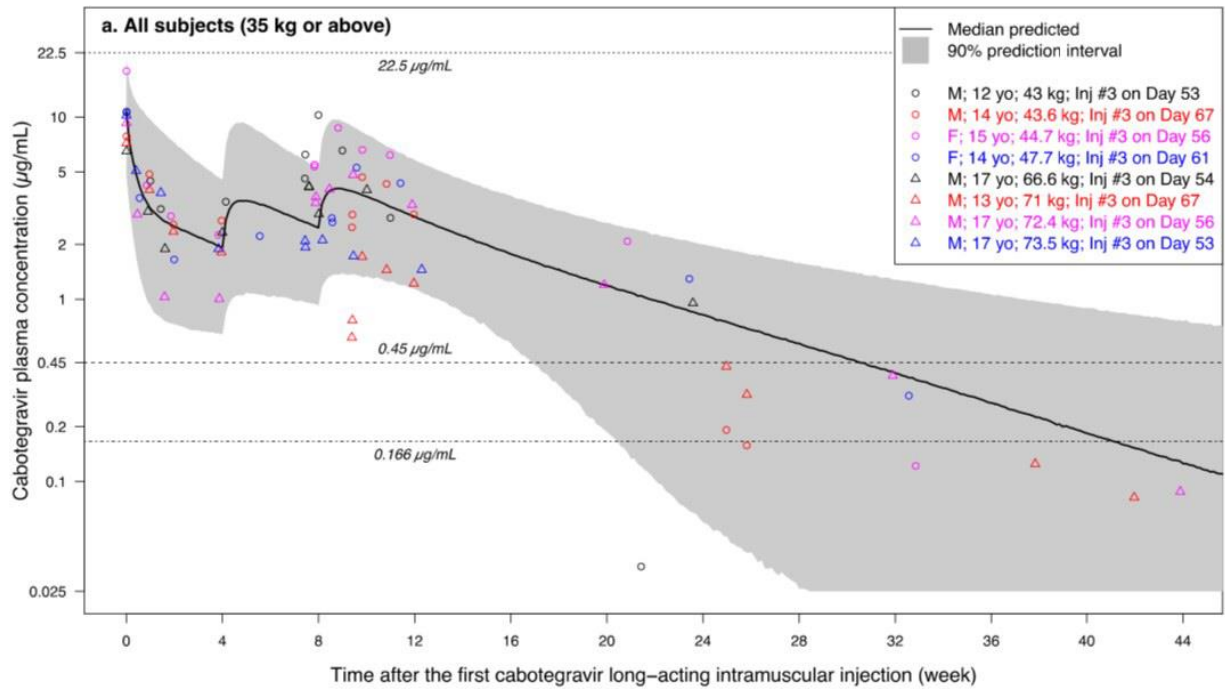


Figure 3. Observed IMPAACT 2017 Cohort 1R preliminary data and predicted RPV plasma concentrations in adolescents after PO RPV 25 mg once daily (left panel) and IM RPV LA 900-600-600 mg (right panel)

Note: Black line and blue shaded area: median and 90% prediction interval for adolescents; black dots: observed data in Cohort 1R adolescents.

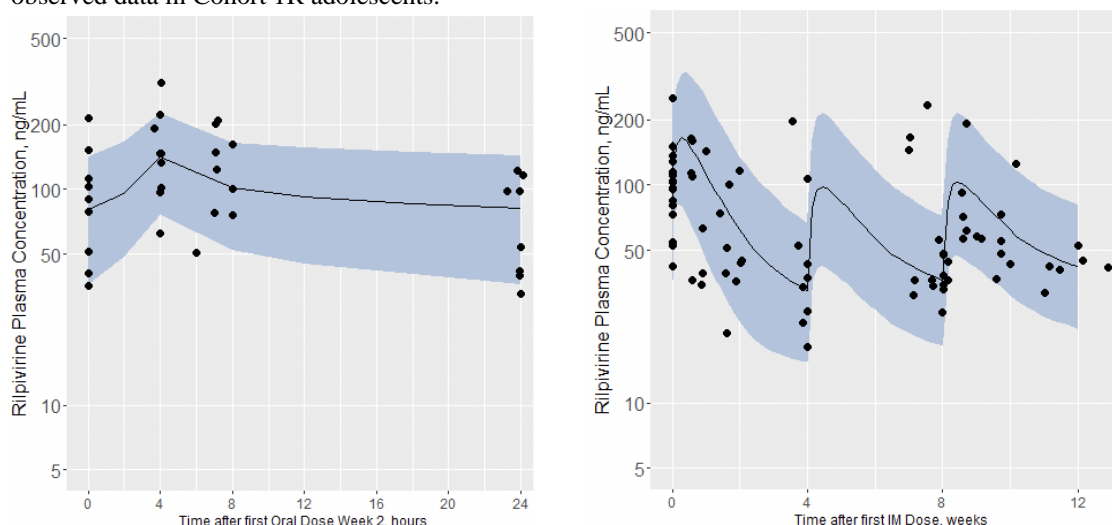
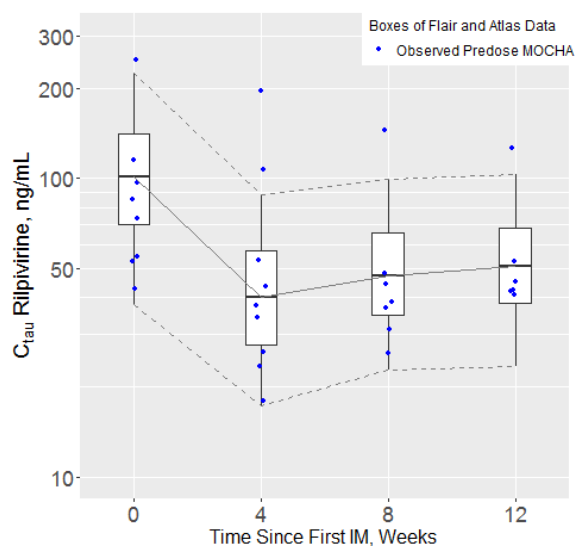


Figure 4. Observed trough RPV plasma concentrations in Cohort 1R adolescents (blue dots) and adults (boxplots, ATLAS/FLAIR) after PO RPV 25 mg once daily (Week 0; last day of PO lead-in), and IM RPV LA 900-600-600 mg (Weeks 4, 8 and 12; concentrations four weeks after injection)



1.2.5 Summary of safety data of CAB LA + RPV LA combination therapy

Overall, over 3000 participants have been exposed to oral and/or LA CAB + RPV during ViiV Healthcare-sponsored HIV-1 treatment clinical studies in Phase II/IIb and Phase III/IIIb (as of March 2022).

The integrated analysis of safety data across the Phase III clinical studies (Studies 201584 [FLAIR] and 201585 [ATLAS]), in combination with Phase I and Phase II data, supports an acceptable CAB + RPV safety profile. The following safety conclusions were drawn:

- The incidence of SAEs reported in FLAIR and ATLAS were comparable between CAB + RPV and the current antiretroviral regimen (CAR). Thirty-one (5%) participants in the CAB + RPV group and 26 (4%) participants in the CAR group had non-ISR SAEs. The most frequently reported SAE with CAB + RPV occurring in more than one participant was hepatitis A (n=4). A single SAE in the CAB + RPV treatment group was considered study drug-related by the investigator: an SAE of right knee monoarthritis.
- At the time of the pooled analysis, no fatalities were reported for participants receiving CAB + RPV during FLAIR and ATLAS. During Phase II studies, there were 5 fatalities. Only one death (myocardial infarction) was considered study drug-related (CAB + RPV) by the investigator. The participant had been on treatment for approximately 3 years and had several risk factors for cardiovascular disease.
- There were no cases of serious reactions such as drug-induced liver injury (DILI) or hypersensitivity reactions (HSR) in FLAIR and ATLAS with CAB + RPV. During Phase I and Phase II, DILI was identified in 5 participants receiving oral CAB (incidence was <1%). In FLAIR and ATLAS, there was a higher incidence of Grade 3/4 ALTs and participants who met Liver Stopping Criteria (LSC) in the CAB + RPV treatment regimen, which is due to the higher incidence of acute viral hepatitis occurring on the regimen.
- ‘AEs of special interest’ (AESI) have been determined for CAB + RPV (oral and IM) based on: non-clinical and/or clinical safety data for CAB and RPV (oral and IM); labelling and/or regulatory authority interest for approved INSTIs; and/or regulatory authority requirements. Results from the Phase III studies indicated that CAB + RPV appears to have no clinically relevant effect on safety related to the following AESI: QT prolongation, seizures, rhabdomyolysis, pancreatitis, or impact on creatinine.
- The rate of discontinuation was low overall for FLAIR and ATLAS. 22 (4%) participants in the CAB + RPV group and 9 (2%) participants in the CAR group had adverse events (AEs) leading to withdrawal/permanent discontinuation of study drug during the Maintenance Phase. The most common AEs leading to withdrawal with CAB + RPV were acute viral hepatitis (n=9) and ISRs (n=5). All individual AEs leading to withdrawal had an incidence of <1%.
- The most frequently reported adverse events (AEs) in the Phase III program were injection site reactions (ISRs), mainly ISR pain. ISRs were generally mild or moderate with no Grade 4 or Grade 5 or serious ISRs. 22 (4%) participants had Grade 3 ISRs, suggesting that ISRs generally did not interfere with daily activities. Most ISRs resolved within seven days. The percentage of participants reporting ISRs at each visit decreased over time. Few ISRs led to withdrawal.
- Other common AEs that were reported more frequently during treatment with CAB+ RPV in FLAIR and ATLAS were hemorrhoids, pyrexia, headache, dizziness, fatigue and back pain. Except for headache, the incidence of these AEs in the CAB + RPV group was <10%. Drug-related AEs, as identified by the investigator, were reported with a higher incidence with CAB + RPV compared with CAR in FLAIR and ATLAS. The most common drug-related non-ISR AEs were headache, pyrexia, nausea, fatigue, asthenia, body temperature increased, myalgia, and dizziness. Most drug-related AEs were Grade 1, although a few Grade 3 and 4 AEs occurred. The most frequent drug-related Grade 3 and 4 AEs were pyrexia (4%), fatigue (3%), and asthenia (2%). Different frequencies of non-ISR, drug-related AEs between treatment groups may be expected for an open-label switch study where the comparator CAR group’s participants had been on a stable and tolerable ART regimen.
- The incidence of neuropsychiatric events was low overall for suicidal ideation/behaviour, depression, and anxiety. Events occurred with similar frequency between treatment groups.
- The incidence of sleep disorder events (including drug-related events), particularly insomnia, was higher in the CAB + RPV group than that of the CAR group during the Phase III studies.
- No dose adjustment in CAB (oral or LA) or RPV (oral or LA) is required for patients with mild or moderate hepatic or renal impairment.
- Studies of co-administered oral RPV-25 mg and oral CAB-30 mg revealed no relevant drug interactions.

- The majority (74.7% CAB + RPV, 80.2% CAR%) of the maximum post-baseline emergent clinical chemistry abnormalities were Grade 1 or Grade 2 in intensity in pooled FLAIR and ATLAS. With the exception of creatine kinase and lipase, there were similar frequencies of Grade 3/4 clinical chemistry abnormalities between the treatment groups. No clinically relevant differences were observed overall in Grade 3 and Grade 4 post-baseline emergent abnormalities between the CAB + RPV and CAR groups.
- Results from FLAIR and ATLAS do not suggest any effect of age, sex, or race on the safety profile of CAB.
- Data from Study 207966 (ATLAS-2M) at the Week 48 analysis, showed the safety data from this randomized, open-label Phase III study of participants switching to Q8W CAB LA+ RPV is favorable and consistent with prior Phase II and III trials examining the Q4W and Q8W regimens.
- Preliminary safety data from the IMPAACT 2017/MOCHA study identified no new or unexpected safety issues or safety concerns and included all available safety data for the eight enrolled participants in Cohort 1C and the 15 enrolled participants in Cohort 1R (13). The safety data included in the analysis showed that in Cohort 1C, only one participant had a Grade 3 study product-related AE (insomnia on day 41 of study that resolved) but remained in the study. In Cohort 1R, only one participant had a Grade 3 study product-related AE (urticaria assessed to be an acute allergic reaction related to study product), resulting in permanent discontinuation of study treatment.

1.2.5.1 Summary of risks/side effects observed and/or monitored for in participants on cabotegravir + rilpivirine

The following risks have primarily been identified either during routine preclinical testing and/or from clinical trial experience in adults to date receiving CAB + RPV and are considered of potential relevance to clinical usage in the context of this protocol. Additional information about clinical experience to date and possible risks/adverse reactions associated with treatment using CAB and/or RPV can be found in the ‘Summary of Data and Guidance for the Investigator’ sections of the respective IBs for CAB and RPV.

Drug Induced Liver Injury (DILI) associated with CAB

A small proportion of participants in the CAB program to date have developed transaminitis (elevated liver transaminases characterised by predominant alanine aminotransferase (ALT) elevation). In most participants, transient transaminitis was explained by acute viral hepatitis infection (majority). In a small number of participants, there was not an alternative explanation, suggesting a mild form of drug induced liver injury (DILI) without hepatic dysfunction, which resolved upon withdrawal of treatment with CAB (15).

Injection Site Reactions (ISRs)

Clinical, experience to date has demonstrated that for adults, ISRs occur in the majority of exposed participants treated with CAB LA and RPV LA but are generally mild (Grade 1) or moderate (Grade 2) and include events of pain, tenderness, erythema, or nodule formation of several days’ duration (median duration for individual events <1 week) (7).

ISRs may occur more than once in an individual participant receiving multiple injections. Although some Grade 3 ISRs were reported, overall ISRs have been well tolerated in adult participants and have not to date been associated with an excess of participants withdrawing.

Hypersensitivity Reactions (HSR) (CAB)

Hypersensitivity reactions have been reported as uncommon occurrences with this class of INSTIs, including the closely related compound dolutegravir, and were characterized by rash, constitutional findings, and sometimes, organ dysfunction, including liver injury (15).

While there have been no severe clinical cases of hypersensitivity reported to CAB to date, there is a theoretical risk of systemic or severe hypersensitivity reactions with or without hepatic symptoms associated with use of IM CAB (15). The long exposures anticipated after IM CAB injection may complicate the management of a drug hypersensitivity reaction, were it to occur.

Rash (RPV)

Some observations of rash with oral RPV have been reported in clinical studies executed to date (the majority are Grade 1 or 2) (16).

Effects in late-stage pregnancy observed in non-clinical studies with CAB

Nonclinical data from rat pre- and postnatal (PPN) studies have indicated reduced survival and viability rates amongst rat pups during the first 4 days of life at the maximum tested dose of 1000 mg/kg/day (maternal exposure). NOAEL was established at the mid dose 5 mg/kg/day, the maternal exposure at this dose calculated using systemic exposure from non-pregnant rats is >20 fold predicted C_{max} and Area under the curve (AUC) exposures for anticipated clinical CAB LA exposures for HIV treatment.

In animal reproduction studies, CAB when administered to rats at >30 times the systemic exposure at the maximum recommended oral human dose (MRHD) of 30 mg during organogenesis through delivery, had adverse effects on labor and delivery that may be related to a delay in the onset of parturition, resulting in increased fetal mortality (stillbirths) and neonatal deaths immediately after birth.

The clinical significance in humans of these findings is unknown (15).

Residual concentrations and risk of resistance following discontinuation of CAB LA or RPV LA

Residual concentrations of CAB and RPV can remain in the systemic circulation for prolonged periods (more than 1 year in some cases) in participants who stop CAB LA or RPV LA treatment (e.g., for tolerability issues or treatment failure) (7).

Participants discontinuing a CAB LA + RPV LA regimen may therefore be at risk for developing HIV-1 resistance to CAB and/or RPV after discontinuing injectable therapy (7).

Drug-Drug Interactions (DDIs)

For a complete listing of permitted and prohibited concurrent medications for CAB/CAB LA or RPV/RPV LA, refer to the IMPAACT 2036 Prohibited and Precautionary Medications listing in [Appendix III](#).

Inadvertent Intravenous Injection (Accidental Maladministration)

As with any intramuscular injection, it is possible that CAB LA or RPV LA can be inadvertently administered intravenously instead of intramuscularly possibly resulting in higher-than-expected concentrations of CAB or RPV shortly after injection and lower concentrations thereafter. This could

be due to administrator error, improper injection technique and / or improper needle length used based on body type.

Post-injection reactions (RPV LA)

In clinical trials in adults, there have been occurrences of serious and non-serious post-injection reactions which were reported within minutes after the injection of RPV LA. Some of these events may have been associated with accidental partial intravenous (IV) administration of RPV during the intramuscular injection procedure, as suggested by pharmacokinetic (PK) assessments showing unexpectedly high plasma RPV concentrations post-dose. Symptoms ranged from mild to severe, with some participants receiving supportive care. These events have included symptoms such as dyspnea, bronchospasm, agitation, abdominal cramping, rash/urticaria, dizziness, flushing, sweating, oral numbness and, changes in blood pressure, and pain (e.g., back and chest). Symptoms typically began to resolve within a few minutes after the injection. These participants made a full recovery after the event resolved (16).

These events are infrequent and occurred in less than 0.5% of participants receiving repeat doses of RPV LA in clinical trials in adults. Of the symptomatic patients who had confirmed RPV PK elevations consistent with accidental partial IV administration, no patients had loss of virological control within weeks after the event (16).

Risk of Virologic Failure

This study employs a relatively novel 2 drug LA ART maintenance regimen for the treatment of HIV-1 infection. CAB LA + RPV LA have demonstrated antiviral activity in large clinical studies in adults and the two-drug combination has demonstrated sustained antiviral activity in studies LAI116482 (LATTE), 200056 (LATTE-2), 201584 (FLAIR), 201585 (ATLAS) and 207966 (ATLAS-2M) (7).

To limit the risk of virological failure and the chance of participants with archived NNRTI or INSTI resistance to be enrolled, virally suppressed participants on a stable oral ART regimen without prior evidence of NNRTI or INSTI resistance based either on prior HIV Drug resistance tests or clinical suspicion of prior resistance will be eligible for enrollment into this study.

Doses of CAB LA and RPV LA have been selected for this study, involving children, to achieve exposures that are expected to maintain virologic efficacy on the basis of available data with the oral and LA formulations in adults. Due to administration error, it is possible that a participant could receive an inadequate dose of CAB LA or RPV LA. Sub-therapeutic concentrations of either CAB LA or RPV LA could lead to virologic failure and possibly the development of viral resistance (7).

1.3 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.

1.3.1 Rationale for the oral lead-in prior to injectable dosing in Cohort 1

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 one-month 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.

1.3.2 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 (16). 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 (7, 17, 18). 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 direct-to-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 real-world 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.

1.3.3 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 long-acting 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.

1.3.4 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

data from both 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.

1.3.5 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]) (20). 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.

1.3.6 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" (21). 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 in [Section 6.15](#) as well as 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.

1.4 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.

2 OBJECTIVES

All objectives pertain to the study population of virologically suppressed children living with HIV-1, two to less than 12 years of age and weighing ≥ 10 kgs and < 40 kgs.

2.1 Primary Objectives: Cohort 1

The primary objectives of this cohort are to:

- 2.1.1** To describe the repeat-dose pharmacokinetics of CAB + RPV (oral and injectable) through Week 24
- 2.1.2** To assess the safety of the oral lead-in of CAB + RPV, and the safety of CAB + RPV (oral and injectable) through Week 24

2.2 Secondary Objectives: Cohort 1

The secondary objectives of this cohort are to:

- 2.2.1** To assess the safety of CAB + RPV (oral and injectable) through Week 48 and through Week 72
- 2.2.2** To describe the repeat-dose pharmacokinetics of injectable CAB LA + RPV LA through Weeks 48 and 72
- 2.2.3** To assess the maintenance of viral suppression of CAB + RPV (oral and injectable) through Weeks 24, 48, and 72
- 2.2.4** To evaluate the tolerability and acceptability of injectable CAB LA + RPV LA through Weeks 24, 48, and 72
- 2.2.5** To describe HIV-1 genotypes and phenotypes for children who experience virologic failure during study treatment
- 2.2.6** To assess immunologic activity of CAB + RPV (oral and injectable) through Weeks 24, 48, and 72

2.3 Secondary Objectives: Cohort 2

- 2.3.1** To describe tolerability and acceptability of 48 weeks of CAB + RPV (oral and injectable) and 44 weeks of CAB LA + RPV LA (injectable only)

- 2.3.2** 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)
- 2.3.3** 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)
- 2.3.4** 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)

2.4 Other Objectives: Cohorts 1 and 2

The other objectives of this study are

- 2.4.1** To characterize long-term safety and washout PK through 48 weeks after permanent discontinuation of injectable CAB LA + RPV LA
- 2.4.2** To characterize PK of CAB + RPV oral formulations when dispersed in liquid vs. directly ingested (Weight Bands 3, 4 and 5)

3 STUDY DESIGN

3.1 Overview

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 (see [Section 6.15](#)). In-depth qualitative interviews with a subset of enrolled parents/caregivers will also be conducted as described in [Section 3.4](#). Unless otherwise noted, the term ‘participant’ will refer to the children enrolled in the study.

Refer to [Section 4](#) for the study eligibility criteria for participants and caregivers, as well as a description of the study recruitment, screening, and enrollment process. 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 weight bands as follows: Weight Band 1 (35- < 40 kg), 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 (defined in [Section 3.2](#)) 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).

Accrual into Weight Bands 1, 2, and 3 will begin first. 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 (see [Section 3.2](#)). 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, as outlined in [Section 10.3](#). 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 Sampling Schedule to the Limited Sampling Schedule (see [Section 10.3](#)).

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. Participants who meet the eligibility criteria outlined in [Section 4.3](#) and [Section 4.4](#) based on Week 4a visit will transition to Step 2 and receive injectable CAB LA + RPV LA through Week 72. Additional information about transitioning from Step 1 to Step 2 is provided in [Section 3.3](#). 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 (See [Section 6.3.3](#)). 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 (See [Section 3.2](#)), with the last injections administered at the Week 72 visit. In both steps, participants will follow the dosing regimens outlined in [Section 5.1](#).

Once Cohort 1 has completed accrual (defined as having enrolled either 50 evaluable participants, as described in [Section 3.2](#), 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/or the 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.

Section 6.6 provides details for 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.

3.2 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 (1) completed all treatment through Cohort 1 Week 12 visit 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 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 dose-evaluable 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.

See [Section 5.1.2](#) for more information on dosing regimen modifications. 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 (see [Section 9.5.4](#)). Once accrual is reopened, newly enrolling participants will begin on the modified dose. See [Section 9](#) for further details regarding the review of safety data at interim analyses, study monitoring, the Safety Guidelines, and triggered SMC reviews. See [Section 10.3.1](#) for further details regarding the review of PK data at interim analyses.

3.3 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 (See [Section 4.3](#) and [Section 4.4](#)). 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.

3.4 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.

4 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](#).

4.1 Inclusion Criteria, Step 1: Entry for Cohort 1, Cohort 2a, and Cohort 2b

Potential participants must meet all of the criteria specified below to be included in this study; in these criteria, “at entry” is used to refer to the day of enrollment in the study:

- 4.1.1** Parent or legal guardian is willing and able to provide written permission for child’s study participation and, when applicable per institutional review board/ethics committee (IRB/EC) policies and procedures, child is willing and able to provide written assent for study participation.

Note: All sites must follow all applicable IRB/EC policies and procedures; for US sites, this includes single IRB (sIRB) policies and procedures.

- 4.1.2** Age two years old to less than 12 years old at entry

- 4.1.3** Body weight ≥ 10 kgs and < 40 kgs at entry

- 4.1.4** At entry, willing and able to comply with the study visit schedule and other study requirements, as determined by the site investigator or designee.

- 4.1.5** Confirmed HIV-1-infection based on documented testing of two samples collected from two separate blood collection tubes per Sample #1 and Sample #2 requirements. Test results may be obtained from medical records or from testing performed during the study screening period:

- For results obtained from medical records, adequate source documentation, including the date of specimen collection, date of testing or date of test result, name of test/assay performed, and test result, must be available in study records prior to study entry. Requirements related to laboratory operations (e.g., Clinical Laboratory Improvements Amendment (CLIA), Good Clinical Laboratory Practice (GCLP), or Virology Quality Assurance Program (VQA)) and related to regulatory authority approvals (e.g., FDA) do not apply to results obtained from medical records.
- If adequate source documentation is not available, Sample #1 and/or Sample #2 should be collected during the study screening period and tested in the study site’s designated testing laboratory. At least one of the tests used to confirm infection must be performed in CLIA-certified or equivalent laboratory (for US sites) or in a DAIDS-monitored laboratory that is GCLP compliant and participates in an approved external quality assurance proficiency testing program (for non-US sites).

For participants with no exposure to breast milk in the past 28 days:

Sample #1 may be tested using any of the following:

- Two rapid antibody-based tests from different manufacturers or based on different principles and epitopes; combination antigen-antibody-based rapid tests may be used.
- One enzyme immunoassay (EIA) OR western blot (WB) OR immunofluorescence assay OR chemiluminescence assay
- One HIV-1 DNA polymerase chain reaction (PCR)
- One quantitative HIV-1 RNA PCR (above the limit of detection of the assay)
- One qualitative HIV-1 RNA PCR
- One HIV-1 total nucleic acid test

Sample #2 may be tested using any of the following:

- Rapid antibody-based test. If this option is used in combination with two rapid antibody-based tests for Sample #1, at least one of the three rapid tests must be FDA-approved and the third rapid test must be from a third manufacturer or based on a third principle or epitope; combination antigen-antibody-based rapid tests may be used.
- One EIA OR WB OR immunofluorescence assay OR chemiluminescence assay
- One HIV-1 DNA PCR
- One quantitative HIV-1 RNA PCR (above the limit of detection of the assay)
- One qualitative HIV-1 RNA PCR
- One HIV-1 total nucleic acid test

For participants with any exposure to breast milk in the past 28 days:

Sample #1 may be tested using any of the following:

- One HIV-1 DNA PCR
- One quantitative HIV-1 RNA PCR (above the limit of detection of the assay)
- One qualitative HIV-1 RNA PCR
- One total HIV-1 nucleic acid test

Sample #2 may be tested using any of the following:

- One HIV-1 DNA PCR
- One quantitative HIV-1 RNA PCR (above the limit of detection of the assay)
- One qualitative HIV-1 RNA PCR
- One total HIV-1 nucleic acid test

All study-specific samples tested to determine HIV-1 status must be whole blood, serum, or plasma. Testing methods and algorithms must be approved for each site by the IMPAACT Laboratory Center (for NIAID-funded sites) or Westat (for NICHD-funded sites). All testing methods should be FDA-approved, if available. On demand nucleic acid-based methods may be acceptable for use in site testing algorithms (for either Sample #1 or Sample #2).

4.1.6 Has been on a stable unchanged ART regimen consisting of two or more drugs from two or more antiretroviral drug classes for at least six consecutive months (defined as 180 consecutive days) prior to entry.

4.1.7 Has no prior history of switching ART regimens for reasons related to treatment failure based on parent/guardian report and/or available medical records.

Note: Participants undergoing dose modifications for growth or who have switched to a new formulation due to toxicity, tolerability, or changes in national treatment guidelines are considered eligible per this inclusion criterion. Treatment failure should be defined by local guidelines.

4.1.8 From a specimen collected less than six months (defined as within 179 days) prior to entry, has at least one of the following documented plasma HIV-1 RNA results:

- <50 copies/mL, or
- less than the lower limit of detection of the assay

- 4.1.9** From a specimen collected in the 6-18 months (defined as 180 to 545 days) prior to entry, has at least one of the following documented plasma HIV-1 RNA results:
- <50 copies/mL, or
 - less than the lower limit of detection of the assay

- 4.1.10** At screening, a documented plasma HIV-1 RNA <50 copies/mL.

Note: HIV-1 RNA test results at screening cannot be used to satisfy inclusion criterion [4.1.8](#). If participant does not have a documented HIV-1 RNA test result at screening that satisfies [4.1.8](#), they should be referred for standard of care testing and return at a later date for screening.

- 4.1.11** Has normal, Grade 1, or Grade 2 results for all the following laboratory tests at screening (i.e., within 28 days prior to entry) based on grading per the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events:

- 4.1.11.1** AST (<5.0 x ULN)
- 4.1.11.2** ALT (<5.0 x ULN)
- 4.1.11.3** Total bilirubin (<2.6 x ULN)
- 4.1.11.4** Lipase (<3 x ULN)
- 4.1.11.5** Estimated glomerular filtration rate (eGFR; ≥ 60 ml/min/1.73 m²)
- 4.1.11.6** Platelets ($\geq 50,000$ cells/mm³ or $\geq 50.00 \times 10^9$ cells/L)
- 4.1.11.7** Hemoglobin (≥ 8.5 g/dL or ≥ 5.25 mmol/L)
- 4.1.11.8** Neutrophils (≥ 600 cells/mm³)

Note: Laboratory tests may be repeated during the study screening period (i.e., within 28 days prior to entry), with the latest result used for eligibility determination. ALT and total bilirubin should also be assessed in consideration of [Section 4.2.7](#).

- 4.1.12** Has no evidence of chronic hepatitis B infection based on hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), and hepatitis B surface antibody (HBsAb) testing at screening; any of the following three combinations of test results are acceptable for inclusion:

- HBsAg negative, HBcAb negative, HBsAb negative
- HBsAg negative, HBcAb negative, HBsAb positive
- HBsAg negative, HBcAb positive, HBsAb positive

- 4.1.13** At screening, has a mean QTc interval (based upon a triplicate reading) less than or equal to 450 msec based on an electrocardiogram (ECG) automated machine readout or calculated using the Fridericia formula.

- 4.1.14** *For participants of childbearing potential*, not pregnant based upon negative blood or urine pregnancy test at entry. Childbearing potential is defined as:
- Nine years of age or older and having reached menarche or
 - Nine years of age or older, assigned female sex at birth, and engaging in sexual activity (self-reported) that could lead to pregnancy

- 4.1.15** *For participants of childbearing potential who are engaging in sexual activity (self-reported) that could lead to pregnancy*, at entry, currently using at least one allowable highly effective method of contraception and agrees to use at least one allowable highly

effective method of contraception throughout study participation and for at least 30 days after last oral product use and 48 weeks after last injectable study product use.

Highly effective methods of contraception include:

- Surgical sterilization (i.e., hysterectomy, bilateral oophorectomy, tubal ligation, or salpingectomy)
- Contraceptive intrauterine device or intrauterine system
- Subdermal contraceptive implant
- Progestogen injections
- Combined estrogen and progestogen oral contraceptive pills
- Percutaneous contraceptive patch
- Contraceptive vaginal ring

Note: See [Section 6.1.3](#) for details regarding contraceptive counseling. Internal or external condom use is recommended with all other methods of contraception for dual protection against pregnancy and to avoid transmission of HIV-1 and other sexually transmitted infections. Hormonal-based contraceptives must have been initiated within the prescribed time, per the respective contraceptive method, to be considered effective at the time of entry. The site IoR or designee is responsible for ensuring that the contraceptive is used in accordance with the approved product label, and counseling participants on proper use of chosen methods of contraception, including barrier methods.

4.2 Exclusion Criteria, Step 1: Entry for Cohort 1, Cohort 2a, and Cohort 2b

Potential participants must be excluded from the study if any of the conditions specified below are identified during the screening period (i.e., within 28 days prior to study entry). The screening period begins when parental permission and informed assent (if applicable) are obtained and ends immediately prior to enrollment. For criteria involving a potential participant's medical history, it is expected that each exclusionary condition will be assessed at screening and subsequently reviewed and confirmed on the day of study entry, prior to enrollment. In these criteria, "at entry" is used to refer to the day of enrollment in the study.

4.2.1 Within 6 months prior to entry, any HIV-1 RNA value >400 copies/mL OR two consecutive "viral blips," defined as an HIV-1 RNA value ≥ 50 copies/mL but ≤ 400 copies/mL.

4.2.2 As determined by the IoR or designee, and based on available medical records, known or suspected resistance to NNRTIs.

Note: Prior receipt of NNRTIs for prophylaxis or treatment is not exclusionary.

4.2.3 As determined by the IoR or designee, and based on available medical records, known or suspected resistance to INSTIs.

4.2.4 Ongoing congestive heart failure, symptomatic arrhythmia, or any current clinically significant cardiac disease, as determined by the IoR or designee, and based on available medical records.

- 4.2.5** Has any of the following, as determined by the IoR or designee based on participant/parent/guardian report and available medical records:
- 4.2.5.1** Current hepatitis C infection
 - 4.2.5.2** Current clinically significant hepatic disease
 - 4.2.5.3** Current or anticipated need for chronic anti-coagulation
 - 4.2.5.4** History of known or suspected bleeding disorder, including a history of prolonged bleeding
 - 4.2.5.5** History of sensitivity to heparin or heparin-induced thrombocytopenia, as determined by the IoR or designee, based on available medical records
 - 4.2.5.6** Risk factors for Torsade de Pointes (e.g., heart failure, hypokalemia, hypomagnesemia)
 - 4.2.5.7** Known or suspected allergy to study product components.
 - 4.2.5.8** Known phobia to needles
- 4.2.6** More than one seizure within one year (defined as within 365 days) prior to entry, or unstable or poorly controlled seizure disorder, as determined by the IoR or designee, and based on available medical records.
- 4.2.7** Has the following combination of laboratory test results at screening (i.e., from specimens collected within 28 days prior to entry): ALT greater than or equal to 3 x ULN and total bilirubin greater than or equal to 1.5 x ULN and direct bilirubin greater than 35% of total bilirubin.
- 4.2.8** At entry, known active tuberculosis infection, as determined by the IoR or designee based on participant/parent/guardian report and available medical records.
- 4.2.9** At entry, any ongoing pancreatitis as determined by the IoR or designee based on participant/parent/guardian report and available medical records.
- 4.2.10** At entry, has symptoms suggestive of active coronavirus disease 2019 (COVID-19) or test results or contacts that require quarantine per local clinical practice, public health, and/or infection control guidelines as determined by the IoR or designee based on participant/parent/guardian report and available medical records.
- Note:* Potential participants with symptoms suggestive of active COVID-19, test results, and/or contacts that require quarantine may resume screening (or be re-screened) after symptoms have resolved and applicable quarantine requirements have been completed.
- 4.2.11** Receipt of any prohibited medication within 7 days prior to entry, with the exception of antiviral agents that are part of the participant's ART regimen, as determined by the site investigator based on participant/parent/guardian report and available medical records, see [Section 5.7](#).
- Note:* Medications and vaccines approved for emergency use (e.g., COVID vaccines) that do not appear in the IMPAACT 2036 Prohibited and Precautionary Medications listing are not exclusionary may be administered as per standard of care.
- 4.2.12** Any past or current exposure to CAB LA or RPV LA

- 4.2.13** At entry, based on physical examination, has a current inflammatory skin condition that compromises the safety of intramuscular injections, as determined by the IoR or designee.
- 4.2.14** At entry, based on physical examination, has a dermatological condition overlying the buttock or upper thigh region, which, in the IoR or designee's opinion, may interfere with the interpretation of injection site reactions.
- 4.2.15** Enrolled in another clinical trial of an investigational agent, device, or vaccine.
- 4.2.16** Has any documented or suspected clinically significant medical or psychiatric condition or any other condition or social circumstance that, in the opinion of the site investigator, would make participation unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives.

4.3 Inclusion Criteria, Step 2: Continuation for Cohort 1 and Cohort 2a to injection phase

All participants enrolled in Cohort 1 or Cohort 2a will be assessed for eligibility to progress from the oral lead-in phase (Step 1) to the injection phase (Step 2), primarily based on the safety assessments from the Step 1 Week 4a study visit. Clinical assessments conducted prior to administering the first injection at the Week 4b visit will also be used to confirm eligibility to receive the injectable study product. See [Sections 6.3.3](#) and [6.3.4](#) for Week 4a and Week 4b visit scheduling and order of procedures, respectively.

All of the following criteria must be met in order for a participant enrolled in Cohort 1 or Cohort 2a to be included in Step 2:

- 4.3.1** Currently enrolled as a participant in Step 1.
- 4.3.2** Has normal, Grade 1, or Grade 2 results from all of the following laboratory test results based upon specimens collected at the Week 4a study visit or from confirmatory repeat testing of Week 4a study visit laboratory tests:

- 4.3.2.1** AST ($<5.0 \times \text{ULN}$)
- 4.3.2.2** ALT ($<5.0 \times \text{ULN}$)
- 4.3.2.3** Lipase ($< 3 \times \text{ULN}$)
- 4.3.2.4** Estimated glomerular filtration rate (eGFR; $\geq 60 \text{ ml/min/1.73 m}^2$)
- 4.3.2.5** Platelets ($\geq 50,000 \text{ cells/mm}^3$ or $\geq 50.00 \times 10^9 \text{ cells/L}$)
- 4.3.2.6** Hemoglobin ($\geq 8.5 \text{ g/dL}$ or $\geq 5.25 \text{ mmol/L}$)
- 4.3.2.7** CK ($\geq 6 \text{ u/l}$)

Note: For a Grade 2 ALT test result from this visit, refer to [Section 8.1.6](#) for required participant management.

- 4.3.3** *For participants of childbearing potential*, defined as having experienced menarche or assigned female sex at birth and engaging in sexual activity (self-reported) that could lead to pregnancy, not pregnant based upon negative blood or urine pregnancy test at the Week 4b study visit.

- 4.3.4** Assessed by the IoR or designee as sufficiently adherent to study products in Step 1 to permit an adequate evaluation of safety and tolerability as part of the oral lead in phase prior to entry into the injection phase. See protocol [Section 6.14](#).

4.4 Exclusion Criteria, Step 2: Continuation for Cohort 1 and Cohort 2a to injection phase

Participants in Cohort 1 or Cohort 2a who meet any of the following criteria will be excluded from Step 2:

- 4.4.1** Has permanently discontinued oral study product.
- 4.4.2** Occurrence of any grade 3 or higher adverse event assessed as related to study product during Step 1.
- 4.4.3** Any other condition or social circumstance situation that, in the opinion of the IoR or designee, would make continued study participation unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives.

4.5 Inclusion Criteria for Parents/Caregivers

Parents/caregivers of participants will be considered for enrollment to complete quantitative behavioral surveys and/or qualitative in-depth interviews (IDIs), as indicated in the SoE. One parent/caregiver per participant should be enrolled to complete all behavioral assessments, including the IDI, when applicable. Informed consent for parent/caregiver enrollment should be obtained at the entry visit, after the child participant's eligibility has been confirmed, and may be completed at a later date, if necessary. However, parent/caregiver consent must occur prior to any study assessments being conducted. The enrolled caregiver may be the different than the parent or legal guardian who provided written permission for the child to participate. If, at any point the enrolled parent/caregiver for a given participant withdraws from the study or is unable to complete remaining study assessments for any reason, they may be replaced.

Caregivers must meet the following criteria to be eligible to enroll in IMPAACT 2036:

- 4.5.1** 18 years of age or older
- 4.5.2** Able and willing to provide written informed consent consistent with site IRB/EC policies and procedures
- 4.5.3** Caregiver, defined as a biological parent, legal guardian, or other person who provides significant emotional, psychological, and/or physical care to a child enrolled in IMPAACT 2036, based on self-report

4.6 Exclusion Criteria for Parents/Caregivers

- 4.6.1** Any condition or social circumstance situation that, in the opinion of the IoR or designee, would make study participation unsafe for the caregiver or the child study participant, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives.

4.7 Co-Enrollment Considerations

Co-enrollment in other studies is allowable for parents/caregivers. For participants, co-enrollment in other studies that do not involve an investigational agent, device, or vaccine may be allowed, although careful consideration must be given to visit burden, blood draw volumes, and interpretation of outcome data across studies. Given these considerations, requests for co-enrollment must be approved in advance by teams of both studies. Requests for such approval should be emailed to the IMPAACT 2036 Clinical Management Committee (CMC).

4.8 Recruitment, Screening, and Enrollment Process

This section provides a description of the recruitment methods, screening and enrollment processes, and the definition of enrollment for participants.

Recruitment methods for this study may vary across sites. In general, recruitment of participants, is expected to rely on current clients being seen at a study clinic or from active identification and referral of children living with HIV-1 who are ART-experienced and virologically suppressed; participants may have acquired HIV-1 perinatally or behaviorally. Any study advertising materials must undergo approval by the sIRB (for US sites), or site IRBs/ECs (for non-US sites). Sites are encouraged to solicit input and feedback on recruitment materials from their local Community Advisory Board.

Upon identification of a potentially eligible participant, study staff will provide information about the study to the parent or legal guardian and/or the potential participant (as applicable). Each parent or legal guardian and/or potential participant (as applicable) who expresses interest in learning more about the study will be provided additional information, education, and counseling as part of the study parental permission and informed assent process. The process will include detailed review of the study parental permission and informed assent forms, time to address any questions or concerns the potential participant, parent, or legal guardian may have, and an assessment of understanding, before proceeding to parental permission and informed assent decisions. The parental permission and informed assent processes will be fully documented, consistent with the DAIDS policies referenced in [Section 13.3](#).

Each site must establish standard operating procedures (SOPs) for eligibility determination that describe where and when screening procedures will be performed; roles and responsibilities for performing the required procedures; roles and responsibilities for assessing and confirming eligibility; and procedures for documenting the process, taking into consideration the required timing of enrollment. Sites are encouraged to minimize the time from screening to enrollment.

Eligibility screening will be initiated after written parental permission and informed assent (as applicable) is provided. The Study Enrollment System (SES) will assist in tracking of the screening process and obtaining a study-specific screening number. Screening will include confirmatory HIV-1 testing (if needed) and assessment of other entry criteria. If at any time it is determined that an individual is not eligible for the study, or that study participation may not be feasible or in the participant's best interest, the eligibility screening process will be discontinued; these individuals should be actively referred to non-study sources of care. Screening assessments, unless otherwise noted (see [Section 6.2](#)), must be completed within 28 days prior to entry. Re-screening is permitted one time and will require most screening procedures to be repeated, as specified in [Section 6.1](#).

The IMPAACT Data Management Center (DMC) SES will be used to assist with tracking the screening and enrollment process, within and across weight bands. When parental permission and informed assent (as applicable) are obtained, a participant identification number (PID) will be assigned to the potential participant and a study-specific screening number will be obtained through the SES. For participants found to be eligible, enrollment will occur upon successful entry of

required eligibility data into the SES. Successful entry into the SES will generate a study identification number and study drug prescribing information. For potential participants found to be ineligible for the study, or who do not enroll in the study for any reason, limited demographic information and reasons for non-enrollment will be entered into electronic case report forms (eCRFs).

4.9 Recruitment, Screening, and Enrollment Process for Parents/Caregivers

Recruitment of parents/caregivers will generally rely on site staff identification of potentially eligible caregivers as they present to the study clinic. A brief description of the parent/caregiver component should be provided to the parent or legal guardian who is providing written parental permission for the child's study participation at the child's screening visit. The parent or legal guardian may indicate their own interest and willingness to participate or may identify a different parent/caregiver to participate in this component of the study. One parent/caregiver of each enrolled child should be approached to complete the caregiver behavioral assessments, assessed for eligibility, and enrolled if eligible (if ineligible, additional parents/caregivers may be approached/assessed for eligibility, as needed, with the goal of enrolling one parent/caregiver per child participant). Sites must source document parent/caregiver recruitment and follow their IRB/EC approved recruitment methods for approaching a potential parent/caregiver participant. Parent/caregiver recruitment, screening, and enrollment may only occur after child participant enrollment in the main study.

Parents/caregivers must provide informed consent prior to their enrollment and completion of the quantitative survey and/or qualitative interview(s). Eligibility criteria are provided in [Section 4.5](#) and [Section 4.6](#) and must be confirmed and source documented after obtaining informed consent. Eligibility determination for parents/caregivers must also be included in site SOPs, which describe how, where and when recruitment and confirmation of eligibility criteria will be performed; roles and responsibilities for assessing and confirming eligibility; and procedures for documenting the process.

The Data Management Center (DMC) system will not be used for tracking the parent/caregiver screening process. However, sites will source document reasons for any consenting caregiver found to be ineligible. For parents/caregivers found to be eligible, enrollment into the study will occur upon successful entry of required eligibility data into the IMPAACT DMC Study Enrollment System (SES). Successful entry into the SES will generate a study identification number (SID).

The IMPAACT 2036 MOP provides further guidance on operational and logistical considerations of assessing and confirming eligibility, and enrolling parents/caregivers to the study for completion of quantitative surveys and qualitative interviews.

4.10 Participant Retention

Once a participant is enrolled in this study, study staff will make every effort to retain them in follow-up for the protocol-specified duration of follow-up, thereby minimizing potential biases and loss of statistical power associated with loss-to-follow-up. Refer to [Section 9.5.3](#) for more information on monitoring participant retention in this study.

5 STUDY PRODUCT

Site pharmacists should consult the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* for standard pharmacy operations. For this study, the term study product refers to CAB (tablet, dispersible tablet, injection) and RPV (tablet, tablet which must be dispersed, injection). Refer to the Investigator's Brochure (IB) for Cabotegravir and the IB for TMC278 (rilpivirine, oral and parenteral) for further information about these study drug formulations.

5.1 Study Product Regimen

At Entry, all participants will discontinue their pre-study cART regimen and will be assigned to a dosing regimen based on their weight at entry to the applicable cohort. Weight-based dose adjustments will be made according to guidance provided in [Section 5.1.1](#) below. Dosing regimens may be modified following the Cohort 1 interim analyses or based on experience in the study, in which case, the new regimen will be specified per [Section 5.1.2](#) below.

Cohort 1 participants will receive oral CAB + oral RPV followed by intramuscular CAB LA + RPV LA as shown in [Table 1](#) (for oral dosing) and [Table 2](#) (for LA injections).

Cohort 2a participants will receive oral CAB + oral RPV followed by intramuscular CAB LA + RPV LA. Cohort 2b participants will receive intramuscular CAB LA + RPV LA only. As described in [Section 3](#), Cohort 2a and Cohort 2b will be opened to accrual following the Cohort 1 interim analyses and full accrual of Cohort 1. The oral and injectable dosing regimens for both Cohort 2a and Cohort 2b will also be communicated, per weight band, at that time; see [Section 5.1.2](#) below.

Table 1.
Cohort 1: Initial Oral Lead-In Dosing Regimen

Weight Band	Daily Oral Dose (through the Week 4b visit)
Weight Band 1 35-<40 kg	30mg CAB + 25mg RPV <ul style="list-style-type: none">Administered as one 30mg CAB tablet + one 25mg RPV tablet
Weight Band 2 25-34.9 kg	10mg CAB + 25mg RPV <ul style="list-style-type: none">Administered as two 5mg CAB DT + one 25mg RPV tablet
Weight Band 3 20-24.9 kg	10mg CAB + 15mg RPV <ul style="list-style-type: none">Administered as two 5mg CAB DT + six 2.5mg RPV tablets
Weight Band 4 14-19.9 kg	10mg CAB + 12.5mg RPV <ul style="list-style-type: none">Administered as two 5mg CAB DT + five 2.5mg RPV tablets
Weight Band 5 10-13.9 kg	10mg CAB + 12.5mg RPV <ul style="list-style-type: none">Administered as two 5mg CAB DT + five 2.5mg RPV tablets

Table 2.
Cohort 1: Initial (Q4W) IM Injection Dosing Regimen

Weight Band	Q4W Long-acting IM Dose Regimen
Weight Band 1 35-<40 kg	Initial injections (Wk 4b): 600mg CAB LA + 900mg RPV LA Subsequent injections (following Wk 4b), every four weeks: 400mg CAB LA + 600mg RPV LA
Weight Band 2 25-34.9 kg	Initial injections (Wk 4b): 300mg CAB LA + 600mg RPV LA Subsequent injections (following Wk 4b), every four weeks: 200mg CAB LA + 450mg RPV LA
Weight Band 3 20-24.9 kg	Initial injections (Wk 4b): 300mg CAB LA + 600mg RPV LA Subsequent injections (following Wk 4b), every four weeks: 200mg CAB LA + 450mg RPV LA
Weight Band 4 14-19.9 kg	Initial injections (Wk 4b): 300mg CAB LA + 450mg RPV LA
Weight Band 5 10-13.9 kg	Subsequent injections (following Wk 4b), every four weeks: 200mg CAB LA + 300mg RPV LA

5.1.1 Dose Adjustments Due to Changes in Weight Band

Participant weight at the Entry visit will establish the participant's weight band and the assigned oral dosing for the full duration of the oral lead-in phase. Oral dosing will not be adjusted due to weight band changes (increases or decreases in weight) which may occur during the oral lead-in phase.

At each injection visit, participant weight will be assessed prior to administering study product to determine the appropriate weight band and injectable dosing regimen to be administered at that visit. Participants who increase in weight bands will begin the dosing regimen corresponding to their new applicable weight band. However, decreases in weight band will not result in a dose change; participants will remain on the dose regimen of the largest weight band achieved.

5.1.2 Dosing Regimen Modifications

Dosing regimen modifications for each weight band may occur as needed following the Cohort 1 interim analyses and/or based on ongoing reviews of safety, PK, viral load, tolerability, and all other relevant data within the study or from other ongoing studies of the study drugs in pediatric populations. If a dose modification is indicated, accrual will be paused in the relevant weight band(s) until an SMC review is convened, and the proposed dose modification is approved. Dose modifications, and the initial doses for Cohort 2 as noted above, will be selected from the tables in [Appendix VII](#). Accrual pauses, resuming accrual, and dose modifications will be communicated to sites by Memoranda of Operational Instruction, approved by the CMC. See [Section 9.5.1](#). Currently enrolled and newly enrolling participants will be assigned to the updated dosing regimens.

In the event of an injection regimen modification from Q4W to Q8W dosing, enrolled participants still in the oral lead-in phase will receive injections on the Q8W schedule. Enrolled participants who have initiated injections on a Q4W injection schedule and have completed the Week 12 visit will continue to receive injections on a Q4W schedule through the Week 24 (Cohort 1 and Cohort 2a) or Week 20 (Cohort 2b) visit. The Memorandum of Operational Instruction will provide additional dosing regimen transition guidance for participants already on treatment, including those who have only received the first two sets of injections of CAB LA + RPV LA (Week 4b and Week 8), at the time of any modifications. See [Section 6.1.2](#) for more information.

5.1.3 Oral Bridging for Participants Receiving Long-Acting Injectables

In exceptional circumstances and following consultation with the CMC, sites may provide daily oral CAB + RPV as a bridging strategy for participants who will miss a scheduled injection. Oral study product may be dispensed to study staff for providing to a participant off-site or shipped from the site directly to the participant. The pharmacist should refer to the Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks for detailed procedures regarding shipping study product. When supplying oral bridging for participants on long acting injectables (Cohort 1 and 2a, Step 2 and Cohort 2b), the site should ensure sufficient coverage for daily use until the participant can resume study product injections. The oral study product weight band dosing regimen will be assigned according to the participant's weight obtained at the most recent study visit (whether a regularly scheduled visit or an interim visit).

Participants are to ideally begin the oral bridging regimen on the same target visit date (or within the same target visit window) as that of the missed injection visit. The last dose of the short-term oral bridging regimen should be taken on the same day as and prior to resuming injectable study product. The CMC must be consulted prior to resuming study product injections. Step 2 participants may be required to have interim injection visits upon resuming the study product injections to appropriately reinitiate the dosing regimen or to realign to the original injection visit dosing schedule.

See [Section 6.9](#) for required procedures prior to dispensing oral study products or administering study product injections. See [Section 6.5](#) for interim injection visits.

5.2 Study Product Formulation and Storage

5.2.1 Oral CAB (Tablets and DT)

Cabotegravir 30 mg tablets are formulated as white to almost white oval-shaped film-coated tablets for oral administration. Cabotegravir 30 mg tablets may also be debossed with the code "SV CTV" on one face. The tablets are packaged in high density polyethylene (HDPE) bottles with child resistant closures that include induction seal liners. The bottles contain 30 tablets and a desiccant. The tablets must be stored up to 30° C (86° F) in the original container with the desiccant, and protected from moisture.

Cabotegravir 5 mg dispersible tablets will be provided in HDPE bottles containing 30 tablets with a child-resistant closure that includes an induction seal. Bottles will also contain a desiccant canister to protect the tablets from moisture. Each tablet contains 5 mg of CAB and is a pink, film-coated, oral, biconvex tablet debossed with "SV C5" on one side and plain on the other side. CAB dispersible tablets must be stored at controlled temperatures up to 30°C (86°F) in the original packaging, protected from light and moisture.

5.2.2 Oral RPV (Tablets)

RPV 25 mg tablets are formulated as white to off-white, film-coated, round, biconvex tablets for oral administration. Each tablet is debossed with “TMC” on one side and “25” on the other side. Tablets are packaged in bottles containing 30 tablets. Tablets should be stored in their original bottles to protect from light. The tablets must be stored at 25° C (77° F) with excursions permitted to 15°-30°C (59°-86°F). Further information on the study product is available in the EDURANT® Prescribing Information.

Rilpivirine 2.5 mg tablets will be provided in a carton containing seven blister strips, each strip containing 24 individually packaged tablets. Each tablet contains 2.5 mg of RPV and is a round tablet white to off-white in color. RPV 2.5mg tablets must be stored at 15°C to 30°C (59°F to 86°F) and protected from moisture.

5.2.3 Injectable CAB LA

CAB LA is formulated as a sterile white to slightly pink suspension containing 200mg/mL of cabotegravir free acid for administration by IM injection. The product is packaged in a glass vial with stopper and an aluminum seal with a plastic flip-off lid. Each vial is for single use and contains a nominal fill volume of 2 mL (400 mg of CAB LA) or 3 mL (600 mg of CAB LA). Dilution is not required prior to administration. Store vials up to 30° C (86° F) in the study site pharmacy; do not freeze.

5.2.4 Injectable RPV LA

RPV LA is formulated as a sterile white to off-white suspension containing 300 mg/mL of RPV free base for administration by IM injection. The product is packaged in single-use vials, containing a nominal fill volume of 2 mL (600 mg of RPV LA) or 3 mL (900 mg of RPV LA). Dilution is not required prior to administration. Vials must be stored refrigerated at 2° to 8° C (36° to 46° F) in the study site pharmacy; protect from light and do not freeze.

5.3 Study Product Dispensing, Preparation, and Administration

See [Section 6.9](#) for required study procedures to be conducted prior to dispensing oral study product or administering a study product injection.

For each injection visit, the site pharmacists must receive a new prescription(s) from an authorized prescriber that documents the participant's current weight and dosing regimen prior to dispensing study products (tablets, dispersible tablets or tablets which must be dispersed, or injectable). The prescription, at a minimum, must include the name of each individual study product to be prepared, dispensed and administered to the participant along with the specific dose, quantity or volume, and directions for administration in addition to any in country and/or institutional requirements.

For injectable study product prescriptions, if the pharmacy needs to attach a needle for administration prior to dispensation (versus a syringe cap) per institutional policy, the prescription should also include the size and gauge of the needle to be attached to each prepared study product.

5.3.1 Oral Study Product

Dispensing

At the Entry visit for Cohort 1 and Cohort 2a, the site pharmacist should dispense enough CAB + RPV oral study products so the participant has enough tablets to administer the required dosing through their Week 4b Visit. The last dose of oral study product is generally expected to be administered during the Week 4b visit, after which the participant will receive their first doses of intramuscular CAB LA + RPV LA during the same study visit. If needed, an additional supply of both CAB + RPV oral study products may be dispensed at the Week 2 or Week 4a visits to ensure sufficient coverage for daily use through the participant's scheduled Week 4b visit and their first set of study product injections. See [Section 6.3.4](#) for more details on the Week 4b visit.

Administration

Regardless of formulation, the first doses of oral CAB + RPV will be administered in the clinic at the Entry visit for Cohort 1 and Cohort 2a and must be directly observed by study staff. At the Week 2, Week 4a, and Week 4b (if indicated) study visits, the oral study product dose must also be administered and/or witnessed by clinic staff. If desired, the observed doses during these visits can be prepared and/or administered by the participant (or caregivers, as applicable) as part of the study product adherence assessment process.

CAB + RPV Tablet Administration

Oral CAB + RPV tablets are to be taken at the same time, once daily with a meal. Refer to the IMPAACT 2036 MOP for additional instructions and guidance on the administration of these doses.

CAB 5 mg DT + RPV 2.5 mg tablets Preparation and Administration

Oral CAB 5mg DT + RPV 2.5 mg tablets are to be prepared individually and taken separately, but at the same time, once daily with a meal.

At Entry for Cohort 1 and Cohort 2a, the study staff will instruct the participant (or caregiver, as applicable) how to properly prepare the oral CAB 5 mg DT and oral RPV 2.5 mg tablets and administer the doses to the participant. Refer to [Appendix VI](#) for detailed instructions on the preparation of oral CAB 5mg DT and oral RPV 2.5mg tablet doses.

For participants in Cohort 1 who are of the appropriate weight band to utilize CAB dispersible tablets (DT) and RPV 2.5 mg tablets, both types of tablets must be dispersed in liquid prior to use per instructions in [Appendix VI-A](#) and [Appendix VI-B](#). However, participants in Cohort 2a will have the option to disperse the tablets in liquid prior to ingesting or ingest by swallowing the tablets whole followed by swallowing liquid to push the medications to the stomach. Cohort 2a participants may choose different administration methods for CAB and RPV and may switch between methods, as preferred, but should be consistent in their chosen method for each medication during the 3 days prior to the Week 2 and Week 4b study visits.

For all doses observed in the clinic, as well as for the three days prior to the Weeks 2 and 4b visits (as applicable), the following will be source documented and entered into eCRFs:

- Dates and times of each oral product dosing
- Food intake
- Administration method

Competency of the caregiver to properly prepare and administer the dispersible tablet/2.5 mg tablet doses to the participant must be documented in the participant's chart by study staff prior to completion of the study visit.

Refer to the IMPAACT 2036 MOP for additional instructions and guidance on the administration of these doses.

Redosing

If the participant vomits within the first 30 minutes after administration (of either oral formulation), the dose should be repeated for the specific oral study product (CAB and/or RPV). See [Section 6.3.2](#) for details regarding PK sampling scheduling during the Week 2 visit (intensive PK visit).

5.3.2 Injectable Study Product

Preparation and Dispensing

The Pharmacist of Record must be proficient in the preparation of products requiring aseptic technique under a pharmacy biological safety cabinet/isolator. Local regulations and site institutional policies and procedures for use of protective equipment, such as gloves, gowns, and masks, and safety glasses, must be followed. Refer to [Appendix VI](#) for detailed instructions on the preparation of injectable study products.

Injectable study product should be dispensed to authorized study staff after being prepared as described above.

Administration and Observation

All injections will be administered using standard IM injection technique in the gluteus medius or lateral aspect of the thigh. See IMPAACT 2036 MOP for additional information about injection sites and injection techniques. Injectable study product must be administered within the respective study visit windows or per CMC guidance (for participants requiring an interim injection visit); see [Appendix II](#) visit window requirements.

The following information must be source documented and entered into eCRFs with each injection of each study product:

- Location of administration, including whether the gluteus medius or thigh, and which side of the body (left or right)
- Needle length and needle gauge used
- Volume of each injectable study product administered
- Date and time of administration

Whenever possible, CAB LA is to be administered in the contralateral gluteus medius muscle (or thigh) from the RPV LA. However, if the participant/caregiver prefers, injections can be administered on the same side with the injection sites at least 2 cm apart. In these instances, site staff must source document where on the gluteus medius muscle (or thigh) each injection has been administered to assess the injections' adverse reactions.

Persons administering injections should carefully follow the instructions for use to avoid accidental intravenous administration. It is important that the vials are brought up to room temperature before administering the injection and the suspension is injected slowly.

In order to monitor for any post-injection reaction, participants should be observed briefly (approximately 10 minutes) after the injections are given. See [Section 8.1.3](#) for guidance on suspected IM maladministration.

Refer to the IMPAACT 2036 MOP for additional guidance on the administration of the injectable study products, including injection techniques.

5.4 Study Product Supply

CAB (tablet, DT, and LA) will be manufactured and supplied by ViiV Healthcare Ltd.

RPV (tablet, 2.5 mg tablet, and LA) will be manufactured by Janssen Pharmaceutical, Inc. and supplied by ViiV Healthcare Ltd.

All of the above-listed study drugs will be made available to study sites through the NIAID Clinical Research Products Management Center (CRPMC). Upon successful completion of protocol registration procedures, these study drugs may be obtained by the site pharmacist following instructions provided in the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks*.

Dosing cups will be provided to study sites by CRPMC, but all other ancillary supplies such as oral syringes, needles and syringes should be obtained locally by the site. Should supplies not be available locally (e.g., due to stock outs), the protocol team may be able to assist with procurement.

5.5 Study Product Accountability

Site pharmacists must maintain complete records of all study products received from the CRPMC and subsequently dispensed to study participants. All study products must be stored in the pharmacy.

5.6 Final Disposition of Study Product

Participants who temporarily or permanently discontinue oral study product will be instructed to return all oral study products to the site clinic as soon as possible. Participants who complete the OLI period will be instructed to return all leftover oral study products to the site clinic at their Week 4b visit upon completion of their oral dosing regimen.

All unused study products remaining at U.S. sites after the study is completed or terminated will be returned to the CRPMC (unless otherwise directed by DAIDS). At non-U.S. sites, any remaining unused study products will be quarantined for destruction. Study products may also be returned to the CRPMC for other reasons, as requested by DAIDS. Site pharmacists will follow the relevant instructions for return or destruction of unused study products provided in the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks*.

5.7 Concomitant Medications

The term “concomitant medications” is used in this study to refer to medications other than the study products listed in [Section 5.7](#). All concomitant medications received by enrolled participants must be source documented as part of the medical and medication histories obtained at each study visit. This includes prescription and non-prescription (over-the-counter) medications; vaccines (including COVID vaccines), childhood immunizations, and other preventive medications; therapeutic foods and nutritional supplements; and alternative, complementary, and traditional medications and

preparations. All concomitant medications (except herbal or traditional) are to be entered into eCRFs.

Precautionary and Prohibited Concomitant Medications

For a list of medications that should be used with caution and prohibited medications while on study product, refer to [Appendix III](#).

Any study participant who requires a medication considered prohibited while on study product must have the study product held or permanently discontinued. Upon identification of the need for a prohibited medication, the site investigator should consult the CMC for further guidance on determining next steps for clinical management, study product management, and per [Section 8.4](#).

6 STUDY VISITS AND PROCEDURES

An overview of the study visits, evaluation schedule, and blood draw volumes is provided in [Appendix I](#). This section contains additional information on visit-specific study procedures.

In addition to the protocol-specified procedures listed in this section, study staff may complete other tasks consistent with site SOPs, including but not limited to collecting, reviewing, and updating demographic and locator information; conducting additional clinical assessments, reviewing elements of parental permission and informed assent; scheduling visits; providing instructions for contacting study staff between visits; providing visit reminders; and following up on missed visits. All such tasks should be documented consistent with site SOPs. Study staff should inform parents or legal guardians of clinically meaningful physical exam findings and laboratory test results when available.

All visits and procedures must be documented in accordance with the DAIDS requirements for source documentation; refer to [Section 11](#) for more information on documentation requirements and entry of data on eCRFs. Refer to [Section 7](#) for information on expedited adverse event (EAE) reporting, which may be required at any time during follow-up.

All injections and blood draws must be performed at the approved clinical research site or approved associated facilities, unless otherwise noted. Other study visit procedures may be conducted off-site at an agreed upon location and with written permission. Some procedures may also be conducted telephonically, where noted throughout this section. For sites that may experience operational disruptions due to COVID-19, additional guidance for study implementation during periods of disruption is provided in [Appendix VIII](#).

In the event that a participant re-locates away from the study site, options for transfer to another site should be explored; when a transfer is possible, procedures for transferring and receiving sites should be carried out consistent with guidance provided in the IMPAACT Manual of Procedures.

6.1 Study Visit Windows, Split and Interim Visits

6.1.1 Study Visit Windows and Additional Considerations for Injection Visits

All visits should be conducted as close as possible to specified target visit dates and within specified visit windows. Target visit dates, visit windows, and minimum/maximum days between injections are summarized for all cohorts and all visit types in [Appendix II](#).

For study product injection visits, target visit dates and target visit windows are based on the participant's first study product injection. In addition, study product injections must be administered within the minimum and maximum ranges from the previous injection. Depending on when the previous injection was administered, the requirements related to minimum/maximum days between injections may impact the number of days falling within the target visit window of the subsequent injection visit. Scheduled injection visits that do not occur within the target window and satisfy minimum/maximum requirements are considered missed, and the CMC must be consulted regarding clinical considerations and study product management in instances when the scheduled injection visit does not occur within these timeframes.

In the event that a scheduled visit is missed (i.e., no procedures for a given visit type are completed within the applicable window), the missed safety and PK evaluations should be completed as soon as possible as an interim visit or made up at the next scheduled visit.

Sites are expected to make every effort to schedule and conduct each study visit on the respective target visit date, or, when necessary, within the target visit window. Further guidance on scheduling study visits is provided in the IMPAACT 2036 MOP.

6.1.2 Additional Considerations for a Q8W Injection Schedule

In the event of a dosing regimen modification (see [Section 5.1.2](#)), the follow-up visit schedule for each cohort will remain per [Sections 6.3](#) through [6.6](#) and per [Appendix I](#). However, injections and other select visit procedures, as specified below, will only occur at a Q8W frequency.

Participants newly enrolling into the study on a Q8W injection schedule will have injectable study product administered at the following visits:

- For Cohort 1 (through Week 72) and Cohort 2a (through Week 48 only): Weeks 4b, 8, 16, 24, 32, 40, 48, 56, 64, and 72.
- For Cohort 2b: Entry, Week 4, and at Weeks 12, 20, 28, 36, 44.

When receiving injectable study products on a Q8W schedule, acceptability/tolerability assessments for participants and parents/caregivers and all laboratory evaluations (including urine pregnancy tests and all bloodwork) will be administered on a Q8W schedule and will only take place at injection visits. Non-injection visits for participants on a Q8W injection schedule may be conducted in person or telephonically.

See the IMPAACT 2036 MOP for further details regarding implementation of a dosing regimen modification and associated procedural changes when moving from Q4W to Q8W dosing.

6.1.3 Split and Interim Visits

All visit procedures specified to be performed at scheduled visits should ideally be performed on the same day. However, if it is not possible to conduct all visit procedures on the same day (e.g., if a participant must leave the clinical research site before all procedures can be performed), visits may be split, with procedures performed on more than one day, unless otherwise noted. See [Section 6.9](#) for required study visit procedures to be performed on the same day as and prior to dispensing of oral study product or prior to administration of injectable study product.

Interim contacts and visits (those between regularly scheduled follow up visits) may be performed at participant request or as deemed necessary by the site investigator or designee at any time during the study. Interim visits at which no data are collected should be source documented but not entered into eCRFs. When interim contacts or visits are completed in response to participant reports of adverse events, study staff will assess the reported event clinically, enter the event into

eCRFs and provide or refer the participant to appropriate medical care. See [Section 8.1](#) for participant management and specified adverse event management. In rare circumstances, the CMC may provide guidance to collect additional PK samples and conduct clinical procedures or laboratory evaluations during an interim visit. For participants initiating oral bridging, an interim visit may be conducted to dispense oral study products and conduct required procedures per [Section 6.9](#) or when resuming injections. [Section 6.5](#) provides additional information on interim injection visits.

Further details and guidance on scheduling and conducting visits are provided in the IMPAACT 2036 MOP.

6.2 Screening Visit: Cohort 1 and Cohort 2

Screening may be initiated after written parental permission and informed assent (as applicable) are obtained. All screening procedures must be performed within 28 days prior to study entry. Multiple visits may be conducted within the 28-day time frame to complete all required procedures and to repeat laboratory tests for confirmation, if necessary. For potential participants who do not meet the eligibility criteria, screening is expected to be discontinued once ineligibility is determined. Participants may rescreen once. If any participant is rescreened, all screening procedures listed in the table below must be repeated, with the following exceptions:

- A new PID should not be assigned (Note: Obtain new screening number from SES for second screening attempt)
- Confirmatory HIV-1 testing, if conducted during first screening attempt, need not be repeated
- Previously documented medical and medications history information should be reviewed and updated through the date of re-screening (it is not necessary to re-record history information that was previously documented)

Information about Cohort 2a and Cohort 2b should be provided to potential Cohort 2 participants as part of the parental permission and informed assent process and a decision about which group to join should be made by the study participant and parent/legal guardian in consultation with the IoR or designee and other healthcare providers, as applicable.

Screening Visit Procedures		
Administrative and Regulatory		<ul style="list-style-type: none"> • Obtain written parental permission/informed assent • Assign PID • Obtain screening number from SES • Collect demographic and locator information
Behavioral and Counseling		<ul style="list-style-type: none"> • Provide HIV-1 pre-/post-test counseling, <i>if indicated</i> • Provide contraceptive counseling[^]
Clinical		<ul style="list-style-type: none"> • Obtain available medical records and medical and medications history • Assess documentation of HIV-1 infection • Assess ARV history • Assess HIV-1 RNA test result history • Perform complete physical exam • Perform an ECG (in triplicate)
Laboratory	Blood	Collect blood for: <ul style="list-style-type: none"> • Confirmatory HIV-1 testing, <i>if indicated</i> • Hematology: CBC (WBC, RBC, hemoglobin, hematocrit, MCV, MCHC) with differential, ANC (absolute neutrophil count), and platelet count • Chemistries: Creatinine, eGFR, Direct bilirubin, Total bilirubin, Blood Urea Nitrogen (BUN), AST, ALT, Lipase • Hepatitis B testing: HBsAg, HBcAb, HBsAb • HIV-1 RNA
	Blood or Urine	<ul style="list-style-type: none"> • Pregnancy test[^]

[^] For participants of childbearing potential.

6.3 Cohort 1 and Cohort 2a

6.3.1 Step 1 Entry Visit: Cohort 1 and Cohort 2a (oral phase)

The Step 1 Entry visit must occur within 28 days (inclusive) from the Screening Visit and may not be split over multiple days. Step 1 Entry visit procedures that may provide information relevant to eligibility for the study should be performed first, prior to final eligibility determination and enrollment. In the event a participant is found to be ineligible on the day of enrollment, enrollment should not occur.

The following visit procedures must be conducted during the Step 1 Entry Visit in the sequence specified below:

- Complete final eligibility determination and confirmation: medical and medications history including ARV history assessment, targeted physical exam, and a pregnancy test for participants of childbearing potential, defined as having reached menarche or assigned female sex at birth and engaging in sexual activity that could lead to pregnancy.
- Complete a paper-based Step 1 eligibility checklist
- Enroll the participant and obtain SID
- Prescribe oral study product
- Facilitate and observe administration of oral study product. Note that participants should be provided with a meal with the observed oral study product dose; see [Section 5.3](#) regarding RPV oral dosing regimen and food intake requirements.

In addition, specimens for all laboratory evaluations at the Entry visit should be collected prior to the first oral dose. Note that acceptability and tolerability assessments should be administered relative to other Entry visit procedures as specified in the IMPAACT 2036 MOP. Parents/caregivers are

generally expected to be enrolled to the study at the participant's Entry visit; see [Section 6.15](#) for additional details regarding the acceptability and tolerability assessments.

Cohort 1 and Cohort 2a Step 1 Entry Visit Procedures		
Administrative and Regulatory		<ul style="list-style-type: none"> • Complete final eligibility determination and confirmation* • Complete paper-based eligibility checklist*, enter checklist data into SES to enroll the participant and generate SID; print and file a copy of the confirmation file • Obtain written informed consent for parent/caregiver* • Complete paper-based eligibility checklist for parent/caregiver*, enter checklist data into SES to enroll the parent/caregiver and generate SID; print and file a copy of the confirmation file • Complete final eligibility confirmation for caregiver, see Section 4.5 and 4.6* • Assign parent/caregiver PID*
Behavioral and Counseling		<ul style="list-style-type: none"> • Provide adherence counseling • Provide contraceptive counseling^ • Administer participant acceptability/tolerability assessment based upon participant age, as specified in the IMPAACT 2036 MOP • Administer parent/caregiver acceptability/tolerability assessment
Clinical		<ul style="list-style-type: none"> • Update medical and medications history* • Perform targeted physical exam* • Assess ARV history*
Laboratory (prior to oral dosing)	Blood	Collect blood for: <ul style="list-style-type: none"> • Hematology: CBC (WBC, RBC, hemoglobin, hematocrit, MCV, MCHC) with differential, ANC (absolute neutrophil count), and platelet count • Chemistries: Creatinine, eGFR, CK, Direct bilirubin, Total bilirubin, BUN, AST, ALT, Lipase, Albumin • HIV-1 RNA • CD4 count and percentage • Stored whole blood for genotypic resistance testing and HIV-1 subtyping
	Blood or Urine	<ul style="list-style-type: none"> • Pregnancy test^*
Study Product		<ul style="list-style-type: none"> • Prescribe, dispense, and facilitate administration of oral study products (including provision of a meal)

*Perform prior to enrollment.

^ For participants of childbearing potential.

During the Entry visit adherence counseling, instructions on the preparation and administration of oral study products will be provided and per the applicable formulation. Participants will also be advised to take the oral study product at the same time of day (morning or evening) as the Week 2 visit pre-dose PK collection time point. Per [Section 5.3.1](#), competency of the caregiver to properly prepare and administer the oral study products, should be confirmed and documented in the participant's chart for any participant prescribed the CAB DT and RPV 2.5 mg tablets.

6.3.2 Week 2 Visit: Step 1 – oral phase for Cohort 1 and Cohort 2a

In preparation for the Week 2 visit, sites may contact participants and parents/guardians, to reinforce adherence within the three days prior to the scheduled PK evaluation, as well as to remind the participant to hold the oral study product dose due on the day of the Week 2 visit.

For the Rich Sampling Schedule, PK samples will be collected at the Week 2 visit and over a period of 8 hours; for the Limited Sampling Schedule, over a period of 3 hours. The pre-dose PK sample collection should be performed prior to and on the same day as the oral study product dose observed at the site. See the procedural table below for the specific PK collection time points and collection windows.

For the three days prior to the Week 2 visit, participants should be fully adherent to their oral study product regimen and the oral study product should be taken at the same time of day (morning or evening) as the scheduled Week 2 pre-dose PK collection time point. If either a missed dose is reported during the three-day period or the participant has not adjusted the timing of their oral dosing (to align with the pre-dose PK collection time point), the Week 2 visit should be rescheduled, if able to conduct the visit within the allowable window.

Additional guidelines for scheduling and conducting the Week 2 visit are below.

- Participants and their parents/guardians should be reminded to return all oral study product at the Week 2 visit, for the adherence assessment.
- Height and weight must be obtained on the same day as performing the Week 2 PK evaluation.
- Participants should be provided with a meal with the observed oral study product dose; see [Section 5.3](#) regarding RPV oral dosing regimen and food intake requirements.
- For participants who report intercurrent illness immediately prior to or on the day of the scheduled PK visit that may have interfered with study product administration or resulted in malabsorption of study product (e.g., fever, vomiting, diarrhea), the Week 2 visit should be rescheduled in full, if able to conduct the visit within the allowable window.
- If the observed oral study product dose is not retained within 30 minutes (inclusive) of administration (e.g., vomiting), the Week 2 visit should be rescheduled, if able to conduct the visit within the allowable window.
- Depending on site capacity and participant preferences, participants and their parents or guardians may stay at the clinical research facility overnight for the PK sampling.

Additional oral study product may be dispensed at this visit if needed to provide coverage until the Week 4a visit.

Following the Week 2 visit, the timing of oral study product dosing may be changed, if desired. However, participants should be encouraged to maintain the timing of their oral study product dosing (morning or evening) through the Week 4b visit. Additional guidance regarding the timing of oral study product dosing prior to the Week 2 visit is provided in the IMPAACT 2036 MOP.

Cohort 1 and Cohort 2a Week 2 Visit Procedures (Step 1 – oral phase)		
Behavioral and Counseling		<ul style="list-style-type: none"> • Provide adherence counseling • Provide contraceptive counseling[^]
Clinical (prior to dispensing oral study product)		<ul style="list-style-type: none"> • Update medical and medications history • Perform targeted physical exam • Perform adherence assessment • Identify/review/update adverse events
Laboratory	Blood	Collect blood for: <ul style="list-style-type: none"> • Hematology: CBC (WBC, RBC, hemoglobin, hematocrit, MCV, MCHC) with differential, ANC (absolute neutrophil count), and platelet count • Chemistries: Creatinine, eGFR, CK, Direct bilirubin, Total bilirubin, BUN, AST, ALT, Lipase, Albumin • HIV-1 RNA • PK evaluation <ul style="list-style-type: none"> ○ If on Rich Sampling Schedule: Pre-dose, 1, 2, 3, 4, and 8 hours post-dose (6 PK collection timepoints) ○ If on Limited Sampling Schedule: Pre-dose and 3 hours post-dose <i>± a 15-minute window is allowed for the 1, 2, and 3-hours post-dose samples; ± a 30-minute window is allowed for the 4-hours post-dose sample; ± 1 hour window is allowed for the 8 hours post-dose sample</i>
	Blood or Urine	<ul style="list-style-type: none"> • Pregnancy test, <i>prior to dispensing oral study product[^]</i>
Study Product		<ul style="list-style-type: none"> • Prescribe and dispense oral study products, <i>if indicated</i> • Facilitate administration of oral study products (including provision of a meal)

[^] For participants of childbearing potential.

6.3.3 Week 4a Visit: Step 1 – oral phase for Cohort 1 and Cohort 2a

Participants and their parents/guardians should be reminded to return all oral study product at the Week 4a visit, for the adherence assessment, and to hold administration of the oral product for observed dosing at the clinic. Additional oral study product may be dispensed at this visit if needed to provide coverage until the Week 4b visit.

Data collected through the Week 4a study visit will be assessed to determine eligibility to enter Step 2 and receive injectable CAB LA + RPV LA. Week 4a visit laboratory test results should be reviewed as soon as they are available, for determining Step 2 eligibility and scheduling the Week 4b visit. Abnormal laboratory test result values from the Week 4a visit may be repeated prior to scheduling the Week 4b visit. If laboratory test results confirm Step 2 eligibility, and all other eligibility criteria are met, the Week 4b visit may be scheduled within the target visit window for Step 2 Entry and injectable study product administration, and may be combined with the Week 4a visit. See [Section 4.3](#) and [Section 4.4](#) for Step 2 eligibility criteria.

If participants are ineligible to receive injectable study product in Step 2, they will permanently discontinue oral study product use and complete an Early Termination visit 28 days after their last oral study product dose (see [Section 6.6.2](#)).

Cohort 1 and Cohort 2a Week 4a Visit Procedures (Step 1 – oral phase)		
Behavioral and Counseling		<ul style="list-style-type: none"> • Provide adherence counseling • Provide contraceptive counseling[^]
Clinical (prior to dispensing oral study product)		<ul style="list-style-type: none"> • Update medical and medications history • Perform complete physical exam[§] • Perform adherence assessment • Identify/review/update adverse events
Laboratory	Blood	Collect blood for: <ul style="list-style-type: none"> • Hematology: CBC (WBC, RBC, hemoglobin, hematocrit, MCV, MCHC) with differential, ANC (absolute neutrophil count), and platelet count • Chemistries: Creatinine, eGFR, CK, Direct bilirubin, Total bilirubin, BUN, AST, ALT, Lipase, Albumin
	Blood or Urine	<ul style="list-style-type: none"> • Pregnancy test, <i>prior to dispensing oral study product</i>[^]
Study product		<ul style="list-style-type: none"> • Prescribe and dispense oral study product, <i>if indicated</i> • Facilitate administration of oral study products (including provision of a meal)

[^] For participants of childbearing potential.

[§] SMR should not be conducted as part of the completed physical exam; all other procedures should be conducted per [Section 6.11](#).

6.3.4 Week 4b Visit: Step 2 Entry- injection phase for Cohort 1 and Cohort 2a

The Week 4b visit must take place after Week 4a laboratory test results are available. This visit should be scheduled to minimize the time between the Week 4a visit and initiation of the injectable study product in Step 2. Additional guidance regarding scheduling the Week 4b visit is provided in the IMPAACT 2036 MOP.

Participants who meet eligibility criteria to progress to Step 2 will receive their last oral dose of CAB + RPV on the same day as their first injection of CAB LA + RPV LA at the Week 4b study visit, which also serves as the Step 2 Entry visit.

PK samples will be collected at the Week 4b visit. For the three days prior to the Week 4b visit, participants should ideally take their oral study product at the same time of day (morning or evening) as the scheduled pre-dose PK collection time point, and be fully adherent to their assigned daily oral study product regimen. To facilitate this, participants should be advised to begin this alignment following the Week 2 visit by starting to take the oral study product at the same time of day (morning or evening) as the Week 4b visit pre-dose PK collection time point. However, the Week 4b visit may continue as scheduled if a missed dose is reported, or the participant has not adjusted the timing of their oral study product dosing to align with the pre-dose PK collection time point.

In preparation for the Week 4b visit, sites may contact participants and parents and guardians, to reinforce adherence and oral study product dose timing within the three days prior to the scheduled PK evaluation. Participants and their parents/guardians should be reminded to hold administration of the daily oral study product due on the day of the Week 4b visit, to allow for a pre-dose PK sample collection and for the dose to be observed at the site. Participants and their parents/guardians should also be reminded to return all oral study product at the Week 4b visit. Additionally, for participants on the Rich Sampling Schedule (see [Section 10.3](#)), participants and their parents/guardians should be reminded about the need for a 24-hour post-dose PK specimen.

All Week 4b visit procedures must be conducted on the same day (may not be conducted over a multi-day split visit), with the exception of the 24-hour post-dose PK specimen collection. The pre-dose PK sample must be collected prior to the participant's first study product injection. The timing

of the pre-dose PK sample collection in relation to observed oral dosing will depend upon the participant's most recent oral study product dose, as follows:

- If the participant's most recent oral study product dose was taken more than 12 hours from the Week 4b pre-dose PK sample collection, the pre-dose PK sample should be collected prior to observing the participant's last oral dose. Sites should provide participants with a meal with the observed oral study product dose; see [Section 5.3.1](#).
 - In the event the participant vomits within 30 minutes of an observed oral dose, then the pre-dose PK sample should be redrawn (if already collected) followed by a second observed oral dose. If vomiting occurs more than 30 minutes after an observed oral dose during the Week 4b visit, then a second dose should not be administered, and the PK sampling may proceed as scheduled. Any vomiting episodes should be source documented.
- If the participant's most recent oral study product dose was taken within 12 hours (inclusive) of the Week 4b pre-dose PK sample collection, an oral study product dose may not be administered during Week 4b visit. The Week 4b visit may still occur as scheduled and the pre-dose PK sample collection will be prior to the participant's first study product injection.

The below procedures must be conducted in the following sequence:

- Complete final Step 2 eligibility determination and confirmation: medical and medications history, targeted physical exam, adherence assessment, adverse event review/reporting, adherence counseling, and pregnancy test (if applicable).
- Complete a paper-based Step 2 eligibility checklist
- Enroll the participant to Step 2
- Prescribe injectable study product
- Dispense injectable study product
- Administer injectable study product
- Collect post-dose PK samples

Contraceptive counseling must be provided to applicable participants, but the timing of this counseling may occur at any point during the visit. The 24-hours post-dose PK sample will be collected on the day following the Week 4b visit. Height and weight must again be collected with the 24-hours post-dose PK sample collection. Note that acceptability and tolerability assessments should be administered relative to other Entry visit procedures as specified in the IMPAACT 2036 MOP; see [Section 6.15](#) for additional details regarding the acceptability and tolerability assessments.

Cohort 1 and Cohort 2a Week 4b Visit Procedures (Step 2 Entry – injection phase)	
Administrative and Regulatory	<ul style="list-style-type: none"> • Complete final eligibility confirmation for Step 2 Entry* • Complete paper-based eligibility checklist*, enter checklist data into SES to enroll the participant and generate SID; print and file a copy of the confirmation file
Behavioral and Counseling	<ul style="list-style-type: none"> • Provide contraceptive counseling^ • Provide adherence counseling* • Administer participant acceptability/tolerability assessment based upon participant age, as specified in the IMPAACT 2036 MOP • Administer parent/caregiver acceptability/tolerability assessment
Clinical	<ul style="list-style-type: none"> • Update medical and medications history* • Perform targeted physical exam* • Identify/review/update adverse events* • Perform adherence assessment* • Perform ECG 2 hours post-injection dose (\pm 1 hour window allowed)

Laboratory	Blood	Collect blood for: <ul style="list-style-type: none"> • HIV-1 RNA • Stored plasma for genotypic and phenotypic resistance testing • PK evaluation: <ul style="list-style-type: none"> ○ Rich Sampling Schedule: Pre-dose and 2- and 24-hours post-dose ○ Limited Sampling Schedule: Pre-dose and 2-hours post-dose <i>± 30 minutes window is allowed for the 2-hours post-dose samples; ± 4-hour window is allowed for the 24 -hours post-dose</i>
	Blood or Urine	<ul style="list-style-type: none"> • Pregnancy test[^]*
Study product		<ul style="list-style-type: none"> • Facilitate and observe administration of oral study products, <i>if indicated, see above</i>* • Prescribe, prepare, and administer injectable study products

*Prior to Step 2 enrollment.

[^] For participants of childbearing potential.

6.3.5 Week 5: Step 2- injection phase for Cohort 1 and 2a (Step 2- Injection phase)

Cohort 1 and Cohort 2a Week 5 Visit Procedures (Step 2 – injection phase)		
Clinical		<ul style="list-style-type: none"> • Update medical and medications history • Perform targeted physical exam Identify/review/update adverse events
Laboratory	Blood	Collect blood for: <ul style="list-style-type: none"> • Hematology: CBC (WBC, RBC, hemoglobin, hematocrit, MCV, MCHC) with differential, ANC (absolute neutrophil count), and platelet count • Chemistries: Creatinine, eGFR, CK, Direct bilirubin, Total bilirubin, BUN, AST, ALT, Lipase, Albumin • PK evaluation: Single sample

6.3.6 Week 6 and Week 9: Step 2- injection phase for Cohort 1

These visits will be scheduled for at least the first 8 participants across Weight Bands 1 and 2 and the first 8 participants across Weight Bands 3, 4, and 5 of Cohort 1 only as part of the Rich Sampling Schedule (see [Section 10.3](#) for more details).

Cohort 1 Week 6 and Week 9 Visit Procedures (Step 2 – injection phase – Rich Sampling Schedule only)		
Clinical		<ul style="list-style-type: none"> • Update medical and medications history • Perform targeted physical exam • Identify/review/update adverse events
Laboratory	Blood	<ul style="list-style-type: none"> • Collect blood for PK evaluation: Single sample

6.3.7 Week 8, 12, 16, and 20 Visits: Step 2 - injection phase for Cohort 1 and Cohort 2a (Step 2 – injection phase)

Week 8, 12, 16, and 20 Visit Procedures (Step 2 – injection phase)		
Behavioral and Counseling		<ul style="list-style-type: none"> • Provide adherence counseling • Provide contraceptive counseling[^] • Administer participant acceptability/tolerability assessment based upon participant age, as specified in the IMPAACT 2036 MOP • Administer parent/caregiver acceptability/tolerability assessment (Week 8 only)
Clinical		<ul style="list-style-type: none"> • Update medical and medications history • Perform targeted physical exam • Identify/review/update adverse events
Laboratory	Blood	Collect blood for: <ul style="list-style-type: none"> • Hematology: CBC (WBC, RBC, hemoglobin, hematocrit, MCV, MCHC) with differential, ANC (absolute neutrophil count), and platelet count • Chemistries: Creatinine, eGFR, CK, Direct bilirubin, Total bilirubin, BUN, AST, ALT, Lipase, Albumin • HIV-1 RNA • PK evaluation: Single pre-dose sample at Week 8 and 16 for all participants and at Week 12 for participants on rich sampling schedule
	Blood or Urine	<ul style="list-style-type: none"> • Pregnancy test[^]
Study product		<ul style="list-style-type: none"> • Prescribe, prepare, and administer injectable study products

[^] For participants of childbearing potential.

6.3.8 Week 24 Visit: Step 2 – injection phase for Cohort 1 and Cohort 2a

The in-depth interview (IDI) will be conducted with a subset of parents and caregivers at select sites, during the Week 24 window. The interview may be conducted in person or via telephone. The interview must be completed within the specified Week 24 window but may be conducted as part of the regular study visit or can occur as a stand-alone visit, per site discretion and parent/caregiver preferences.

Week 24 Visit Procedures (Step 2 – injection phase)		
Behavioral and Counseling		<ul style="list-style-type: none"> • Provide adherence counseling • Provide contraceptive counseling[^] • Administer participant acceptability/tolerability assessment based upon participant age, as specified in the IMPAACT 2036 MOP • Administer parent/caregiver acceptability/tolerability assessment • Conduct parent/caregiver qualitative interview[*]
Clinical		<ul style="list-style-type: none"> • Update medical and medications history • Perform complete physical exam • Identify/review/update adverse events • Perform an ECG
Laboratory	Blood	Collect blood for: <ul style="list-style-type: none"> • Hematology: CBC (WBC, RBC, hemoglobin, hematocrit, MCV, MCHC) with differential, ANC (absolute neutrophil count), and platelet count • Chemistries: Creatinine, eGFR, CK, Direct bilirubin, Total bilirubin, BUN, AST, ALT, Lipase, Albumin • CD4 count and percentage • HIV-1 RNA • Store plasma for genotypic and phenotypic resistance testing • PK evaluation: Single pre-dose sample
	Blood or Urine	<ul style="list-style-type: none"> • Pregnancy test[^]
Study product		<ul style="list-style-type: none"> • Prescribe, prepare, and administer injectable study products

*If indicated

^ For participants of childbearing potential.

6.3.9 Weeks 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72 Visits: Step 2 – injection phase for Cohort 1 (through Week 72) and Cohort 2a (through Week 48 only)

Week 72 is considered the final scheduled follow-up visit for participants in Cohort 1 who wish to continue receiving the injections external to the study; Week 48 is the final scheduled follow-up visit for participants in Cohort 2a. See [Section 6.8](#) for Study Exit considerations and [Section 13.11](#) for more information regarding post-trial access to study drugs.

Weeks 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72 Visit Procedures (Step 2 – injection phase)		
Behavioral and Counseling		<ul style="list-style-type: none"> • Provide contraceptive counseling[^] • Provide adherence counseling (Week 48 only, and if indicated at all other visits) • Administer participant acceptability/tolerability assessment based upon participant age, as specified in the IMPAACT 2036 MOP • Administer parent/caregiver acceptability/tolerability assessment (Weeks 48 and 72 only)
Clinical		<ul style="list-style-type: none"> • Update medical and medications history • Perform complete physical exam (Weeks 48 and 72 only) • Perform targeted physical exam (All other visits except Weeks 48 and 72) • Identify/review/update adverse events
Laboratory	Blood	Collect blood for: <ul style="list-style-type: none"> • Hematology: CBC (WBC, RBC, hemoglobin, hematocrit, MCV, MCHC) with differential, ANC (absolute neutrophil count), and platelet count • Chemistries: Creatinine, eGFR, CK, Direct bilirubin, Total bilirubin, BUN, AST, ALT, Lipase, Albumin • CD4 count and percentage (Weeks 48 and 72 only) • HIV-1 RNA • PK evaluation (Weeks 32, 40, 48, 56, 64, and 72 only): Single pre-dose sample
	Blood or Urine	<ul style="list-style-type: none"> • Pregnancy test[^]
Study product		<ul style="list-style-type: none"> • Prescribe, prepare, and administer injectable study products

[^] For participants of childbearing potential.

6.4 Cohort 2b

6.4.1 Entry Visit: Cohort 2b (straight to injection)

The Cohort 2b Entry visit must occur within 28 days (inclusive) from the Screening Visit and may not be split over multiple days (with the exception of the 24-hour post-dose PK sample, which will be collected the day after Entry). Entry visit procedures that may provide information relevant to eligibility for the study should be performed first, prior to final eligibility determination and enrollment. In the event a participant is found to be ineligible on the day of enrollment, enrollment should not occur.

The following visit procedures must be conducted during the Entry Visit in the sequence specified below:

- Complete final eligibility determination and confirmation (medical and medications history including ARV history assessment, targeted physical exam, and a pregnancy test for participants

of childbearing potential defined as having reached menarche or assigned female sex at birth and engaging in sexual activity that could lead to pregnancy.)

- Complete a paper-based Step 1 eligibility checklist
- Enroll the participant and obtain SID
- Provide adherence counseling to confirm the participant/parent/guardian is willing for the participant to receive injectable study product.
- Prescribe injectable study product
- The pre-dose PK sample must be collected prior to the participant's first study product injection.
- Administer the injectable study product
- Collect the post-dose PK samples at the specified timepoints

In addition, specimens for all laboratory evaluations at the Entry visit should be collected prior to the first injection, with the exception of the post-dose PK sample collections. The 24-hours post-dose PK sample will be collected on the day following the Cohort 2b Entry visit. Height and weight must again be collected with the 24-hours post-dose PK sample collection. Note that acceptability and tolerability assessments should be administered relative to other Entry visit procedures as specified in the IMPAACT 2036 MOP. Parents/caregivers are generally expected to be enrolled to the study at the participant's Entry visit; see [Section 6.14](#) for additional details regarding the acceptability and tolerability assessments.

Cohort 2b Entry Visit Procedures		
Administrative and Regulatory		<ul style="list-style-type: none"> • Complete final eligibility determination and confirmation* • Complete paper-based eligibility checklist*, enter checklist data into SES to enroll the participant and generate SID; print and file a copy of the confirmation file • Obtain written informed consent for parent/caregiver* • Complete paper-based eligibility checklist for parent/caregiver*, enter checklist data into SES to enroll the parent/caregiver and generate SID; print and file a copy of the confirmation file • Complete final eligibility confirmation for caregiver, <i>see Section 4.5 and 4.6*</i> • Assign parent/caregiver PID*
Behavioral and Counseling		<ul style="list-style-type: none"> • Provide contraceptive counseling^ • Administer participant acceptability/tolerability assessment based upon participant age, as specified in the IMPAACT 2036 MOP • Administer parent/caregiver acceptability/tolerability assessment
Clinical		<ul style="list-style-type: none"> • Update medical and medications history* • Perform targeted physical exam* • Assess ARV history* • Perform an ECG 2 hours post injection dose (\pm 1 hour window allowed)
Laboratory (prior to first injection dosing)	Blood	Collect blood for: <ul style="list-style-type: none"> • Hematology: CBC (WBC, RBC, hemoglobin, hematocrit, MCV, MCHC) with differential, ANC (absolute neutrophil count), and platelet count • Chemistries: Creatinine, eGFR, CK, Direct bilirubin, Total bilirubin, BUN, AST, ALT, Lipase, Albumin • HIV-1 RNA • CD4 count and percentage • Stored whole blood for genotypic resistance testing and HIV-1 subtyping • PK evaluation: Pre-dose and 2- and 24-hours post-dose \pm 30 minutes window is allowed for the 2-hours post-dose; \pm 4-hour window is allowed for the 24-hours post-dose

	Blood or Urine	<ul style="list-style-type: none"> • Pregnancy test^{^*}
Study Product		<ul style="list-style-type: none"> • Prescribe, dispense, and administer injectable study products

*Perform prior to enrollment.

[^] For participants of childbearing potential.

6.4.2 Day 3 Visit: Cohort 2b

Cohort 2b Day 3 Visit Procedures (straight to injection)		
Clinical		<ul style="list-style-type: none"> • Update medical and medications history • Perform targeted physical exam • Identify/review/update adverse events
Laboratory	Blood (PK evaluation)	Collect blood for: <ul style="list-style-type: none"> • Hematology: CBC (WBC, RBC, hemoglobin, hematocrit, MCV, MCHC) with differential, ANC (absolute neutrophil count), and platelet count • Chemistries: Creatinine, eGFR, CK, Direct bilirubin, Total bilirubin, BUN, AST, ALT, Lipase, Albumin • PK evaluation: Single sample

*If indicated and/or per local standard of care

6.4.3 Week 2 Visit: Cohort 2b

Cohort 2b Week 2 Visit Procedures		
Behavioral and Counseling		<ul style="list-style-type: none"> • Provide contraceptive counseling^{*^}
Clinical		<ul style="list-style-type: none"> • Update medical and medications history • Perform targeted physical exam • Identify/review/update adverse events
Laboratory	Blood	Collect blood for: <ul style="list-style-type: none"> • Hematology: CBC (WBC, RBC, hemoglobin, hematocrit, MCV, MCHC) with differential, ANC (absolute neutrophil count), and platelet count • Chemistries: Creatinine, eGFR, CK, Direct bilirubin, Total bilirubin, BUN, AST, ALT, Lipase, albumin • HIV-1 RNA • PK evaluation: Single sample

*If indicated

[^] For participants of childbearing potential.

6.4.4 Week 4 Visit: Cohort 2b

Cohort 2b Week 4 Visit Procedures		
Behavioral and Counseling		<ul style="list-style-type: none"> • Provide contraceptive counseling[^] • Administer participant acceptability/tolerability assessment based upon participant age, as specified in the IMPAACT 2036 MOP • Administer parent/caregiver acceptability/tolerability assessment
Clinical		<ul style="list-style-type: none"> • Update medical and medications history • Perform targeted physical exam • Identify/review/update adverse events
Laboratory	Blood	Collect blood for: <ul style="list-style-type: none"> • Hematology: CBC (WBC, RBC, hemoglobin, hematocrit, MCV, MCHC) with differential, ANC (absolute neutrophil count), and platelet count • Chemistries: Creatinine, eGFR, CK, Direct bilirubin, Total bilirubin, BUN, AST, ALT, Lipase, Albumin • HIV-1 RNA • PK Evaluation: Single pre-dose sample

	Blood or Urine	<ul style="list-style-type: none"> • Pregnancy test
Study product		<ul style="list-style-type: none"> • Prescribe, prepare, and administer injectable study products

^ For participants of childbearing potential.

6.4.5 Week 8, 12, and 16 Visits: Cohort 2b

Cohort 2b Week 8, 12, and 16 Visit Procedures		
Behavioral and Counseling		<ul style="list-style-type: none"> • Provide adherence counseling • Provide contraceptive counseling^ • Administer participant acceptability/tolerability assessment based upon participant age, as specified in the IMPAACT 2036 MOP
Clinical		<ul style="list-style-type: none"> • Update medical and medications history • Perform targeted physical exam • Identify/review/update adverse events
Laboratory	Blood	Collect blood for: <ul style="list-style-type: none"> • Hematology: CBC (WBC, RBC, hemoglobin, hematocrit, MCV, MCHC) with differential, ANC (absolute neutrophil count), and platelet count • Chemistries: Creatinine, eGFR, CK, Direct bilirubin, Total bilirubin, BUN, AST, ALT, Lipase, Albumin • HIV-1 RNA • PK evaluation (Week 12 only): Single pre-dose sample
	Blood or Urine	<ul style="list-style-type: none"> • Pregnancy test^
Study product		<ul style="list-style-type: none"> • Prescribe, prepare, and administer injectable study products

^ For participants of childbearing potential.

6.4.6 Week 20 Visit: Cohort 2b

The in-depth interview (IDI) will be conducted with a subset of parents and caregivers at select sites, during the Week 20 visit window. The interview may be conducted in person or via telephone. The interview must be completed within the specified Week 20 window, but may be conducted as part of the regular study visit or can occur as a stand-alone visit, per site discretion and parent/caregiver preferences.

Cohort 2b Week 20 Visit Procedures		
Behavioral and Counseling		<ul style="list-style-type: none"> • Provide adherence counseling • Provide contraceptive counseling^ • Administer participant acceptability/tolerability assessment based upon participant age, as specified in the IMPAACT 2036 MOP • Administer parent/caregiver acceptability/tolerability assessment • Conduct qualitative interview*
Clinical		<ul style="list-style-type: none"> • Update medical and medications history • Perform complete physical exam • Identify/review/update adverse events • Perform an ECG
Laboratory	Blood	Collect blood for: <ul style="list-style-type: none"> • Hematology: CBC (WBC, RBC, hemoglobin, hematocrit, MCV, MCHC) with differential, ANC (absolute neutrophil count), and platelet count • Chemistries: Creatinine, eGFR, CK, Direct bilirubin, Total bilirubin, BUN, AST, ALT, Lipase, Albumin • CD4 count and percentage • HIV-1 RNA

		<ul style="list-style-type: none"> • Store plasma for genotypic and phenotypic resistance testing • PK evaluation: Single pre-dose sample
	Blood or Urine	<ul style="list-style-type: none"> • Pregnancy test^
Study product		<ul style="list-style-type: none"> • Prescribe, prepare, and administer injectable study products

*If indicated

^ For participants of childbearing potential.

6.4.7 Weeks 24, 28, 32, 36, 40, 44 Visits: Cohort 2b

Week 44 is considered the study end visit for Cohort 2b participants that have continued receiving injections per schedule.

Cohort 2b Week 24, 28, 32, 36, 40, 44 Visit Procedures		
Behavioral and Counseling		<ul style="list-style-type: none"> • Provide contraceptive counseling^ • Provide adherence counseling (Week 44 only, and if indicated at all other visits) • Administer participant acceptability/tolerability assessment based upon participant age, as specified in the IMPAACT 2036 MOP • Administer parent/caregiver acceptability/tolerability assessment (Week 44 only)
Clinical		<ul style="list-style-type: none"> • Update medical and medications history • Perform complete physical exam (Week 44 only) • Perform targeted physical exam (All other visits except Week 44) • Identify/review/update adverse events
Laboratory	Blood	Collect blood for: <ul style="list-style-type: none"> • Hematology: CBC (WBC, RBC, hemoglobin, hematocrit, MCV, MCHC) with differential, ANC (absolute neutrophil count), and platelet count • Chemistries: Creatinine, eGFR, CK, Direct bilirubin, Total bilirubin, BUN, AST, ALT, Lipase, Albumin • CD4 count and percentage (Week 44 only) • HIV-1 RNA • PK evaluation (Weeks 28, 36, 44only): Single pre-dose sample
	Blood or Urine	<ul style="list-style-type: none"> • Pregnancy test^
Study product		<ul style="list-style-type: none"> • Prescribe, prepare, and administer injectable study products

^ For participants of childbearing potential.

6.5 Interim Injection Visit

For participants resuming injectable study products following oral bridging or in other rare circumstances, one or more interim visits may be required to appropriately reinitiate a participant on the dosing regimen or realign to the original injection visit schedule or dose. The CMC must be consulted prior to initiating oral bridging and prior to conducting an interim injection visit regarding clinical considerations, and injectable study product management and scheduling.

Interim injection visit procedures are provided below, and study data will be entered into eCRFs. Further details and guidance on scheduling and conducting interim injection visits are provided in the IMPAACT 2036 MOP.

Interim Injection Visit Procedures		
Behavioral and Counseling		<ul style="list-style-type: none"> • Provide adherence counseling* • Provide contraceptive counseling, <i>if indicated</i>[^]
Clinical		<ul style="list-style-type: none"> • Update medical and medications history since last visit* • Perform targeted physical exam* • Identify/review/update adverse events*
Laboratory	Blood	Collect blood for: <ul style="list-style-type: none"> • Hematology: CBC (WBC, RBC, hemoglobin, hematocrit, MCV, MCHC) with differential, ANC (absolute neutrophil count), and platelet count • Chemistries: Creatinine, eGFR, CK, Direct bilirubin, Total bilirubin, BUN, AST, ALT, Lipase, Albumin • HIV-1 RNA* • PK evaluation: Single pre-dose sample*
	Blood or Urine	<ul style="list-style-type: none"> • Pregnancy test[^]
Study product		<ul style="list-style-type: none"> • Prescribe, prepare, and administer injectable study products

*Perform prior to administration of injectable study products.

[^] For participants of childbearing potential.

6.6 Long-Term Safety and Washout PK Follow-Up (LSFU) Visits

Participants who prematurely and permanently discontinue injectable study product, or participants who discontinue study product use (either oral or injectable study product) due to pregnancy, will be followed for an additional 48 weeks to assess long-term safety and washout PK of the study products. Additionally, participants who receive their injections at their final scheduled follow-up visit (Week 72 for Cohort 1, Week 48 for Cohort 2a, and Week 44 for Cohort 2b) but do not wish to continue the CAB LA + RPV LA regimen outside of the study will resume (non-study provided) ART and enter into the LSFU visit schedule. Participants will resume (non-study provided) oral cART as soon as possible, and within 4 weeks, or 8 weeks (± 7 days), of discontinuing study product depending on the study product dosing regimen which was discontinued (i.e., Q4W or Q8W dosing regimen). The LSFU visits will be scheduled approximately 4, 8, 24, 36, and 48 weeks after the last injection, after which participants will exit the study. Participants who permanently discontinue study product (either oral or injectable study product) due to pregnancy will be followed for 48 weeks, based on the date of the positive confirmatory pregnancy test result. For participants who become pregnant during LSFU visits, the LSFU visits will continue as scheduled and not restart. All LSFU visit procedures will be conducted, with the exception that pregnancy testing will not be required for participants who are currently pregnant. See [Section 8.2](#) for further details on management of pregnant participants and pregnancy outcome.

During LSFU, a single random PK sample will be collected at each visit as shown in the procedural tables below.

6.6.1 LSFU Week 4, 8, 24, and 36 Visit

LSFU Week 4, 8, 24, and 36 study visits have the following target dates as calculated from the last administration of injectable study product (or confirmatory positive pregnancy test result):

- LSFU Week 4 target date is 28 days after last injection/positive pregnancy test
- LSFU Week 8 target date is 56 days after last injection/positive pregnancy test
- LSFU Week 24 target date is 168 days after last injection/positive pregnancy test
- LSFU Week 36 target date is 252 days after last injection/positive pregnancy test

These visits each have a target window of -14 days/+28 days from the target visit date.

LSFU Week 4, 8, 24, and 36 Visit Procedures		
Behavioral and Counseling		<ul style="list-style-type: none"> • Provide contraceptive counseling, <i>if indicated</i>[^] • Provide adherence counseling
Clinical		<ul style="list-style-type: none"> • Update medical and medications history • Perform targeted physical exam • Identify/review/update adverse events
Laboratory	Blood	Collect blood for: <ul style="list-style-type: none"> • Hematology: CBC (WBC, RBC, hemoglobin, hematocrit, MCV, MCHC) with differential, ANC (absolute neutrophil count), and platelet count • Chemistries: Creatinine, eGFR, CK, Direct bilirubin, Total bilirubin, BUN, AST, ALT, Lipase, Albumin • HIV-1 RNA • PK evaluation: Single sample
	Blood or Urine	Pregnancy test [^]

[^] For participants of childbearing potential.

6.6.2 LSFU Week 48 /Early Termination Visit

The LSFU Week 48 Visit is targeted to take place 336 days after the last administration of injectable study product (or confirmatory positive pregnancy test result), with a target window of ± 42 days from the target visit date. These same visit procedures will be conducted as an Early Termination visit for participants withdrawing or terminating from the study prior to scheduled completion of study follow-up, instead of their regularly scheduled study visit, for a final series of evaluations. All participants completing this visit, whether as the LSFU Week 48 Visit (per the LSFU visit schedule) or as an Early Termination visit, will exit the study.

Scheduling and completion of Early Termination visits will be in consideration of participant withdrawal or termination; visit procedures may be combined with an ongoing study visit. Any procedures conducted within 14 days of an Early Termination visit need not be repeated, with the following target dates for completing the Early Termination visit:

- For Cohort 1 and Cohort 2a Step 1 participants not progressing to the injection phase, an Early Termination visit is targeted to be completed 28 days after the participant's last oral study product use; the Early Termination visit may be completed sooner, if necessary. For these participants, a PK evaluation will not be performed at this visit.
- For any participant being followed per the LSFU visit schedule and withdrawing from the study, an Early Termination visit is targeted to be completed within 28 days (inclusive) of the previous study visit.

Participants completing an Early Termination visit will be followed until resolution (return to baseline) or stabilization of any adverse events per [Section 8.1](#).

Refer to [Section 6.8](#) for the definition of scheduled completion of follow-up, and additional considerations for participants exiting the study (whether scheduled completion of follow-up or an early termination visit). Refer to [Section 8.5](#) for criteria for participant withdrawal or premature termination from the study. The IMPAACT 2036 MOP provides further guidance on Early Termination visit scheduling considerations.

LSFU Week 48 /Early Termination Visit Procedures		
Behavioral and Counseling		<ul style="list-style-type: none"> • Provide contraceptive counseling, <i>if indicated</i>[^] • Administer participant acceptability/tolerability assessment based upon participant age, as specified in the IMPAACT 2036 MOP (only for early termination visit) • Parent/caregiver acceptability/tolerability assessment (only for early termination visit)
Clinical		<ul style="list-style-type: none"> • Update medical and medications history • Perform complete physical exam • Identify/review/update adverse events Perform additional evaluations per Section 8.3 and/or if clinically indicated (consult CMC if indicated)
Laboratory	Blood	Collect blood for: <ul style="list-style-type: none"> • Hematology: CBC (WBC, RBC, hemoglobin, hematocrit, MCV, MCHC) with differential, ANC (absolute neutrophil count), and platelet count • Chemistries: Creatinine, eGFR, CK, Direct bilirubin, Total bilirubin, BUN, AST, ALT, Lipase, Albumin • HIV-1 RNA • Stored whole blood for genotypic resistance testing and HIV-1 subtyping (only for Early Termination visit) • PK evaluation: Single sample (except not at the Early Termination visit for Step 1)
	Blood or Urine	Pregnancy test [^]

[^] For participants of childbearing potential.

6.7 Confirmation of Virologic Failure Visit

Any participant with a plasma HIV-1 RNA level ≥ 200 copies/mL after enrollment should be recalled to the clinic for completion of the Confirmation of Virologic Failure visit for confirmatory testing 2-4 weeks after specimen collection for the initial test. Scheduling of this visit within the timeframe specified should also be in consideration of potential causes for virologic failure such as intercurrent illness, recent immunizations, inadequate adherence, interruptions of study product, or other extenuating circumstances. For participants receiving injectable study product, confirmatory test results should ideally be obtained and reviewed prior to the next scheduled administration of injectable study product. While injection study visits for these participants may be delayed within the respective target visit window, injectable study product must not be withheld for pending confirmatory testing or results.

Confirmation of Virologic Failure visit procedures may be combined with regularly scheduled visit procedures if they are performed within the target window of a regularly scheduled visit. In addition to the protocol-specific procedures listed in this section, study staff may complete other tasks and assessments consistent with local standards of care and site SOPs.

The viral load results from the Confirmation of Virologic Failure visit will determine whether the participant has met the criteria of virologic failure for the study (See [Section 8.3](#) for the definition and management of virologic failure). Viral load results should be provided to participants and may be used to guide adherence counseling. See [Section 6.14](#) for additional details on adherence counseling.

Confirmation of Virologic Failure Visit Procedures		
Behavioral and Counseling		<ul style="list-style-type: none"> • Provide contraceptive counseling*^ • Provide adherence counseling*
Clinical		<ul style="list-style-type: none"> • Obtain interval medical and medications history • Perform targeted physical exam • Identify/review/update adverse events • Perform additional evaluations per Section 8.3 and/or if clinically indicated (consult CMC if indicated)
Laboratory	Blood	Collect blood for: <ul style="list-style-type: none"> • HIV-1 RNA • Plasma for genotypic and phenotypic resistance testing • PK evaluation: Single sample
	Blood or Urine	Pregnancy test^

*If indicated

^ For participants of childbearing potential.

6.8 Study Exit

Participants may exit the study at different timepoints, with the following considered as scheduled study completion of follow-up:

- Cohort 1 participants completing all follow-up visits per protocol, through Week 72; Cohort 2a participants completing all follow-up visits per protocol, through Week 48; Cohort 2b participants completing all follow-up visits per protocol, through Week 44
- Participants completing all follow-up visits through LSFU Week 48, for participants in the LSFU visit schedule (see [Section 6.6](#) above)

Any participant withdrawing or terminating from the study prior to these timepoints is considered as prematurely terminating from the study and the LSFU Week 48 study visit will be conducted as an Early Termination visit, instead of their regularly scheduled study visit, for a final series of evaluations. All visit procedures as described in and applicable to [Section 6.6.2](#) will be completed for an Early Termination visit, with additional procedures and exceptions as noted.

At any study exit visit (scheduled completion of follow-up or an early termination visit), arrangements should be made to provide all clinically meaningful results to the participant and the participant's parent or guardian. Study staff should provide the participant and parent or guardian with information on how to remain in contact with study staff (if desired) and how to learn about the results of the study when available. Study staff should also provide information, counseling, and referrals to non-study sources of care and treatment for the participant, as applicable. See [Section 8.1](#) regarding management of adverse events at study exit, and [Section 8.6](#) for additional considerations regarding participant withdrawal or termination.

Planning for transition to non-study care and treatment for participants exiting the study should begin prior to the participant's scheduled study exit visit, and the transition should be implemented at the participant's scheduled study exit visit. Study staff will complete a final study contact, with the participant and the participant's parent or guardian, if applicable, within 4 weeks of the participant's study exit visit to confirm the transition and should be documented in each participant's study chart. These contacts are not expected to be entered into eCRFs.

6.8.1 Reasons to Postpone Study Exit

In the following circumstances, a participant's planned study exit may need to be postponed to allow for additional participant management and eCRF data collection:

- If a participant becomes pregnant while on study: Refer to [Section 8.2](#) for comprehensive guidance on pregnancy management
- If, based upon results from the LSFU Week 48 visit, a Confirmation of Virologic Failure visit is indicated: A Confirmation of Virologic Failure visit should be conducted (refer to [Section 6.7](#)).
- If the participant has any Grade 3 or higher adverse event at their last scheduled study visit: Refer to [Section 8.1](#).

Participants who meet the above criteria will exit the study upon completion of the last required data collection point.

6.9 Procedures for Oral Study Product Dispensing and Continued Injectable Study Product Administration

The following procedures must be performed on the same day as and prior to dispensing oral study product or administering a study product injection, to assess for any indication of study product hold or permanent discontinuation:

- Clinical evaluations per the respective scheduled study visit (including participant weight to confirm the appropriate weight-band injectable dosing regimen)
- Laboratory test results from the previous study visit obtained and reviewed for indication of study product hold or permanent discontinuation (see [Section 8.4-8.5](#))
- For participants of childbearing potential, a negative pregnancy test result. For participants of childbearing potential, assessment of contraceptive requirements and use (See [Section 6.13](#))

See [Section 8](#) for details regarding participant management, including additional details related to deferring study product due to managing adverse events and other indications.

6.10 Medical and Medications History

Collection of medical and medication history information is required at each scheduled visit. A baseline history is established at Screening and Entry, and interval (since the last visit) histories are obtained at subsequent follow-up visits. All history information may be obtained based on participant self-report or as reported by the parent or guardian, but available medical records should be obtained when possible to supplement self-reported information.

Documented medical conditions will be assessed for severity as described in [Section 7.3.3](#), and new conditions occurring during follow-up will also be assessed for relationship to study drug as described in [Section 8.1](#). Relevant dates will be recorded for all conditions and medications; see [Section 5.7](#) for more information on concomitant medications. [Table 3](#) specifies the baseline and interval medical and medications history elements that must be source documented, as well as associated eCRF entry requirements.

Table 3.
Documentation Requirements for Medical and Medication Histories

Assess for and Source Document	Enter into eCRFs or SES
<i>Baseline Medical and Medication History Elements</i>	
Date of birth, sex assigned at birth, race, ethnicity	Yes
Date of HIV diagnosis, mode of transmission, and current WHO clinical stage	Yes
Documented resistance to any ARV (ever)	Yes
All documented HIV-1 RNA test results within the 18 months prior to enrollment	Yes
History of allergy and/or hypersensitivity (including to ARVs)	Yes
History of depression, suicidal ideation or attempt, and other psychiatric conditions	Yes
History of all prior significant central nervous system disorders (including seizures and migraines/headaches)	Yes
History of significant liver disease, including hepatitis C infection, resulting in hospitalization or interfering with daily activities	Yes
Medical conditions ongoing or occurring within the 28 days prior to enrollment	Yes
ARVs taken within the six months prior to enrollment	Yes
All medications (including contraceptives) taken within the 28 days prior to enrollment or on the day of enrollment	Yes
<i>For participants nine years of age or older and assigned female sex at birth, reproductive history as applicable: menstrual history, sexual activity, and contraceptive use</i>	Yes
Any other information needed to determine eligibility for the study	No
<i>Interval Medical and Medication History Elements</i>	
Current status of conditions that were ongoing at the previous visit	Any updates of previous entries (e.g., resolution dates)
Occurrence of any new conditions since the last visit	All newly identified adverse events
Current status of medications that were ongoing at the previous visit	Any updates of previous entries (e.g., stop dates)
Use of any new medications since the last visit	Yes
<i>For participants nine years of age or older, updates of reproductive history as applicable: menstrual history, sexual activity, and contraceptive use</i>	Yes
<i>For participants who become pregnant: pregnancy outcome, any congenital anomalies identified in the fetus or infant</i>	Yes

6.11 Physical Examinations

A physical examination is required at each scheduled visit, either as a complete physical exam or as a targeted physical exam, per the specified procedures for each visit.

Complete exams should include the following:

- Height and weight
- Vital signs, including heart rate, temperature, and blood pressure
Note: Blood pressure should only be collected for participants less than 3 years of age if clinically indicated.
- Examination of:
 - General appearance
 - Head
 - Eyes
 - Ears
 - Nose
 - Neck
 - Mouth and throat
 - Lymph nodes
 - Lungs
 - Heart
 - Abdomen
 - Musculoskeletal system
 - Skin
 - Neuro
 - Sexual Maturity Rating (SMR) for participants ≥ 6 years of age (at all visits with a complete physical exam except Week 4a for Cohort 1 and Cohort 2a participants)
- Examination of other body systems driven by other identified signs or symptoms

Targeted exam should include the following:

- Height and weight
- Vital signs, including heart rate, temperature, and blood pressure
- Examination of body systems driven by identified signs or symptoms

Additional assessments may be performed at any time at the discretion of the examining clinician. Weight-for-height z-scores (for children up to and including five years of age) or body mass index z-scores (for children older than five years of age) based upon the WHO growth standards should be calculated at every visit when weight and height are collected.

All exam findings, including z-scores, should be source documented. All height and weight measurements, and vital signs will be entered into eCRFs.

In addition to the above, abnormal findings identified prior to enrollment will be entered into medical history eCRFs; abnormal findings identified after enrollment will be entered into adverse events eCRFs, as specified in [Section 7.2](#).

6.12 Performing an Electrocardiogram (ECG/EKG)

For all ECG readings, a 12-lead ECG should be performed with the participant in a semi-supine position. An ECG machine that automatically calculates the heart rate and measures QTc intervals is preferred, and the automated calculations can be used for reporting purposes. The IoR or designee can review the ECG reading and a cardiologist reading is not required. Otherwise, an appropriately

qualified ECG reader must interpret the results. The Fridericia QT correction formula must be used in this study for all protocol-required ECG readings. All ECG readings should be entered into eCRFs.

At the Screening visit, the ECG reading should be done in triplicate such that three, single automated QTc readings will be done, each separated by at least 2 minutes, with the mean value establishing baseline. During study treatment, single automated readings will be conducted. A result of ≥ 500 msec or a >60 msec increase from baseline requires two repeat readings (each separated by at least 2 minutes, for a total of three readings). See [Section 8.1.11](#) for Protocol-Specific Grading and Management of QTc Prolongation.

6.13 Pregnancy Testing, Contraceptive Counseling, and Contraceptive Use

[Section 4.1.14](#) defines childbearing potential for this study.

Pregnancy testing and contraceptive counseling are required for all participants of childbearing potential at specified study visits and prior to administration of study product. Counseling about contraceptive use (described below) and available options should begin during the screening visit and continue for these participants throughout their participation in the study, as applicable. If a participant meets the definition of “childbearing potential” for the first time during follow-up, pregnancy testing and contraceptive counseling should be added at that time. Contraceptive counseling should be tailored to be age-appropriate, and will be provided by clinic and/or pharmacy staff consistent with local standards of care and site SOPs. At any point during study participation, additional counseling and instructions on contraceptive methods should also be offered according to site SOPs; this will include information on correct use of barrier methods.

Use of at least one allowable effective method of contraception is required to enroll to the study for participants of childbearing potential who are engaging in sexual activity (self-reported) that could lead to pregnancy. During study follow-up, participants who become of childbearing potential and self-report engaging in sexual activity that could lead to pregnancy will be counseled to initiate, and maintain throughout the study, use of at least one allowable effective method of contraception. Counseling messages regarding continued use of at least one allowable effective method of contraception while on study treatment will also be included, ideally prior to administering or dispensing study product, for participants who are of childbearing potential and self-report engaging in sexual activity that could lead to pregnancy. During follow-up, participants who discontinue contraception or decline to initiate a contraceptive method will be allowed to continue product use at the visit where this is reported, provided a negative pregnancy test result is obtained prior to study product administration, but will receive counselling on the importance of adopting and maintaining a contraceptive method during study participation. Participants who meet the requirements for contraception (of childbearing potential and engaging in sexual activity that could lead to pregnancy), but indicate they have no intention of either beginning or resuming contraception where required will be permanently discontinued from study product.

When indicated, contraceptive counseling will include maintaining contraceptive use for 30 days after the last oral study product use and for 48 weeks after any single injection of study product. For LSFU participants, contraceptive counseling will also reflect the ARVs which participants are currently taking for the potential interactions between these ARVs and available contraceptive methods. See [Section 8.2](#) for participant management regarding management of pregnancy.

The effective methods of contraception allowed for this study are listed below.

- Consistent and correct use of 1 of the following methods of birth control listed below.

- Surgical sterilization (i.e., hysterectomy, bilateral oophorectomy, tubal ligation, or salpingectomy)
- Contraceptive intrauterine device or intrauterine system
- Subdermal contraceptive implant
- Progestogen injections
- Combined estrogen and progestogen oral contraceptive pills
- Percutaneous contraceptive patch
- Contraceptive vaginal ring

Use of any methods of contraception not included in the listing which have a < 1% failure rate, per the product label, may be allowed in consultation with the CMC.

Study sites should ideally integrate provision of contraceptive methods with other services offered to study participants, and should provide referrals to non-study sources of methods that cannot be provided at the study site.

Pregnancy test results will be disclosed to participants and their parent/guardians consistent with local standards of care; local standard procedures will be noted in site-specific parental permission and informed assent forms.

6.14 Study Product Adherence Assessment and Adherence Counseling (Study Product and Study Visits)

Prior to progressing to the injection phase, participants should be assessed for adherence to oral study product and whether sufficient evaluations of safety and tolerability were permitted to be conducted during the oral lead-in phase. Information obtained through the participant self-report and adherence counseling discussions should be used in combination as a broader adherence assessment evaluation when assessing each participant for eligibility to receive injectable study product. The IoR, or designee, should source document all contributing information leading to and final determination of Step 2 eligibility.

Adherence counseling will be provided to all study participants and parents/guardians throughout study participation at specified study visits, and as needed based on IoR discretion. Topics discussed during adherence counseling will vary depending on the Cohort and the participant's current study product regimen:

- For Cohort 1 and Cohort 2a Step 1 participants, counseling on adhering to the oral study product will be provided in relation to the purpose of the oral lead-in phase, allowing for sufficient evaluations of safety and tolerability, and aligning oral dosing to the same time of day as the Week 2 and Week 4b pre-dose PK sample collections.
- For all participants receiving injectable study products, counseling will include discussion with participants regarding the importance of adhering to the study visit schedule. Any updates to changes to the injectable study product dosing regimen schedule based on information learned throughout the course of the study will also be discussed during these sessions.
- For LSFU participants, counseling will include discussion on the importance of adhering to the study visit schedule and adhering to the (non-study provided) cART regimen.

Counseling may be provided by clinic and/or pharmacy staff consistent with local standards of care and site SOPs. Counseling should be provided in a client-centered manner, tailored as needed to the information, skills building, and support needs of each participant. Information on correct use of oral study products will be provided. Counseling will also address challenges to consistent use of oral

study product or attending injectable study visits over time, with the aim of supporting participants in identifying strategies to address any such challenges.

6.15 Acceptability and Tolerability Assessments

Questionnaires to assess acceptability and tolerability of the study products will be administered at specified study visits. The number and type of assessments administered to participants will differ based upon participant age. Participants ages three and above will complete a brief assessment using a visual analog scale, pictorial scale, or other age-appropriate assessment at injection visits, both pre- and post-injection. Brief questionnaires will be administered by site staff to parents/caregivers and children ages seven and older at study visits as specified in [Appendix I](#); questionnaires will also be triggered for administration in the event of premature permanent study product discontinuation. The questionnaires may be administered in-clinic or, where necessary, telephonically and may cover topics such as perceptions of the study product injections, reasons for switching from daily oral cART to long-acting study products, satisfaction with treatment, quality of life, and treatment preferences. Following completion of the questionnaires, study staff should review the responses and refer any potential adverse events to a study clinician to be assessed.

Further guidance and considerations for conducting and reviewing the acceptability and tolerability assessments, the timing of administering the assessments relative to other visit procedures, as well as guidance regarding the appropriate site staff to administer specified assessments is provided in the IMPAACT 2036 MOP.

A subset of parents/caregivers will be invited to participate in a single semi-structured Qualitative In-Depth Interview (IDI) around the Week 24 visit for Cohort 1 and Cohort 2a, and around Week 20 for Cohort 2b. Interview questions will expand upon topics explored in the questionnaires described above. All interviews will be conducted by trained and experienced interviewers in the preferred language of the interviewee. Interviews will be conducted in person or telephonically, audio-recorded, and transcribed and translated into English by trained study staff. Depending on participant availability and visit length, it may be necessary to conduct these IDIs as a separate visit. Coding will identify main themes emerging from each of the areas explored in the interview.

6.16 Additional Considerations for Laboratory Procedures

Each study site and laboratory involved in this study will comply with the DAIDS policy on Requirements for DAIDS Funded and/or Sponsored Laboratories in Clinical Trials Policy, which is available at: <https://www.niaid.nih.gov/research/daids-clinical-research-laboratory-specimens-management>.

6.16.1 Specimen Collection

Specimens will be collected for this study as indicated in the Schedule of Evaluations and per detailed guidance provided in the Laboratory Processing Chart (LPC), which will be posted on the study-specific webpage: <https://www.impaactnetwork.org/studies/impaact2036>.

Consistent with US National Institutes of Health (NIH) Guidelines for Limits of Blood Drawn for Research Purposes at the NIH Clinical Center, pediatric blood collection will not exceed 5 mL/kg in a single day or 9.5 mL/kg in any eight-week period.

Urine pregnancy testing will be required unless a blood draw is otherwise required at the visit, in which case sites may choose to use either urine or serum pregnancy testing.

In the event blood collection must be limited, specimens will be prioritized in the following order: (1) safety (chemistries, hematology, pregnancy testing), (2) PK, (3) HIV-1 viral load, and (4) resistance testing. For the Confirmation of Virologic Failure visit, prioritization of specimens will be: (1) Safety, if indicated, (2) HIV-1 viral load, (3) resistance testing, and (4) PK.

The date and time of collection should be source documented for all samples collected for laboratory evaluations. All pre-dose PK sample collections should be performed on the same day as, but prior to, administration of the specified study product. The date and time of each PK sample collection timepoint must be source documented and entered into laboratory eCRFs or transferred electronically to the DMC through the LDMS.

Site staff collecting specimens for PK evaluations must prepare workspace and supplies with regards to protecting all PK specimens from light, as specified in the LPC. The PK sample collection must be sufficient for the number of aliquots specified in the LPC for CAB and for RPV. See [Appendix I](#) for required blood volumes.

6.16.2 Specimen Preparation, Testing, Storage, and Shipping

All specimens collected for this study will be labeled, transported, processed, tested, stored and/or shipped in accordance with the DAIDS policy referenced in [Section 6.16](#) above, site and local laboratory SOPs, and the LPC. The frequency of specimen collection and testing will be directed by the Schedules of Evaluations in [Appendix I](#) and specifications for clinical management provided in [Section 8](#). The Laboratory Data Management System (LDMS) will be used to document specimen collection, testing, storage, and shipping as specified in the LPC. Any specimens stored at the Screening Visit for participants who do not subsequently enroll in the study will be destroyed.

All HIV-1 RNA assays must be performed in a CLIA-certified (US) or VQA-certified (non-US) laboratory. CD4+ cell counts must be performed in a CLIA-Certified (US) or IQA-certified (non-US) laboratory.

HIV-1 genotypic and phenotypic resistance samples collected at the Confirmation of Virologic Failure visit must be processed and retained at the site laboratory, as specified in the LPC, pending HIV-1 RNA test results to confirm virologic failure. If virologic failure is confirmed, plasma from the Confirmation of Virologic Failure visit will be shipped to the designated testing laboratory (residual aliquots will be stored at the site laboratory) and resistance testing will be performed in real time. If virologic failure is not confirmed, all aliquots will remain stored at the site laboratory. Testing of resistance samples collected at the Entry and/or other visits will be directed by the CMC.

Specimens collected, processed, and stored at site laboratories for PK evaluations are generally expected to be shipped to the designated testing laboratory as follows, with more frequent shipping as requested by the protocol team:

- For Cohort 1 participants with the Rich Sampling Schedule, all available PK samples should be shipped upon completion of the following visits: Weeks 2, 12, 24, 48, and 72.
- For Cohort 1 participants with the Limited Sampling Schedule and Cohort 2a participants, all available PK samples should be shipped upon completion of the following visits: Weeks 24, 48, and 72 (Cohort 1 only).
- For Cohort 2b participants: all available PK samples should be shipped upon completion of the following visits: Week 4, 20, and 44.
- For all participants following the LSFU visit schedule, and for the PK samples collected during a Confirmation of Virologic Failure visit, PK samples will be batched and shipped upon request from the protocol team.

After all protocol-specified laboratory testing has been performed, residual specimens may be of interest for future research use. Written parental permission must be obtained for future research use of these specimens, if permitted by site IRBs/ECs and other applicable review bodies. Parents or legal guardians may choose to provide or to decline permission for future research use of residual specimens with no impact on other aspects of participation in the study. If permission for future research use of residual specimens is initially provided but participants' parents or legal guardians subsequently change their mind and withdraw that permission, all remaining residual samples will be destroyed.

6.16.3 Biohazard Containment

As the transmission of HIV-1 and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study as currently recommended by the US Centers for Disease Control and Prevention, NIH, and other applicable agencies. All specimens will be shipped using packaging that meets requirements specified by the International Air Transport Association Dangerous Goods Regulations for UN 3373, Biological Substance, Category B, and Packing Instruction 650. Culture isolates, if obtained in this study, are to be shipped as specified for UN 2814 Category A Infectious Substances.

7 SAFETY ASSESSMENT, MONITORING, AND REPORTING

Participant safety will be carefully assessed, monitored, and reported at multiple levels throughout this study. [Sections 7.1-7.3](#) describe safety-related roles, responsibilities, and procedures for site investigators. The safety monitoring roles of the Clinical Management Committee (CMC) and the IMPAACT Study Monitoring Committee (SMC) are briefly referenced in [Section 7.1](#) and described in greater detail in [Section 9.5](#).

Unless otherwise noted, the specifications of this section only apply to participants (not enrolled parents/caregivers).

7.1 Safety-Related Roles and Responsibilities

7.1.1 Site Investigators

Site investigators are responsible for continuous monitoring of all study participants and for alerting the Protocol Team if unexpected concerns arise. Site investigators will enter safety-related data into eCRFs as indicated in [Section 7.2](#) and complete expedited adverse event (EAE) reporting as indicated in [Section 7.3](#).

Site investigators are also responsible for prompt reporting of any unanticipated problems involving risks to participants or others to all applicable IRBs/ECs and other applicable review bodies, per the procedures of each applicable review body.

7.1.2 Clinical Management Committee (CMC)

The following Protocol Team members comprise the CMC: Chair, Vice Chair, Medical Officers, Statisticians, Data Managers, Clinical Research Managers, Laboratory Representatives, Pharmacologists, and one site Investigator. The CMC will also include Protocol Team members from ViiV and Janssen, including Medical representatives (or designee), Pharmacologist, and/or

Statistician. The CMC will provide guidance as needed to site investigators regarding all aspects of participant management, including but not limited to questions of participant eligibility and management of adverse events, study drug regimens, and concomitant medications. Refer to [Section 8](#) for more information on participant management.

On behalf of the full Protocol Team, the CMC will monitor participant safety through routine review of study data reports as described in [Section 9.5](#).

7.1.3 Study Monitoring Committee (SMC)

An independent IMPAACT Study Monitoring Committee (SMC) will monitor participant safety through routine and as needed reviews of study data. Refer to [Section 9.5](#) for more information on the role of the SMC in monitoring this study.

7.2 Safety-Related Data Collection

This section describes eCRF data collection for pre-existing conditions and adverse events. As part of this description, reference is made to severity grading and criteria for EAE reporting; refer to [Section 7.3.3](#) and [7.3.2](#), respectively, for detailed information on these topics.

The definition of the term adverse event provided in Version 2.0 of the Manual for Expedited Reporting of Adverse Events to DAIDS (DAIDS EAE Manual) will be used in this study. This definition will be applied to all child participants, beginning at the time of first exposure to either study drug. Any untoward medical conditions identified prior to or ongoing at enrollment will be considered pre-existing conditions. Refer to [Section 4.8](#) for more information on defining the effective point of enrollment in the study.

Pre-existing conditions and adverse events will be entered into eCRFs as specified below.

Pre-Existing Conditions

The following pre-existing conditions will be entered into medical history eCRFs:

- All conditions (i.e., grade 1 or higher) identified during the 28 days prior to or ongoing at study entry
- All prior to study entry significant central nervous system disorders (including seizures and migraines/headaches), mood disorders (such as depression), and significant liver disease resulting in hospitalization or interfering with daily activities
- Any other medical condition (i.e., grade 1 or higher) occurring prior to study entry and deemed clinically significant by the IoR/designee

Adverse Events

Adverse events will be entered into the adverse events eCRFs:

- Grade 1 and higher clinical adverse events
- Grade 3 or higher laboratory-only adverse events
- Grade 1 or 2 laboratory adverse events that result in temporary study product hold or permanent discontinuation of study product
- Adverse events that meet criteria for expedited reporting per protocol [Section 7.3.2](#)

Laboratory Test Results

All protocol-required laboratory test results will be entered into laboratory eCRFs. HIV-1 RNA will be entered into laboratory eCRFs or transferred electronically to the DMC through the LDMS. ARV resistance test results will be transferred electronically to DMC using data submission utilities. Additionally, any non-protocol-required laboratory test results deemed clinically relevant by the investigator may be collected and reported on eCRFs.

7.3 Expedited Adverse Event (EAE) Reporting

7.3.1 EAE Reporting to DAIDS

Requirements, definitions and methods for expedited reporting of adverse events are outlined in Version 2.0 of the DAIDS EAE Manual, which is available at:
<https://rsc.niaid.nih.gov/clinical-research-sites/manual-expedited-reporting-adverse-events-daids>

The DAIDS Adverse Experience Reporting System (DAERS), an internet-based reporting system, must be used for EAE reporting to DAIDS. In the event of system outages or technical difficulties, EAEs may be submitted using the DAIDS EAE Form. This form is available at:
<https://rsc.niaid.nih.gov/clinical-research-sites/paper-eae-reporting>.

For questions about DAERS, please contact NIAID CRMS Support at:
CRMSSupport@niaid.nih.gov

Queries may also be sent from within the DAERS application itself.

For questions about expedited reporting, please contact the DAIDS RSC Safety Office at:
DAIDSRSCSafetyOffice@tech-res.com

7.3.2 EAE Reporting Requirements for this Study

The SAE (serious adverse event) reporting category, as defined in Version 2.0 of the DAIDS EAE Manual, will be used for this study. In addition, the following must also be reported in an expedited manner (i.e., as EAEs), regardless of relationship to study drug:

- Grade 2 or higher ALT or AST with total bilirubin $\geq 2\times$ ULN
- Grade 2 or higher baseline ALT or AST with signs/symptoms of clinical hepatitis
- Grade 3 ALT or AST that persists >2 weeks
- Grade 4 ALT or AST
- Any seizure event

The study agents for which expedited reporting are required are oral cabotegravir (CAB), long-acting injectable cabotegravir (CAB LA), oral rilpivirine (RPV), and long-acting injectable rilpivirine (RPV LA).

Information on adverse events will be included in reports to the US FDA, and other government and regulatory authorities, as applicable.

7.3.3 Grading Severity of Events (applies to EAEs and all other adverse events)

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Corrected Version 2.1, dated July 2017, will be used in this study,

except where otherwise noted below. This table is available on the RSC website at <https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables>.

QTc Intervals: QTc intervals must be calculated using the Fridericia QT correction formula (provided in the IMPAACT 2036 MOP), with the below specified grading:

	Grade 1	Grade 2	Grade 3	Grade 4
QTc Prolongation Interval	QTc \geq 460msec, but < 480msec	QTc \geq 480msec, but < 500msec	QTc \geq 500msec OR QTc > 60 msec greater than baseline AND QTc \geq 480 ms	Life-threatening consequences (e.g., Torsades de pointes, other serious ventricular dysrhythmias)

Creatinine and eGFR: Grading of creatinine and eGFR should be based on absolute value only (note the Bedside Schwartz formula provided in the IMPAACT 2036 MOP must be used for calculating eGFR), with the below specified grading:

	Grade 1	Grade 2	Grade 3	Grade 4
Creatinine, High	1.1 to 1.3 x ULN	> 1.3 to 1.8 x ULN	> 1.8 to < 3.5 x ULN	\geq 3.5 x ULN
eGFR, Low	NA	< 90 to 60 ml/min/1.73 m ²	< 60 to 30 ml/min/1.73 m ²	< 30 ml/min/1.73 m ²

Fever: When temperatures are collected, clinical discretion should be used to determine if an axillary or non-axillary temperature is most appropriate, with the below specified grading used for participant safety management:

	Grade 1	Grade 2	Grade 3	Grade 4
Fever (axillary temperature)	37.4 to <38.0°C	38.0 to <38.7°C	38.7 to <39.4°C	\geq 39.4°C
Fever (non-axillary temperature)	38.0 to < 38.6°C or 100.4 to < 101.5°F	\geq 38.6 to < 39.3°C or \geq 101.5 to < 102.7°F	\geq 39.3 to < 40.0°C or \geq 102.7 to < 104.0°F	\geq 40.0°C or \geq 104.0°F

7.3.4 EAE Reporting Period

The EAE reporting period for this study is the protocol-specified period of follow-up, beginning at the time of study entry and ending on the latest timepoint: Week 72 (Cohort 1), Week 48 (Cohort 2a), 44 (Cohort 2b), or LSFU Week 48.

After the protocol-defined EAE reporting period, unless otherwise noted, only Suspected, Unexpected Serious Adverse Reactions (SUSARs) as defined in Version 2.0 of the DAIDS EAE Manual will be reported to DAIDS if the study staff become aware of the events on a passive basis (from publicly available information).

8 PARTICIPANT MANAGEMENT

8.1 Management of Adverse Events

All adverse events identified in this study will be source documented in participant research records, consistent with the policies and procedures referenced in [Section 11.2](#). Among other details, source documentation will include the severity of each event (graded as described in [Section 7.3.3](#)) and its relationship to study drug, assessed by the site clinician according to the following categories and definitions:

Related	There is a reasonable possibility that the adverse event may be related to the study agents: oral cabotegravir (CAB), long-acting injectable cabotegravir (CAB LA), and oral rilpivirine (RPV), and long-acting injectable rilpivirine (RPV LA)
Not related	There is not a reasonable possibility that the adverse event may be related to the study agents: oral cabotegravir (CAB), long-acting injectable cabotegravir (CAB LA), and oral rilpivirine (RPV), and long-acting injectable rilpivirine (RPV LA)

Further standardized guidance on determining whether there is a reasonable possibility of a relationship is available in the DAIDS EAE Manual, referenced in [Section 7.3.1](#) above.

Adverse events identified in enrolled participants will be managed based on their severity and assessed relationship to study product, as described in greater detail below.

Individual dose adjustments or reductions of study products for management of toxicity-related adverse events are not allowed. In the event of a temporary study product hold or a permanent discontinuation of study product, both study products will always be held (or discontinued). For additional considerations regarding participants resuming (non-study provided) cART, see [Section 8.4](#) regarding temporary product holds, and [Section 8.5](#) regarding permanent discontinuation of study product.

All adverse events must be followed to resolution (return to baseline) or stabilization (absence of further deterioration), with the frequency of repeat evaluations determined by the clinical significance of each event. Additional evaluations beyond those listed in the Schedules of Evaluations (see [Appendix I](#)) may be performed at the discretion of the site investigator to determine the etiology of a given event and/or further assess its severity or relationship to study product. Clinical management of all adverse events should be provided consistent with the best medical judgment of the site investigator and local clinical practice standards.

Participants with Grade 3 or higher adverse events at their last regularly scheduled study visit should remain on study for up to 28 days or until resolution or stabilization, whichever is sooner. The frequency of any additional visits is determined by the site investigator. If this is not possible, the site investigator should actively facilitate referral to local non-study sources of appropriate medical care and treatment.

Unless otherwise specified, when management of an adverse event requires consultation with the CMC, the CMC should be contacted as soon as possible and within two business days of site awareness of the event.

8.1.1 General Management of Adverse Events

Sections 8.1.2–8.3 provide detailed participant and study product management on specified adverse events including specified abnormal laboratory test result values. If an observed adverse event or abnormal laboratory test result value is not listed in those sections below, the guidance in this section (General Management of Adverse Events) should be followed.

In general, the IoR or designee has the discretion to temporarily hold study product at any time if they feel that continued product use would be harmful to the participant or interfere with treatment deemed clinically necessary. See Sections 8.4 and 8.5 below.

- **Grade 1 or Grade 2, regardless of relationship to study drug:** Continue study product and manage participant according to standard of care practice at the site.
- **Grade 3 assessed as not related:** Continue study product and re-evaluate participant at least weekly until improvement to Grade 2 or lower. If improvement to Grade 2 or lower cannot be documented in 2 weeks, consult the CMC.
- **Grade 3 assessed as related:** Temporarily hold study product use, notify the CMC, and re-evaluate the participant at least weekly until improvement to Grade 2 or lower. If within 2 weeks the adverse event has improved to Grade 2 or lower, study product may be resumed. Consult the CMC if improvement to Grade 2 or lower cannot be documented within 2 weeks
 - If study product use is resumed and the same Grade 3 adverse event deemed related to study product, recurs at any time, the IoR/designee must temporarily hold study product and consult the CMC for further guidance on continuing the temporary hold or progressing to permanent discontinuation of the study product.
- **Grade 4 regardless of relationship to study drug:** Temporarily hold study product, re-evaluate the participant as soon as possible or within 2 business days, and consult the CMC. Continue the temporary product hold until a recommendation is obtained from the CMC.

8.1.2 Injection Site Reactions (ISRs)

An ISR is defined as an adverse event which, in the opinion of the IoR or designee, results in pain, tenderness, erythema, redness, induration or swelling, or pruritis. ISRs should be assessed and reported per the Site Reactions to Injections and Infusions section of the DAIDS toxicity tables.

Participants with ISRs should be managed as follows, regardless of relationship to study drug:

- **Grade 1 or Grade 2:** Continue study product, and manage the participant symptomatically (e.g., cold/warm compress, acetaminophen, ibuprofen).
- **Grade 3 or 4:** Consult the CMC to determine etiology and study product management.

Please see the IMPAACT 2036 MOP for more details related to ISRs.

8.1.3 Suspected IM Maladministration and/or Post-Injection Reaction

In the event that a participant experiences a serious post-injection reaction or IM maladministration is suspected at any time (e.g., suspected under or overdose or inadvertent IV dosing), the investigator should request that the participant stay onsite for approximately 2-3 hours post-dose for safety monitoring. An ECG or any other supportive testing may be obtained at the discretion of the investigator. Additionally, PK samples should be drawn approximately 2 hours post-dosing for

evaluation of CAB and RPV plasma concentrations. The CMC should be notified immediately and no later than 24 hours after a suspected maladministration event. Additional safety labs may be requested by the CMC or collected per investigator discretion.

8.1.4 Creatine Kinase (CK/CPK) Elevation

All participants with elevated CK results from baseline should be assessed for physical activity or exercise preceding the CK sample collection. Participants should abstain from exercise for more than 24 hours and be well hydrated prior to any repeat sample collection.

- **Grade 1 or 2:** Continue study product.
- **Grade 3:** Continue study product and repeat testing from a new sample within 14 days. If the repeat test result is Grade 3 or higher, consult the CMC within 48 hours.
- **Grade 4, with no signs/symptoms of rhabdomyolysis:** Continue study product and repeat testing from a new sample within 7 days, and after the participant has abstained from exercise for >24 hours. If the repeat test result is Grade 2 or lower, manage per grade. If the repeat test result is Grade 3 or higher, consult the CMC within 48 hours for further guidance on study product and participant management.
- **Grade 4, with signs/symptoms of rhabdomyolysis:** For Grade 4 CK elevations that are in the opinion of the IoR associated with signs/symptoms of rhabdomyolysis (such as myalgias, muscle pain, dark urine, or clinically significant changes in creatinine clearance or eGFR), temporarily hold study product, repeat testing from a new sample within 7 days, and consult the CMC within 48 hours for further guidance on study product and participant management.

8.1.5 Lipase Elevations and Pancreatitis

Participants with asymptomatic elevations in lipase should be managed as follows, regardless of relationship to study drug:

- **Grade 1 or 2:** Continue study product, and be followed for development of symptoms (i.e., pancreatitis) according to standard of care practice at the site.
- **Grade 3 or higher:** Temporarily hold study product, and repeat testing on a newly obtained sample within 2 weeks. If the repeat test result is Grade 2 or lower, resume study product. If upon resuming study product lipase elevation is Grade 3 or higher, permanently discontinue study product. If the repeat test result is Grade 3 or higher, and in the absence of other diagnoses, permanently discontinue study product.

Participants with a confirmed diagnosis of clinical pancreatitis (i.e., symptomatic elevations in lipase) should be managed as follows:

- **Grade 2 or higher assessed as not related:** Temporarily hold study product, notify the CMC within 48 hours, and re-evaluate the participant weekly until complete resolution (i.e., return to baseline). Upon returning to baseline, resume study product and re-evaluate the participant every 2 weeks for at least 6 weeks. If after resuming study product, any elevation of lipase of Grade 2 or higher, or any recurrence of symptoms, then permanently discontinue study product.
- **Grade 2 or higher assessed as related:** Permanently discontinue study product, and notify the CMC.

8.1.6 Elevations in ALT or AST, Bilirubin

ALT, AST, total bilirubin, and direct bilirubin will be routinely monitored in this study.

In all cases of elevated ALT, AST, and/or elevated bilirubin (total or direct), possible alternative etiology should be assessed, and the underlying illness treated, or the likely causative agent removed. Sites should counsel participants and their parents/guardians about signs and symptoms of hepatotoxicity. Participants should be advised to notify the study site immediately if they develop any concerning signs or symptoms: new or worsening nausea, vomiting, unexplained loss of appetite; yellowing of the skin or eyes; increased weakness or fatigue; pain in the upper abdomen (liver tenderness or hepatomegaly); pale or clay-colored stools; and/or unexplained weight loss.

Elevated bilirubin in the absence elevated ALT or AST should be managed per [Section 8.1.1](#).

ALT or AST results of severity grade 1 or 2 — other than the grade 2 results specified in the first two bullet points below — require no additional action. Study drug should be continued with routine monitoring per the Schedule of Evaluations unless more frequent monitoring is considered clinically indicated in the opinion of the site investigator. If any results of severity Grade 3 or higher are obtained, all four tests (i.e., ALT, AST, total bilirubin, and direct bilirubin) should be repeated as soon as possible and within three business days. Re-evaluation should continue at least weekly until improvement to grade 2 or lower or until stabilized and no longer in need of frequent monitoring, as determined by the site investigator and in consultation with the CMC.

Study drug must be held in the following scenarios (See [Section 7.3.2](#) for EAE reporting requirements):

- Grade 2 ALT or AST with total bilirubin greater than two times the upper limit of normal ($>2\times\text{ULN}$) and direct bilirubin greater than 35% of total bilirubin. In this case, study drug should be permanently discontinued, and the CMC should be notified.
- Grade 2 or higher ALT or AST with signs or symptoms of clinical hepatitis (e.g., fatigue, nausea, vomiting, right upper quadrant pain, jaundice) or hypersensitivity (e.g., rash, fever, facial edema, eosinophilia, difficulty breathing). In this case, if another cause of the ALT or AST elevation is identified, consideration may be given to resuming study drug with approval from the CMC.
- Grade 3 ALT or AST for more than two weeks (with total bilirubin $\leq 2\times\text{ULN}$ and no signs or symptoms of clinical hepatitis or hypersensitivity). In this case, if another cause of the ALT or AST elevation is identified, consideration may be given to resuming study drug, with approval from the CMC.
- Grade 4 ALT or AST. Hold study drug upon first identification of the Grade 4 result, i.e., pending receipt of the repeat test result; inform the CMC of the initial result and the repeat result. In the case of a confirmed grade 4 result, if another cause of the ALT or AST elevation is identified, consideration may be given to resuming study drug, with approval from the CMC.

8.1.7 Hypersensitivity Reaction

Hypersensitivity includes a constellation of symptoms such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia.

If the IoR or designee suspects hypersensitivity reaction, regardless of relationship to study drug, the participant should be managed as follows:

- **Grade 1 or higher:** Temporarily hold study product, and within 24 hours of site awareness repeat hematology and chemistries testing on newly obtained samples, and notify the CMC. Continue to re-evaluate the participant, and repeat testing on newly obtained samples at least twice weekly until any abnormal laboratory test results return to baseline values, or stabilize. Refer participant to a specialist or hepatology consultation, at the discretion of the site investigator, and in consultation with the CMC.

8.1.8 Allergic Reaction

Participants with allergic reactions should be managed as follows:

- **Grade 1 or higher assessed as not related, and Grades 1 or 2 assessed as related:** Continue study product, and antihistamines, topical corticosteroids, or antipruritic agents may be prescribed at the discretion of the IoR or designee. The participant should be advised to contact the site immediately if there is any worsening of symptoms or if further systemic signs or symptoms develop.
- **Grade 3 or higher assessed as related:** Permanently discontinue study product, and notify the CMC within 24 hours. Manage as clinically appropriate including antihistamines, topical corticosteroids, or antipruritic agents. Admission to hospital may be required for severe allergic reactions. Following clinical stabilization, re-evaluate the participant weekly, and manage according to standard of care practice at the site until resolution to baseline.

8.1.9 Skin Rash

All participants experiencing a rash should be assessed for systemic symptoms, laboratory abnormalities, or mucosal involvement.

Participants with skin rash should be managed as follows, regardless of relationship to study drug:

- **Grade 1 (regardless of systemic involvement), or Grade 2 without evidence of systemic involvement:** Continue study product use at the discretion of the site investigator.
- **Grade 2 with evidence of systemic involvement, or Grade 3 or higher (regardless of systemic involvement):** permanently discontinue study product, and consult the CMC within 48 hours. Re-evaluate daily for at least 5 days for systemic symptoms, laboratory abnormalities, mucosal involvement, and for any progression of the rash or increase in severity. Participants may be referred to a dermatologist, at the discretion of the site investigator.

Additionally, for any rash determined to be related to study drug and presenting prior to the Week 4b visit, the CMC must be consulted prior to administering injectable study product at the Week 4b visit.

8.1.10 Depression, Suicidal Ideation or Attempt

Participants living with HIV-1 infection may occasionally present with symptoms of depression and/or suicidal ideation or behavior. Participants who experience symptoms of depression and/or suicidal ideation or behavior, or report delusions and inappropriate behavior, regardless of relationship to study drug, should be managed and re-evaluated according to standard of care

practice at the site, or more frequently, or referred for specialist evaluation and treatment, at the discretion of the site investigator. Refer to the IMPAACT 2036 MOP for additional guidance regarding establishing a baseline screening assessment for depression. Participants reporting new symptoms of depression will be asked to contact the study IoR or designee immediately if symptoms of severe acute depression (including suicidal ideation/attempts) develop. All sites should have a plan in place for managing possible risks for suicide related events.

- **Grades 1 or 2:** Manage per site standard of care and SOPs.
- **Grade 3 or higher:** Manage per site standard of care and SOPs and consult the CMC within 24 hours.

8.1.11 Management of QTc Prolongation

See [Section 6.12](#) for the specifications requiring repeat ECG readings. If any one of the repeated readings confirm a Grade 3 or Grade 4 QTc Prolongation Interval (using the Fridericia formula provided in the IMPAACT 2036 MOP), temporarily hold study product and assess participant for concomitant medications known to cause prolonged QT or Torsades de Pointes. Study product may be resumed in consultation with the CMC, and if the prolonged QTc is assessed as not related to study drug. If the prolonged QTc is assessed as related, or no other likely cause identified, permanently discontinue study product.

For any other abnormality or irregularity reported by the automated read during follow-up that is considered clinically significant by the qualified site clinician, a cardiologist should be consulted, and the CMC notified.

8.2 Management of Pregnancy

[Section 6.13](#) provides details on pregnancy testing, contraceptive counseling, and contraceptive use guidance, including the effective contraception methods allowed in the study.

A pregnancy test result must be obtained from a specimen collected on the same day as and prior to administration of study product for participants of childbearing potential. A temporary product hold should be put into place and the CMC should be notified immediately and no later than 24 hours following receipt of a positive pregnancy test result. A confirmatory pregnancy test should be conducted as soon as possible and within 48 hours. Any participant still on oral lead-in when a pregnancy is confirmed will be permanently discontinued from study product. For participants receiving injectable study products, the CMC will make a determination about continued product use weighing the benefit/risk ratio for the participant and fetus and will communicate their decision to the site team within 3 business days of the original notification. Following the CMC recommendation, and in consultation with the IoR or designee, the participant and parent/legal guardian (as applicable) will make a decision about ongoing treatment options during pregnancy. See [Section 5.1.3](#) and [Section 8.4](#) for more information on oral bridging and temporary product holds and [Section 13.3.2](#) for parental permission, informed assent, and informed consent requirements.

Participants who permanently discontinue study product use due to pregnancy will be followed per the LSFU visit schedule based on their confirmed positive pregnancy test result; see [Section 6.6](#). In these circumstances, the choice of cART regimen is at the site investigator's discretion and in accordance with the local standard of care and available resistance profiles, and appropriate for use in pregnancy. Sites should actively refer pregnant participants to antenatal standard of care, and to engage in antenatal care as early in the pregnancy as possible.

Pregnancy test results and pregnancy outcomes will be ascertained and entered into eCRFs for all pregnant participants. Pregnancy outcomes should be ascertained based on medical records; when medical records are unavailable, maternal report may be used. Pregnancy related complications and diagnoses, and outcomes will be reported as adverse events and EAEs as outlined in the protocol in [Section 7](#).

Participants who are pregnant will remain on study through delivery or other pregnancy outcome; see [Section 6.8](#). If the site becomes aware of a pregnancy complication occurring after the participant has exited the study, and the pregnancy complication is assessed as related to study drug, the CMC should be notified immediately and no later than three business days after site awareness.

Study sites will also be encouraged to prospectively register the participant's pregnancy in the Antiretroviral Pregnancy Registry: <http://www.apregistry.com/> (in US: 1-800-258-4263).

8.3 Monitoring and Management of HIV-1 Viral Load

Monitoring

HIV-1 RNA (viral load) will be monitored closely with frequent testing as specified in the Schedules of Evaluations in [Appendix I](#). All HIV-1 RNA assays must be performed in a CLIA-certified or equivalent (US sites) or VQA-certified (non-US) laboratory using the testing platform specified in the LPC.

Site investigators should review the results of each test as well as trends over time and consult with the CMC regarding any individual test results or trends of concern. Viral load results should be provided to participants and may be used to guide adherence counseling.

Definition and Confirmation of Virologic Failure

Virologic failure is defined as two successive plasma HIV-1 RNA test results ≥ 200 copies/mL, from separate specimens collected at least two weeks apart.

Any participant with a plasma HIV-1 RNA level ≥ 200 copies/mL after enrollment should be recalled to the clinic for completion of the Confirmation of Virologic Failure visit. Refer to [Section 6.7](#) for details regarding this visit.

Definition and Management of Confirmed Virologic Failure

The CMC should be consulted regarding any participant with confirmed virologic failure. All participants with confirmed virologic failure will be permanently discontinued from study product. Refer to [Section 8.5](#) for participant management regarding permanent discontinuation of study product. Participants with confirmed virologic failure during the oral lead-in phase will be terminated from the study and will complete an Early Termination visit 28 days after last oral study product use. Participants with confirmed virologic failure during the injection phase or during the course of the LSFU visit schedule will be followed per the LSFU visit schedule; see [Section 6.6](#).

HIV-1 genotypic and phenotypic resistance samples will be processed and stored per [Section 6.16.2](#) and the LPC. Upon confirmation of virologic failure, shipping and testing of resistance samples will be performed, per [Section 6.16](#) and the LPC. These resistance test results will be reviewed by the site investigator of record, or designee, and used to inform a recommended cART regimen, in consultation with the CMC. Participants should resume the recommended non-study provided oral cART as soon as possible and within 4 weeks.

8.4 Deferring Study Product and Criteria for Temporary Hold of Study Product

At each study product administration time point, the site investigator or designee must confirm participant eligibility to receive study product (see [Section 6.8](#)). Study product administration must be deferred consistent with the guidance provided in [Section 8.4](#).

For any other significant medical condition that, in the opinion of the investigator, would make it unsafe to administer study product or make it difficult to assess for subsequent study drug related adverse events, if present on the scheduled day of study product administration, administration must be deferred, and the CMC should be consulted on next steps and continued study product management.

For all temporary holds, both study products should be held, and the CMC should be consulted as soon as possible and within 48 hours; the CMC may recommend resuming a (non-study provided) cART regimen in these situations. For participants resuming a cART regimen for the duration of a temporary study product hold, site staff should provide the participant and the participant's parent or guardian with referrals to non-study sources of treatment for the participant, as applicable. See the IMPAACT 2036 MOP for operational consideration and guidance.

Study product will be temporarily held from a participant for any of the following reasons:

- Study product management per [Sections 8.1](#) through [8.4](#).
- Report of use of prohibited concomitant medications (See [Section 5.7](#)). Study product use may resume upon consultation with the CMC and when the participant reports that he/she is no longer taking the prohibited medication, provided other reasons for temporary study product hold/permanent discontinuation do not apply. The CMC should be consulted in all cases of a participant reporting taking a prohibited concomitant medication during the course of the study.
- The participant is unable or unwilling to comply with required study procedures, such as protocol-required laboratory assessments or injectable study product visits, or otherwise might be put at undue risk to their safety and well-being by continuing study product use, according to the judgment of the site investigator. The site investigator must consult the CMC on all temporary study product holds instituted for this reason, for further guidance on resuming study product use, continuing the temporary hold, or progressing to permanent discontinuation.

8.5 Criteria for Premature Permanent Discontinuation of Study Product

See [Section 6.6](#) for guidance regarding participant management in the event of early termination or withdrawal from study participation. Administration of study product will be permanently discontinued in the following circumstances:

- Participant intention to discontinue study product or study follow-up
- During the oral lead-in phase, sustained non-adherence to oral regimen that, in the opinion of the investigator and in consultation with the CMC, warrants early study product discontinuation.
- Sustained non-adherence to injection visit schedule that, in the opinion of the investigator and in consultation with the CMC, warrants early study product discontinuation (per IoR discretion, a temporary product hold may be initially implemented; see [Section 8.5](#)).
- The participant requires treatment with prohibited medications (see [Section 5.7](#)).
- During the oral lead-in phase, confirmed pregnancy; see [Section 8.4](#) for product management during injectable phase in the context of a positive pregnancy test.

- Participants of childbearing potential who are engaging in sexual activity that could lead to pregnancy refuse use of an effective contraceptive method without an intention to resume/initiate.
- The participant experiences an adverse event that requires discontinuation as defined in [Section 8.1](#).
- Virologic failure as described in [Section 8.3](#).
- The site investigator determines that further administration of study product would be detrimental to the participant's health or well-being.
- New data become available that indicate study products should be discontinued as determined by the CMC.

Participants who permanently discontinue study product should resume (non-study provided) cART as follows:

- Cohort 1 and Cohort 2a participants during the oral lead-in phase: as soon as possible and within 4 weeks of their last oral study product use.
- All participants during injectable phase and on a Q4W dosing regimen: within 4 weeks of their last study product injection.
- All participants during injectable phase and on a Q8W dosing regimen: at 8 weeks (± 7 days) after their last study product injections.

Participants who permanently discontinue oral study product will be instructed to return all oral study products to the site clinic as soon as possible.

See [Section 6.6](#) for the specified participants who will be followed per the LSFU visit schedule upon permanent discontinuation of study product.

Participants who prematurely permanently discontinue study product during the oral lead-in phase for reasons other than pregnancy or are otherwise not eligible to progress to the injection phase will be terminated from the study. These participants should complete an Early Termination visit 28 days after last oral study product use; see [Section 8.6](#) below for additional guidance in the event of termination from the study.

8.6 Participant Withdrawal or Termination from the Study

Participants may voluntarily withdraw from the study at any time, and the site investigator may also, at their discretion, discontinue the participant from the study at any time under the following circumstances:

- Participant re-locates away from the study site (with no options to transfer to another site) or is otherwise determined to be lost-to-follow-up
- Investigator or designee determines that continued participation in the study would be unsafe or otherwise not in the best interest of the participant, after consultation with the CMC
- The study is stopped or canceled by the sponsors or government or regulatory authorities
- Site participation in the study is canceled by the sponsors, government or regulatory authorities, the sIRB (for US sites), or site IRBs/ECs (for non-US sites)

In each of the circumstances listed above, except the study being stopped or cancelled, the CMC should be consulted before terminating the participant from follow-up. Participants who are withdrawn from the study will not be replaced.

Should the permitting parent or legal guardian of an enrolled participant die or no longer be available for any reason, study product should be temporarily held and no further study products should be

administered and no further study-specific evaluations should be performed until written parental permission for continued study participation is obtained from an authorized guardian, as defined locally. Study sites may continue to provide care for the participant as needed and as appropriate (outside of the study), consistent with the local standard of care, but no study-specific procedures may be performed. If an authorized guardian cannot be identified, or if the authorized guardian does not permit continued study participation, the participant must be terminated from the study. Refer to [Section 8.4](#) for additional guidance on communication with the CMC for temporary study product holds, and [Section 13](#) for legal guardian permission for study participation.

For any participant who withdraws/is withdrawn or is terminated from the study prior to scheduled completion of follow-up, study staff will document the reason for the withdrawal or termination in detail and will make every effort to complete final evaluations as described in [Section 6.6](#). In the event that the circumstances that led to a participant's withdrawal or termination change (e.g., he or she returns to the study site area after having re-located previously), the site investigator or designee should contact the CMC to discuss options for resumption of follow-up.

9 STATISTICAL CONSIDERATIONS

9.1 General Design Issues

This is a Phase I/II, multi-center, open-label, non-comparative study to evaluate the safety, acceptability, tolerability, and pharmacokinetics of CAB and RPV (oral lead-in and injectable formulations). The primary goals of the study are to propose the weight band dosing of oral CAB + oral RPV followed by CAB LA + RPV LA in children two to less than 12 years of age living with HIV-1, and to describe participant choice and experience with the regimen with or without an oral lead-in period.

The study has two cohorts. Cohort 1 is designed to come up with a proposed a weight band dosing for oral CAB + RPV followed by CAB LA + RPV LA based primarily on PK, safety and tolerability data. Cohort 2 is designed to describe the preference between CAB + RPV (oral + injectable) and CAB LA + RPV LA (injectable) and participants and or their parents/caregivers when given a choice between the two treatments. Overall study data can also help inform possible implementation of the CAB + RPV regimens in children two to less than 12 years of age living with HIV-1.

In making dosing decisions, the team will review available data as described in [Section 3](#). The details of the review of safety data during the dose-finding phase are described in this section.

This statistical section also describes the outcome measures and planned analyses for the study objectives on safety, tolerability, acceptability, virologic response and immunologic response. Please refer to [Section 10](#) for all matters which deal with PK study objectives, including the definition of outcome measures and planned analyses.

A minimum of 50 participants will be enrolled to Cohort 1 and will receive CAB and RPV oral lead-in followed by CAB LA + RPV LA. Up to 20-40 participants will be enrolled to Cohort 2 and will receive CAB LA + RPV LA with or without an optional oral lead-in of CAB and RPV. Safety data will be summarized for the cohorts and for the groups based on participant weight at entry and study drug dosing. The precision of the estimates will depend on the number of participants included in the safety analysis. It is recognized that Cohort 2 estimates of safety failures for children on CAB + RPV (oral + injectable) and CAB LA + RPV LA (injectable) may be less precise due to small sample size.

The analysis for the Primary Analysis Report will be performed when Cohort 1 complete data through Week 24 are available. Additional analysis reports for supporting regulatory submissions or publication (e.g., safety update, HTA-health technology assessment) and final reports which include data beyond Week 24 will be generated. The details of analyses for these reports will be specified in the Primary Statistical Analysis Plan (Primary SAP) and other study analysis planning documents.

The study is designed to allow changing the dose regimen as described in [Section 5.1.2](#). The study also allows for the use of oral bridging during the injection phase. Analysis specifications related to any dose changes or the use of oral bridging are in [Section 9.6](#). Additional specifications may be added in the Primary SAP.

Participants assigned or who opt to receive LA injectable regimen with oral lead-in of CAB and RPV, i.e., participants in Cohort 1 and 2a, may fail the Step 2 eligibility criteria and thus are not able to proceed with the injectable phase of the regimen. The Primary SAP will describe the analyses to address the safety objectives in case some Cohort 1 and 2a participants do not proceed with the injectable phase of the regimen.

9.2 Outcome Measures and Estimands

The primary and secondary outcome measures listed in this section will be further described in the study's Primary SAP, which will define the contents of the final analysis reports.

The [Safety Outcome Measures](#) will consider the adverse event's severity (i.e., grade), seriousness (i.e., using ICH criteria for serious events), and attribution to the study drugs. The following specifications will also be used for the safety outcome measures and are referenced in [Table 4](#):

- **Drug-related safety failure events** include the following:
 - Grade 3 or higher adverse events assessed as related to study drug(s)
 - SAEs assessed as related to study drug(s)
 - Premature permanent discontinuation of study drug(s) due to an adverse event assessed as related to study drug(s)
- **Adverse event attribution to the study drugs** will be based on site's assessment.
- **HIV-1 Virologic Outcome Measures** based on HIV-1 RNA (copies/mL), will be calculated according to the US FDA-defined Snapshot Algorithm and will use 50 and 200 copies/mL as threshold with three main categories each.
 - HIV-1 RNA <50 copies/mL, HIV-1 RNA \geq 50 copies/mL, and no virologic data.
 - HIV-1 RNA <200 copies/mL, HIV-1 RNA \geq 200 copies/mL, and no virologic data.
- **Confirmed virologic failure** is defined in [Section 8.3](#).

The primary objectives for Cohort 1 will be supported by the PK outcome measures and safety described in [Section 10.2](#) and in the table below, respectively. As stated above, the PK-related study objectives will be supported by the PK outcome measures and planned analyses as described in [Section 10](#).

Table 4.
Outcome Measures

9.2.1 Cohort 1 Primary Outcome Measures	
9.2.1.1	<p>Safety of the CAB + RPV oral lead-in and 24 weeks of CAB + RPV (oral and injectable)</p> <ul style="list-style-type: none"> • Proportion of children who experience the following during the CAB + RPV oral lead-in period: <ul style="list-style-type: none"> ○ drug-related safety failure event ○ grade 3 or higher adverse event ○ SAE ○ premature permanent discontinuation study treatment due to an adverse event • Proportion of children who experience the following during the 24 weeks of CAB + RPV (oral and injectable): <ul style="list-style-type: none"> ○ drug-related safety failure event ○ grade 3 or higher adverse event ○ SAE ○ premature permanent discontinuation study treatment due to an adverse event
9.2.2 Cohort 1 Secondary Outcome Measures	
9.2.2.1	<p>Proportion of children who experience the following through Weeks 48 and 72 of CAB + RPV (oral and injectable):</p> <ul style="list-style-type: none"> ○ drug-related safety failure event ○ grade 3 or higher adverse event ○ SAE ○ premature permanent discontinuation study treatment due to an adverse event
9.2.2.2	<ul style="list-style-type: none"> • Proportion of children who have HIV-1 RNA <50 and ≥50, copies/ml at Weeks 24, 48, and 72 using the FDA Snapshot algorithm • Proportion of children who have HIV-1 RNA <200 and ≥200 copies/ml at Weeks 24, 48, and 72 using the FDA Snapshot algorithm • Proportion of children with confirmed virologic failure at Weeks 24, 48 and 72 while on CAB + RPV
9.2.2.3	<p>Tolerability: Child and/or parent/caregiver responses to questionnaires about CAB or RPV side effects, pain associated with injections, and injection site reactions at Weeks 24, 48, and 72.</p> <p>Acceptability: Child and/or parent/caregiver reported attitudes about CAB or RPV, including willingness to use at Weeks 24, 48, and 72.</p>
9.2.2.4	<p>Proportion for each group based on genotypic and phenotypic resistance to CAB or RPV for children who experience virologic failure while on CAB + RPV.</p>

9.2.2.5	<p>Median for CD4 count and percentage at Weeks 24, 48 and 72.</p> <p>Median change from baseline CD4 count and percentage at Weeks 24, 48 and 72.</p>
9.2.3 Cohort 2 Secondary Outcome Measures	
9.2.3.1	<p>For children who are on 48 weeks of CAB + RPV (oral and injectable) OR 44 weeks of CAB LA + RPV LA (injectable):</p> <p>Tolerability: Child and/or parent/caregiver responses to questionnaires about CAB or RPV side effects, pain associated with injections, and injection site reactions</p> <p>Acceptability: Child and/or parent/caregiver reported attitudes about CAB or RPV, including willingness to use</p>
9.2.3.2	<p>Safety of 48 weeks of CAB + RPV (oral and injectable) OR 44 weeks of CAB LA + RPV LA (injectable)</p> <p>Proportion of children who experience the following during the 48 weeks of CAB + RPV (oral and injectable) OR the 44 weeks of CAB LA + RPV LA (injectable):</p> <ul style="list-style-type: none"> ○ drug-related safety failure event ○ grade 3 or higher adverse event ○ SAE ○ premature permanent discontinuation study treatment due to an adverse event
9.2.3.3	<p>For children who are on 48 weeks of CAB + RPV (oral and injectable) OR 44 weeks of CAB LA + RPV LA (injectable):</p> <p>Maintenance of virologic suppression</p> <ul style="list-style-type: none"> ○ Proportion of children who have HIV-1 RNA <50 and ≥50, copies/ml using the FDA Snapshot algorithm ○ Proportion of children who have HIV-1 RNA <200 and ≥200 copies/ml using the FDA Snapshot algorithm ○ Proportion of children with confirmed virologic failure while on treatment <p>Immunologic activity:</p> <ul style="list-style-type: none"> ○ Median and Interquartile Range for CD4 count and percentage ○ Median and Interquartile Range change from baseline CD4 count and percentage
9.2.3.4	<p>Proportion for each group based on genotypic and phenotypic resistance to CAB and RPV for children who experience virologic failure while on 48 weeks of CAB + RPV (oral and injectable) OR while on 44 weeks of CAB LA + RPV LA (injectable).</p>
9.2.4 Other Outcome Measures	

9.2.4.1	Proportion of children who experience the following through 48 weeks following permanent discontinuation of CAB LA + RPV LA: <ul style="list-style-type: none"> ○ drug-related safety failure event ○ grade 3 or higher adverse event ○ SAE
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Table 4 shows the specifications for the estimands related to the primary safety outcome measures listed above. Additional details, including additional intercurrent events (e.g., death) for the primary safety outcome measures may be specified in the Primary SAP. Estimands related to the outcome measures for the secondary and other objectives will be included in the Primary SAP.

Table 5.
Safety Estimands

	Primary Safety Estimands	
	Cohort 1 (through week 4)	Cohort 1 (through week 24)
A primary question of interest	What is the safety profile of ~4 weeks of oral CAB+RPV in virologically suppressed children living with HIV-1, two to less than 12 years of age?	What is the safety profile of CAB+RPV (~4 weeks of oral lead-in followed by ~20 weeks of injectable) in virologically suppressed children living with HIV-1, two to less than 12 years of age?
Attributes		
Population	Virologically suppressed children living with HIV, two to less than 12 years of age	
Endpoints/ Variables	Through week 4	Through week 24
	<ul style="list-style-type: none"> ○ Drug-related safety failure event ○ Grade 3 or higher adverse event ○ SAE ○ Permanent discontinuation of study treatment due to an adverse event 	
Treatment condition	Oral CAB + Oral RPV once daily through Week 4 (see Schema on treatment details)	Oral CAB + Oral RPV once daily through Week 4, followed by LA CAB + LA RPV Q4W or Q8W through Week 24 (see Schema on treatment details)
Intercurrent events (ICE)	Premature permanent discontinuation of study drugs for any reasons through week 4 has impact on safety assessment. While-on-treatment strategy will be applied to address this ICE.	Premature permanent discontinuation of study drugs for any reasons through Week 24 has impact on safety assessment. While-on-treatment strategy will be applied to address this ICE.
	Other analysis approaches may also be explored to address missing values due to premature permanent discontinuation as a part of sensitivity analysis. Details will be described in the Statistical Analysis Plan (SAP).	
Population-level summary	Proportions of children experiencing the safety outcome measures and their two-sided 95% confidence interval	

9.3 Randomization and Stratification

There will be no randomization for the study. Participants will be stratified into weight bands based on their weight at study entry (Weight Band 1 25-34.9 kg, Weight Band 2 35-<40 kg, Weight Band 3 20-24.9 kg, Weight Band 4 14-19.9 kg, and Weight Band 5 10-13.9 kg). Cohort 1 has accrual requirements per weight band as well as across Weight Bands 1 and 2 and across Weight Bands 3, 4, and 5, as described in [Section 3](#). There are no weight band accrual requirements in Cohort 2, although there are accrual requirements for Cohort 2a and Cohort 2b, as described in [Section 3](#).

9.4 Sample Size and Accrual

Up to 90 children will be enrolled across Cohorts 1 and 2. Cohort 1 will enroll up to 70 participants in order to achieve at least 50 evaluable participants. Cohort 2 will open to accrual once accrual to Cohort 1 is complete and results on Week 12 interim analyses are available. Additional specifications on weight-band accrual targets (both per weight band and across weight bands) are specified in [Section 3.1](#). Sample size specifications of parents/caregivers of child participants for the behavioral assessments and qualitative in-depth interviews to assess study drug acceptability and tolerability are in [Sections 3.1](#) and [3.4](#). The sample size requirements are primarily driven by consideration for main analyses for the safety study objectives. For example, for the 50 participants included in Cohort 1 primary safety analysis, if 2 (4%) experience a safety failure event as defined in [Section 9.2](#), the 95% Clopper-Pearson Confidence Interval would be 0-14% (please see [Table 6](#)), which provides sufficient precision to exclude a rate $\geq 15\%$ based on the upper limit of CI. Moreover, of the 50 Cohort 1 participants included in the primary safety analysis, the probability of observing at least one participant who experiences such an event is high (87%), assuming a true rate of the safety failure event in the study population of 4% (please see [Table 8](#)).

General specifications for the analysis of safety data are in [Section 9.6](#). To assess the safety of the study drugs, point and 95% Clopper-Pearson Confidence Interval (CI) estimates of proportion of participants who experience at least one safety failure event of interest for a defined safety outcome measure while on CAB+RPV will be generated. Note that the safety failure events of interest will be specific to a safety outcome measure as defined in [Section 9.2](#). [Table 6](#) shows the precision of the 95% CI estimates under different assumptions on sample size and number of safety failures. It shows the precision of the estimates for the main safety analyses, i.e. for a potential of 18 or 32 participants who might contribute data to the per analysis group estimates based on weight at entry (e.g. pooled across Weight Bands 1 and 2, pooled across Weight Bands 3, 4 and 5); and for a potential minimum of 50 and maximum of 70 participants who might contribute data to the overall estimate for Cohort 1 (i.e., pooled across all 5 weight bands), under the likely scenarios that at most 25%-30% of the participants are safety failures and if 50% of the participants are safety failures, as this corresponds to when the confidence interval will be the widest. It also shows the precision of the estimate for a potential of 6 or 10 participants who might contribute to the per weight band estimates, i.e., additional analyses specified in [Section 9.6](#). The table indicates that the 95% CI estimates will be quite wide around the sample size of 6 participants in a Cohort 1 weight band but will be considerably narrower around the target sample size of 50 participants in Cohort 1.

[Table 7](#) shows the point and 95% CI estimates for potential of 20 participants in Cohort 2 overall safety analysis; and potential 5 or 10 participants in Cohorts 2a and 2b safety analyses.

Table 6.
95% Confidence Intervals around Potential Proportions of Cohort 1 Participants Classified as Safety Failures

Number of Participants	Number of Safety Failures	Proportion of Safety Failures^a
6	0	0.00 (0.00, 0.46)
	1	0.17 (0.00, 0.64)
	2	0.33 (0.04, 0.78)
	3	0.50 (0.12, 0.88)
10	0	0.00 (0.00, 0.31)
	1	0.10 (0.00, 0.45)
	2	0.20 (0.03, 0.56)
	3	0.30 (0.07, 0.65)
	5	0.50 (0.19, 0.81)
18	0	0.00 (0.00, 0.19)
	1	0.06 (0.00, 0.27)
	2	0.11 (0.01, 0.35)
	3	0.17 (0.04, 0.41)
	4	0.22 (0.06, 0.48)
	5	0.28 (0.10, 0.53)
	6	0.33 (0.13, 0.59)
	9	0.50 (0.26, 0.74)
32	0	0.00 (0.00, 0.11)
	1	0.03 (0.00, 0.16)
	2	0.06 (0.01, 0.21)
	3	0.09 (0.02, 0.25)
	5	0.16 (0.05, 0.33)
	8	0.25 (0.11, 0.43)
	11	0.34 (0.19, 0.53)
	16	0.50 (0.32, 0.68)
50	0	0.00 (0.00, 0.07)
	1	0.02 (0.00, 0.11)
	2	0.04 (0.00, 0.14)
	4	0.08 (0.02, 0.19)
	6	0.12 (0.05, 0.24)
	9	0.18 (0.09, 0.31)
	12	0.24 (0.13, 0.38)
	15	0.30 (0.18, 0.45)

Number of Participants	Number of Safety Failures	Proportion of Safety Failures ^a
	25	0.50 (0.36, 0.64)
70	0	0.00 (0.00, 0.05)
	1	0.01 (0.00, 0.08)
	2	0.03 (0.00, 0.10)
	3	0.04 (0.01, 0.12)
	5	0.07 (0.02, 0.16)
	35	0.50 (0.38, 0.62)

^a Clopper-Pearson exact confidence interval estimates using SAS Version 9.4.

Table 7.
95% Confidence Intervals around Potential Proportions of Cohort 2 Participants Classified as Safety Failures

Number of Participants	Number of Safety Failures	Proportion of Safety Failures ^a
4	0	0.00 (0.00, 0.60)
	1	0.25 (0.01, 0.81)
	2	0.50 (0.07, 0.93)
10	0	0.00 (0.00, 0.31)
	1	0.10 (0.00, 0.45)
	2	0.20 (0.03, 0.56)
	3	0.30 (0.07, 0.65)
	5	0.50 (0.19, 0.81)
20	0	0.00 (0.00, 0.17)
	1	0.05 (0.00, 0.25)
	2	0.10 (0.01, 0.32)
	3	0.15 (0.03, 0.38)
	4	0.20 (0.06, 0.44)
	5	0.25 (0.09, 0.49)
	10	0.50 (0.27, 0.73)

^a Clopper-Pearson exact confidence interval estimates using SAS Version 9.4.

Table 8 provides the binomial probabilities of observing at least one participant with a safety failure event of interest for a range of Cohort 1 sample sizes and a range of true proportions of children with at least one safety failure event of interest. For example, if the true proportion of children who will experience at least one safety failure event of interest while on CAB + RPV is 5%, the probability of having at least one participant experiencing such event in the study out of 15 and 50 participants are 54% and 92%, respectively.

Table 8.
Probability that at least one Cohort 1 participant will experience at least one safety failure event under different assumptions.

True proportion of children who are safety failures	Sample Size (N)						
	5	10	15	20	35	50	70
0.01	0.05	0.10	0.14	0.18	0.30	0.39	0.51
0.02	0.10	0.18	0.26	0.33	0.51	0.64	0.76
0.03	0.14	0.26	0.37	0.46	0.66	0.78	0.88
0.04	0.18	0.34	0.46	0.56	0.76	0.87	0.94
0.05	0.23	0.40	0.54	0.64	0.83	0.92	0.97
0.06	0.27	0.46	0.60	0.71	0.89	0.95	0.99
0.07	0.30	0.52	0.66	0.77	0.92	0.97	0.99
0.08	0.34	0.57	0.71	0.81	0.95	0.98	>0.99
0.09	0.38	0.61	0.76	0.85	0.96	0.99	>0.99
0.10	0.41	0.65	0.79	0.88	0.97	0.99	>0.99

9.5 Monitoring

Implementation of this study will be monitored at multiple levels, consistent with standard IMPAACT procedures. A Study Progress, Data, and Safety Monitoring Plan (SPDSMP) that details monitoring roles and responsibilities and data to be reviewed at each level will be prepared before the study opens to accrual. [Sections 11](#) and [12](#) provide more information on on-site monitoring and quality management at the site level. Further information on monitoring of study progress, quality of study conduct, and participant safety across sites is provided below.

9.5.1 Dose-Finding Phase

During the dose-finding phase of the study, the CMC will review study data, or data from other ongoing studies of the study drugs in pediatric populations, with the aim of determining the proposed dose, per weight band, while protecting participant safety and as further described in this section.

At a minimum, the PK and safety data will be reviewed during routine monitoring for both cohorts as follows:

- (i) Safety data will be reviewed approximately monthly, and the CMC will take action as needed according to the guidelines described in [Section 9.5.3](#) and
- (ii) PK data will be reviewed as soon as results become available according to specifications in [Section 10](#).

In addition to the routine monitoring of PK and safety data, there will be two Cohort 1 interim analyses, please refer to [Section 3](#). All available PK, safety, viral load, tolerability, and other relevant data will be reviewed by the CMC, and the Safety Guidelines ([Section 9.5.2](#)) will be assessed based on safety data through Week 12. These interim analyses, and/or ongoing reviews of relevant data within the study or from other ongoing studies of the study drugs in pediatric populations, will determine whether any modifications should be made to the weight band dosing, including whether to continue on every 4 weeks(Q4W) or to switch to every 8 weeks(Q8W) for the CAB and RPV injectable. If the Protocol Team determines that a dose modification is needed, accrual will be paused and the SMC will be notified as described in [Section 9.5.4](#).

9.5.2 Safety Guidelines

The Safety Guidelines will consider the adverse event severity, seriousness and attribution to the study drugs. Adverse event attribution to the study drugs will be based on site assessment.

The Safety Guidelines are considered not met, i.e., dose has failed the Safety Guidelines, if:

- at least one participant experienced an adverse event that is fatal or life-threatening and is assessed as related to study drug(s); or
- more than 25% of the participants (e.g., 3 or more of 8 dose-evaluable participants in an interim analysis) experience a Grade 3 or higher adverse event (excluding injection site adverse events, e.g., ISRs) assessed as related to study drug(s) or experience any adverse event assessed as related to study drug(s) that results in permanent discontinuation of the study drug(s).

If none of these conditions are met, then the dose being evaluated has passed the Safety Guidelines.

Given the small sample sizes in a Cohort 1 interim analysis, the information available for safety decisions based on the Safety Guidelines may be imperfect. Two types of sampling errors are possible: 1) if the true rate of toxicity is too high to warrant exposure to the current dose of study drug, the sample data may pass the Safety Guidelines and 2) if the true rate of toxicity is low enough that further exposure to the current dose is warranted, the sample data may fail the Safety Guidelines.

The extent to which the Safety Guidelines protect against the errors described above can be assessed by examining various hypothetical rates of "true toxicity" which could occur if the study drug were used extensively among the participant population at the dose level under question. The hypothetical situations presented in [Table 9](#). (i.e., interim analysis assessment of the Safety Guidelines) range from conditions under which a given dose level would cause a high incidence of severe and life-threatening adverse events to conditions under which severe adverse events would be relatively rare and would not be life-threatening.

[Table 9](#) uses a multinomial response model to assess the probability of failing the Safety Guidelines under each of these hypothetical situations. The calculations are performed as follows: Each of the eight participants represents a trial, which may have 1 of 3 mutually exclusive outcomes: (i) death or life-threatening adverse event assessed as related to study drug; (ii) a Grade 3 or 4 non-life-threatening adverse event assessed as related to study drug; and (iii) a relatively benign outcome, satisfying neither the criteria in (i) nor (ii).

Table 9.
Probability of Eight Dose-Evaluable Participants Failing Safety Guidelines Under Potential Rates of True Toxicity

True Toxicity Rates		Probability of Failing Safety Guidelines
Grade 3 or 4 Non-Life Threatening Drug-Related AE	Life Threatening or Fatal Drug-Related AE	
0.50	0.00	0.86
0.50	0.05	0.93
0.50	0.25	1.00
0.25	0.00	0.32
0.25	0.05	0.57
0.25	0.25	0.95
0.05	0.00	0.01
0.05	0.05	0.34
0.05	0.25	0.90
0.00	0.05	0.34
0.00	0.25	0.90

For each of the hypothetical situations above, it is assumed that a sample of eight participants is drawn from the population and that the Safety Guidelines, summarized above, are followed. The probability of failing the Safety Guidelines represents the sum of the probabilities of these sets of results, and “1 minus the probability of failing the Safety Guidelines” represents the probability of passing the guidelines. The “True Toxicity Rates” presented in the table, along with the true rate of having neither of the two types of adverse events represented by the true toxicity rates (which is “1 minus the sum of the true toxicity rates”), provide the probabilities for the outcomes that are used in the multinomial calculations for each of the hypothetical situations.

As an example of how to read [Table 9](#), the second row shows that there is a 93% chance of failing the Safety Guidelines at doses in which the true rate of drug related life-threatening adverse events is 5% and the true rate of drug-related non-life-threatening adverse events is 50%. Under the conditions specified in row 2 of the table, assuming that further exposure to a dose that has these true rates of adverse events would be undesirable, the 7% chance of NOT failing the Safety Guidelines would represent the probability of error. As a further example, the table also shows that there is 1% chance of failing when the true rate of a drug-related Grade 3 or 4 non-life-threatening adverse event is only 5% and the true rate of drug-related life-threatening or fatal adverse event is zero. Assuming that the potential benefits associated with further exposure to this dose would outweigh the risks associated with this relatively low rate of toxicity, failing the Safety Guidelines under these conditions would be an error.

9.5.3 Monitoring by the Protocol Team

Study Progress and Quality of Study Conduct

The Protocol Team is responsible for continuous monitoring of study progress, including timely achievement of key milestones, and quality of study conduct.

The Protocol Team will monitor participant accrual based on accrual reports that will be generated approximately monthly by the IMPAACT Statistical and Data Management Center (SDMC) as well as site activation. The team will monitor the timing of site-specific study activation, which will determine when each site will begin accruing participants, and actual accrual following activation. The team will monitor site actual accrual relative to site-specific accrual projections. Accrual performance will be reported by the DMC, by site and across sites, and the team will review study progress approximately monthly.

The CMC will determine the dose-evaluability and evaluability status of participants, based on definitions in [Section 3.2](#), and the SDMC will record CMC determinations in the database. Relevant study treatment information and weight band at entry of the participant will be provided to the CMC to facilitate assessment of a participant's dose-evaluability and evaluability status in Cohort 1. For both cohorts, the team will monitor and manage accrual such that fulfillment of the sample size targets specified in [Section 3](#) are achieved. The team will communicate to sites when accrual must be managed and when sample size targets are reached.

The Protocol Team will also monitor participant retention and adherence to study product regimens. On behalf of the Protocol Team, the CMC will monitor other key indicators of the quality of study conduct (e.g., protocol deviations, adherence to the study product regimens, data quality, and data and specimen completeness) based on reports generated by the SDMC and take action with study sites as needed to ensure high quality study conduct throughout the period of study implementation.

Participant Safety

On behalf of the Protocol Team, the CMC will closely monitor participant safety through routine review of safety data reports generated by the SDMC. These reports will be based on the safety-related data collection described in [Section 7.2](#) and will provide listings and/or tabulations of adverse events and laboratory test results. The CMC will review these reports approximately monthly. At the time of each review, the DAIDS Medical Officer will also review any EAEs reported to the DAIDS Safety Office that are not yet reflected in the data reports.

The CMC will continually evaluate the pattern and frequency of reported adverse events and assess for any individual occurrences or trends of concern. The CMC will also monitor for the occurrence of adverse events meeting criteria to convene an *ad hoc* SMC review, as described in [Section 9.5.4](#).

The CMC may discuss the reporting of any adverse event and assessment of relationship to study drug(s) with the site investigator. For adverse events that may trigger an *ad hoc* SMC review specified in [Section 9.5.4](#), the CMC may provide an assessment of adverse event attribution to the study drug(s).

9.5.4 Monitoring by the SMC

An independent IMPAACT Study Monitoring Committee (SMC) will review this study regularly, following policies described in the IMPAACT Manual of Procedures.

The SMC will monitor study progress, quality of study conduct, and participant safety. SMC reviews will occur at least annually and on a more frequent or *ad hoc* basis if any issues or concerns arise. Additionally, an SMC review will occur prior to the CMC finalizing any dosing regimen modifications, as described in [Sections 3.2](#) and [5.1.2](#), including a modification from Q4W to Q8W injection dosing. *Ad hoc* SMC reviews may occur as indicated below (*Participant Safety*).

Based on any of its reviews, the SMC may recommend that the study proceed as currently designed, proceed with design modifications, or be discontinued. The SMC may also provide operational recommendations to help address any study implementation challenges that may be identified during their reviews.

Study Progress and Quality of Study Conduct

The SMC will generally review the same types of study progress and quality of study conduct data reports as the Protocol Team and CMC.

Participant Safety

Routine SMC reviews, as described above, will include a review of safety reports, as described in the SPDSPM. In addition, *ad hoc* SMC reviews may be triggered based on the criteria described below from routine monitoring (see [Section 9.5.3](#)) or from the interim analyses (see [Section 9.5.1](#)) conducted by the CMC. For these *ad hoc* SMC reviews, reports provided to the CMC and relevant to the trigger for the *ad hoc* SMC review will be provided to the SMC. SMC reviews may also include review of additional data, if requested by the CMC.

Ad hoc SMC reviews will occur in the following scenarios:

1. In the event of **any fatal or life-threatening adverse event**, the CMC will review the event as soon as possible:
 - If the site investigator assesses the adverse event as related to study drug(s), participant accrual will immediately be paused and an SMC review will be convened as soon as possible. The CMC may choose to pause administration of study drug(s) pending the outcome of the SMC review.
 - If the site investigator assesses the adverse event as not related to study drug(s), participant accrual and administration of study drug(s) will continue. The SMC will be informed of the adverse event.
2. In the event that three or more of the dose-evaluable participants in a planned interim analysis experience a Grade 3 or higher adverse event (excluding injection site adverse events, e.g. ISRs) assessed by the site investigator as related to study drug(s) or experience any adverse event assessed by the site investigator as related to study drug(s) that results in permanent discontinuation of study drug(s) prior to accruing the eight dose-evaluable participants targeted for the interim analysis, participant accrual will immediately be paused and an SMC review will be convened as soon as possible. The CMC may choose to pause administration of the study drug(s) in the cohort pending the outcome of the SMC review.
3. In the event the CMC identifies any concerns based on review of PK, safety, viral load, tolerability, or other relevant data, an SMC review will be convened. The CMC may choose to pause participant accrual and/or administration of study drug(s) pending the outcome of the SMC review.
4. In the event the CMC recommends a dosing regimen modification, an SMC review will be convened. The CMC will pause participant accrual of the relevant weight band(s) and may pause administration of study drug(s), pending the outcome of the SMC review.

9.6 Analyses

This section provides a brief summary of the planned statistical analyses for outcome measures in [Section 9.2](#). Details will be specified in a separate, comprehensive Primary SAP.

Separate analysis will be done for Cohorts 1, 2a and 2b.

For the main analyses, safety outcome measures including adverse event attribution to the study drug(s) will be done using site assessments. Sensitivity analyses will also be performed for these safety outcome measures but using CMC assessments; the CMC will provide an assessment of attribution to the study drug(s) for adverse events that may potentially be classified as a drug-related safety failure event in the sensitivity analyses.

Baseline:

The **baseline value** will be the latest assessment with a non-missing value prior to the first study drug exposure.

Oral bridging:

Oral bridging will be considered as a part of permitted treatment but will not be counted as a substitute for an injection. Occurrence of oral bridging will be summarized and details will be provided in the Primary SAP.

Supplementary analysis for Cohort 2a: Analyses based on pooled Cohort 1 and 2a data

Participants in Cohort 1 and 2a would have been assigned or opted to receive CAB + RPV oral lead-in followed by CAB + RPV injectable. The main analysis for Cohort 2a will be on Cohort 2a data only, but as an additional analysis; the same analysis may be done on pooled Cohort 1 and Cohort 2a data, as appropriate.

Analysis of Safety and Tolerability Data:

The population of interest for the safety and tolerability analyses are virologically suppressed children living with HIV, two to less than 12 years of age, who received oral CAB + RPV (oral and injectable). Other analysis populations of interest, e.g., children on recommended dose population, may be added and specifications will be included in the Primary SAP.

Separate analyses will be done for each of the safety outcome measures. In addition to the analyses of the safety outcome measures, the proportion of participants who have injection site adverse events, adverse events related to study procedure (e.g., injection site reactions), and any grade adverse event related to the study drug(s) will be provided.

Summaries of worst grade adverse events by MedDRA Preferred Term (PT) grouped by System Organ Class SOC will be generated for: (i) all adverse events, and (ii) all adverse events assessed by site as related to the study drug(s).

Cohorts 1 and 2 analysis groups will be based on weight at entry (i.e., pooled data across Weight Bands 1 and 2; and pooled data across Weight Bands 3, 4 and 5) and study drug dose for the oral lead-in and/or at start of the injectable phase. The main safety analysis will include estimates overall and per analysis group. As additional analysis, per weight band estimates will be provided recognizing that due to small sample size these estimates will be less precise.

Analysis of Virology, Immunology, Phenotypic and Genotypic Resistance Data:

The population of interest for the analyses of virology and immunology data are virologically suppressed children living with HIV, 2 to less than 12 years of age, who received oral CAB + RPV (oral and injectable).

The population of interest for the analysis of phenotypic and genotypic resistance data are the virologically suppressed children living with HIV, 2 to less than 12 years of age, who received oral CAB + RPV (oral and injectable) and are confirmed virologic failure while on CAB + RPV. Cohort 1 and 2 analysis groups will be based on study drug dose for the oral lead-in and/or at start of the injectable phase.

Analysis Sets:

Analysis Set	Descriptions
Screened	All who were screened for study eligibility
Enrolled	All who pass the study entry eligibility criteria and enrolled to the study
All Treated	All study participants who received at least one dose of the study drug. The All Treated population will be used for the safety, tolerability, acceptability, virology and immunology analyses.
Confirmed Virologic Failure	All study participants in the All Treated analysis set who meet the criteria of confirmed virologic failure The Confirmed Virologic Failure' population will be used for the resistance analyses
Pharmacokinetic (PK)	All study participants in the All Treated analysis set with at least one non-missing PK assessment. Note: PK data will be reviewed by the study team to determine whether or not the sample will be excluded from the PK analyses.

Additional analyses sets may be added and will be described in the Primary SAP.

9.6.1 Primary Safety Analyses

9.6.1.1 Cohort 1: Oral lead-in safety

The analyses will focus on safety of the CAB and RPV oral lead-in while on treatment based on Cohort 1 data.

Overall and per group point and 95% Clopper-Pearson CI estimates of the proportion of children who (i) experience at least one drug-related safety failure event, (ii) experience at least one grade 3 or higher adverse event, (iii) experience at least one SAE, and (iv) prematurely permanently discontinue study treatment due to an AE, during the oral lead-in phase will be generated.

- For (i): Point estimates of the proportion of children who experience each of the drug-related safety failure events will be provided.
- For (ii): Point estimates of the proportion of children who (a) experience at least one grade 3 or 4 adverse event, (b) experience a grade 5 adverse event, will be provided.

9.6.1.2 Cohort 1: Safety of 24 weeks of CAB + RPV (oral and injectable)

The analyses will focus on safety of the CAB + RPV (oral and injectable) through Week 24 while on treatment.

Overall and per group point and 95% Clopper-Pearson CI estimates of the proportion of children who (i) experience at least one drug-related safety failure event, (ii) experience at least one grade 3 or higher adverse event, (iii) experience at least one SAE, and (iv) prematurely permanently discontinue study treatment due to an adverse event, through Week 24 will be generated.

- For (i): Point estimates of the proportion of children who experience each of the drug-related safety failure events will be provided.
- For (ii): Point estimates of the proportion of children who (a) experience at least one grade 3 or 4 adverse event, (b) experience a grade 5 adverse event, will be provided.

9.6.2 Secondary Analyses

9.6.2.1 Cohort 1: Secondary Safety Analyses

The analyses will focus on safety of the CAB + RPV (oral and injectable) through Weeks 48 and 72 while on treatment.

Analyses will follow specification similar to Week 24 safety for Cohort 1 ([Section 9.6.1.2](#)) except that the safety timeframe will be through Weeks 48 and 72.

9.6.2.2 Cohort 2: Secondary Safety Analyses

The analyses will focus on safety of the CAB + RPV (oral and injectable) through Week 48 while on treatment OR of CAB LA + RPV LA (injectable) through Week 44 while on treatment.

- Cohort 2a: Analyses will focus on safety of the CAB + RPV (oral and injectable) through Week 48 and will follow specification similar to Week 24 safety for Cohort 1 ([Section 9.6.1.2](#)). As supplementary analyses, summary statistics for safety of the study regimen at Week 24 will also be provided.
- Cohort 2b: Analyses will focus on safety of the CAB LA + RPV LA (injectable) through Week 44 and will follow specification similar to Week 24 safety for Cohort 1 ([Section 9.6.2.1](#)). As supplementary analyses, summary statistics for safety of the study regimen at Week 20 will also be provided.

9.6.2.3 Cohort 1: Drug Tolerability and Acceptability at Weeks 24, 48 and 72

The acceptability and tolerability measures on CAB + RPV (oral and injectable) through Weeks 24, 48, and 72 will be summarized.

Data from social-behavioral assessments and qualitative in-depth interviews will be analyzed to assess acceptability and tolerability. Coding of the transcripts will identify main themes emerging from each of the areas explored in the interview. The qualitative data analysis process will be a descriptive analysis without formal inference, with a more detailed description presented in the qualitative data analysis plan.

9.6.2.4 Cohort 2: Drug Tolerability and Acceptability for 48 weeks of CAB + RPV (oral and injectable) or 44 weeks of CAB LA + RPV LA (injectable)

- Cohort 2a: Analyses will focus on CAB and RPV tolerability and acceptability for children who are on 48 weeks of CAB + RPV (oral and injectable) and will follow specification similar to Cohort 1 ([Section 9.6.2.3](#)). As supplementary analyses to the Week 48 analysis, summary statistics at Week 24 will also be provided.
- Cohort 2b: Analyses will focus on CAB and RPV tolerability and acceptability for children who are on 44 weeks of CAB LA + RPV LA (injectable) and will follow specification similar to Cohort 1 ([Section 9.6.2.3](#)). As supplementary analyses to the Week 44 analysis, summary statistics at Week 20 will also be provided.

9.6.2.5 Cohort 1: Maintenance of Viral Suppression at Weeks 24, 48 and 72

The analyses will summarize plasma HIV-1 RNA data at Weeks 24, 48 and 72 while on treatment, for children on CAB + RPV (oral and injectable)

The overall and per group point and 95% Clopper-Pearson CI estimates of the proportion of children who have HIV-1 RNA <50, ≥50, <200 and ≥200 copies/ml, while on treatment, based on the FDA Snapshot Algorithm at visit weeks above will be generated.

The overall and per group point and 95% Clopper-Pearson CI estimates of the proportion of children with confirmed virologic failure while on treatment at visit weeks above will be generated.

As supplementary analyses,

- Overall and per group point and 95% Clopper-Pearson CI estimates of the proportion of children who have (i) HIV-1 RNA <50 copies/ml and (ii) HIV-1 RNA <200 copies/ml while on treatment at visit weeks above will be generated. The proportions will be calculated using non-missing data only.

Any other virology assessments will be described in the Primary SAP.

9.6.2.6 Cohort 2: Maintenance of Viral Suppression for Children who are on 48 weeks of CAB + RPV (oral and injectable) or 44 weeks of CAB LA + RPV LA (injectable)

- Cohort 2a: Analyses will focus on maintenance of viral suppression while on treatment for children who are on 48 weeks of CAB + RPV (oral and injectable) and will follow specification similar to Cohort 1 ([Section 9.6.2.5](#)). As supplementary analyses to the Week 48 analysis, summary statistics at Week 24 will also be provided.
- Cohort 2b: Analyses will focus on maintenance of viral suppression while on treatment for children who are on 44 weeks of CAB LA + RPV LA (injectable) and will follow specification similar to Cohort 1 ([Section 9.6.2.5](#)). As supplementary analyses to the Week 44 analysis, summary statistics at Week 20 will also be provided.

9.6.2.7 Cohort 1: Immunologic Response at Weeks 24, 48 and 72

The analyses will summarize immunology data at Weeks 24, 48 and 72 while on treatment for children on CAB + RPV (oral and injectable)

At visit weeks above, the overall and per group median and interquartile range for CD4 count, CD4 percent, CD4 count change from baseline, and CD4 percentage change from baseline will be generated.

9.6.2.8 Cohort 2: Immunologic Response for Children who are on 48 weeks of CAB + RPV (oral and injectable) or 44 weeks of CAB LA + RPV LA (injectable)

- Cohort 2a: Analyses will focus on immunologic response while on treatment for children who are on 48 weeks of CAB + RPV (oral and injectable) and will follow specification similar to Cohort 1 ([Section 9.6.2.7](#)). As supplementary analyses to the Week 48 analysis, summary statistics at Week 24 will also be provided.
- Cohort 2b: Analyses will focus on immunologic response while on treatment for children who are on 44 weeks of CAB LA + RPV LA (injectable) and will follow specification similar to Cohort 1 ([Section 9.6.2.7](#)). As supplementary analyses to the Week 44 analysis, summary statistics at Week 20 will also be provided.

9.6.2.9 Cohorts 1 and 2: HIV-1 Genotypic and Phenotypic Resistance for Children with Confirmed Virologic Failure

The number and proportion of children with confirmed virologic failure while on treatment who have HIV-1 genotypic and/or phenotypic resistance at time of virologic failure will be generated. Genotypic and phenotypic resistance data for these children will be summarized.

9.6.3 Other Analyses

Long-term washout safety of CAB LA and RPV LA through 48 weeks following permanent treatment discontinuation

Overall and per group point and 95% Clopper-Pearson CI estimates of the proportion of children who: (i) experience at least one drug-related safety failure event, (ii) experience at least one grade 3 or higher adverse event, and (ii) experience at least one SAE through 48 weeks following permanent discontinuation of CAB LA + RPV LA.

Regulatory Submission

For regulatory submission purposes, the analyses will follow specifications in the Primary SAP. Additional analyses/reports and additional analyses specifications for regulatory submission tables, figures, and listings will be specified in a separate document.

9.7 Additional considerations

Special statistical and data analysis considerations may be warranted in the event that the COVID-19 pandemic or other unanticipated occurrences (e.g., natural disasters) affect the conduct of this study and/or the integrity of study data. To the extent possible, any such considerations will be addressed in the Primary SAP.

10 CLINICAL PHARMACOLOGY PLAN

10.1 Pharmacology Objectives

The clinical pharmacology evaluations for this study are designed to determine the pharmacokinetics (PK) of oral CAB + RPV and CAB LA + RPV LA in virologically suppressed children living with HIV-1, two to less than 12 years of age and weighing ≥ 10 kg and < 40 kg to propose weight-band dosing. For the primary and secondary PK objectives, plasma drug concentrations will be quantified. Multiple PK samples will be collected throughout the oral and LA dose intervals to allow determination of PK parameters for CAB and RPV (see [Section 10.3](#) for details).

All PK samples will be registered in the LDMS and shipped to the designated central pharmacology laboratory; refer to the LPC for shipping details, including the timing of shipments.

The pharmacology-related study objectives are as follows.

Primary – Cohort 1

- To propose an appropriate weight-band dosing regimen for CAB + RPV (oral and injectable).
- To describe the repeat-dose pharmacokinetics of CAB + RPV (oral and injectable) through Week 24.

Secondary – Cohort 1

- To describe the repeat-dose pharmacokinetics of injectable CAB LA + RPV LA through Week 48 and through Week 72.

Secondary – Cohort 2

- To evaluate the repeat-dose pharmacokinetics of CAB + RPV through
 - Weeks 24 and 48 (Cohort 2a: oral followed by injectable)
 - Weeks 20 and 44 (Cohort 2b: injectable only)

Other – Cohort 1 and Cohort 2

- To characterize washout PK through 48 weeks following permanent discontinuation of CAB LA + RPV LA
- To characterize PK of different administration methods of CAB + RPV oral formulations through Week 4b (Weight Bands 3, 4, and 5 only)

In Cohort 2a, participants that opted to receive oral lead-in of CAB and RPV will have the option to take the pediatric formulation tablets (CAB DTs and RPV 2.5 mg tablets) either solubilized/dispersed in liquid or by swallowing intact. Therefore, based on the data collected in CRAYON, we will evaluate the differences between the oral administration methods via population PK or other quantitative approach where feasible.

10.2 Pharmacology Outcome Measures and Estimands

Table 10.
Pharmacology outcome measures

10.2.1 Cohort 1 Primary PK Outcome Measures (CAB and RPV)	
	<ul style="list-style-type: none"> • PO dosing: Wk. 2 AUC, CL/F, C_{max}, T_{max}, and pre-dose concentrations (C_0) • LA dosing (starting at Week 4b): Wk. 5 concentrations (C_{5WK}), Wk. 12 concentrations (C_{12WK}), trough concentrations (C_t) prior to IM doses through Wk. 24 and accumulation ratio (Wk. 24:Wk. 8).
10.2.2 Cohort 1 Secondary PK Outcome Measures (CAB and RPV)	
	<ul style="list-style-type: none"> • LA dosing: C_t prior to IM doses at Wk. 48 and Wk. 72 and accumulation ratios (Wk. 48:Wk. 8 and Wk. 72:Wk. 8).
10.2.3 Cohort 2 Secondary PK Outcome Measures (CAB and RPV)	
10.2.3.1	<p>Cohort 2a LA dosing: C_t prior to IM doses through Wk. 24 and Wk. 48 and accumulation ratios (Wk. 24:Wk. 8 and Wk. 48:Wk. 8).</p> <p>Cohort 2b LA dosing: C_t prior to IM doses through Wk. 20 and Wk. 44 and accumulation ratios (Wk. 20:Wk. 4 and Wk. 44:Wk. 4).</p>
10.2.4 Other Outcome Measures	
	<ul style="list-style-type: none"> • CAB and RPV concentrations 8 to 48 weeks following final IM dose
	<ul style="list-style-type: none"> • PO dosing: Wk. 2 AUC, CL/F, C_{max}, T_{max}, and pre-dose concentrations (C_0) by administration mode

Table 11.
Pharmacology Estimands

Primary PK Estimand (Cohort 1)	
A primary question of interest	What is the PK profile of repeat-dose pharmacokinetics CAB+RPV (~4 weeks of oral lead-in followed by ~20 weeks of injectable) (orally lead-in followed by injectable through Week 24) in virologically suppressed children living with HIV-1, two to less than 12 years of age?
Attributes	
Population	Virologically suppressed children living with HIV, 2 to less than 12 years of age, who received CAB + RPV through Week 24.
Endpoints/ Variables	<ul style="list-style-type: none"> o PO: Wk. 2 AUC, CL/F, C_{max}, T_{max}, and pre-dose concentrations (C_0) o LA: C_{5WK}, C_{12WK}, and C_t prior to IM doses through Wk. 24 and accumulation ratio (Wk. 24:Wk. 8). <p>As shown in Table 10</p>
Treatment condition	Oral CAB + Oral RPV once daily through Week 4, followed by LA CAB + LA RPV Q4W or Q8W through Week 24 (see Schema on treatment details).

Intercurrent events (ICE)	<ul style="list-style-type: none"> o Premature permanent discontinuation of study drugs for any reasons (e.g., death) during treatment phase through Week 24 has impact on PK assessment. While-on-treatment strategy will be applied to address this ICE. o Use of prohibited medications that potentially has significant impact on PK concentrations per clinical pharmacologist will also be addressed by ‘while-on-treatment strategy’.
Population-level summary	Summary statistics e.g., arithmetic mean, geometric mean, median, standard deviation, minimum, maximum, and coefficient of variation, 90% confidence interval, etc.

10.3 Pharmacology Study Design, Modeling, and Analysis

Oral and LA regimens with the proposed initial doses in this pediatric population are expected to achieve plasma concentrations within an acceptable range of those observed clinically in adolescents and adults. Initial doses selected for each weight band, based on prior data and modeling, are described in [Section 5](#).

Pharmacokinetic blood samples will be collected as noted in [Section 6](#) and [Appendix I](#). Of note, PK samples need to be protected from light from sampling through analysis as detailed in the LPC.

Cohort 1 (with oral lead-in): Plasma concentrations for both CAB and RPV will be measured in at least the first 8 participants across Weight Bands 1 and 2, and at least the first 8 participants across Weight Bands 3, 4, and 5 according to the Rich Sampling Schedule as follows:

- Oral dosing
 - o Wk. 2: Pre-dose, 1, 2, 3, 4 and 8h post dose (6 samples)
- Long-acting injectable dosing:
 - o Wk. 4b: Pre-dose and 2h and 24h post dose,
 - o Wk. 5: Day 2-7 post-dose,
 - o Wk. 6: Day 12-16 post-dose,
 - o Wk. 8: pre-dose,
 - o Wk. 9: Day 3-7 post-dose,
 - o Pre-dose prior to injections at Wk. 12, Wk. 16, Wk. 24, Wk. 32, Wk. 40, Wk. 48, Wk. 56, Wk. 64, Wk. 72.

Cohort 1 (with oral lead-in) and Cohort 2a (with oral lead-in): Once the proposed dosing regimens have been evaluated in each weight band and data are sufficient for the PK parameter estimates for both oral and IM dosing, then the Limited Sampling Schedule (below) will be used for the remainder of participants (through Week 72 for Cohort 1 and Week 48 only for Cohort 2a). Operational guidance for implementing the Limited Sampling Schedule for newly enrolling and currently enrolled participants will be provided in the IMPAACT 2036 MOP with additional communication provided to site teams at the time of implementation in a Memorandum of Operational Instruction.

- Oral dosing
 - o Wk. 2: Pre-dose and 3h post dose (2 samples)
- Long-acting injectable dosing:
 - o Wk. 4b: Pre-dose and 2h post dose
 - o Wk. 5: Day 2-7 post-dose,
 - o Pre-dose prior to injections at Wk. 8, Wk. 16, Wk. 24, Wk. 32, Wk. 40, Wk. 48, Wk. 56, Wk. 64, Wk. 72.

Cohort 2b (straight to IM dosing): For participants who do not receive oral doses, and start with IM dosing at Entry, the following IM-only Sampling Schedule will be used:

- Long-acting injectable dosing:
 - Entry: Pre-dose and 2h and 24h post dose,
 - Day 3: Day 2-7 post-dose,
 - Wk. 2: Day 12 – 16 post-dose,
 - Pre-dose prior to injections at Wk. 4, Wk. 12, Wk. 20, Wk. 28, Wk. 36, Wk. 44.

All Cohorts (Cohorts 1, 2a and 2b)

- LSFU
 - Single PK sample collected at LSFU Week 4, 8, 24, 36 and 48 visits.

Assay Site: Plasma pharmacokinetic samples collected will be sent to the IMPAACT Pharmacology Laboratory listed in the IMPAACT 2036 LPC for both CAB and RPV containing specimens. Sample collection, processing, storage and shipping details are provided in the IMPAACT 2036 LPC.

Methods to be used: All assay methods will be standardized with a filed Methods Report, under Good Laboratory Practice (GLP) conditions and cross-validated with primary assay providers used for CAB and RPV. The assays will be performed using high-performance liquid chromatography and tandem mass spectrometry (HPLC/MS/MS).

Reporting of Assay Data: PK samples from participants in Cohort 1 who are following the Rich Sampling Schedule will have assays performed in real-time through Week 24. Assaying of samples from the Wk. 32 through the Wk. 48 and Wk. 72 visits in the Rich Sampling Schedule, and all assays from the Limited Sampling Schedule (Cohorts 1 and 2a) may be performed in batches (refer to LPC for shipping schedule), and upon team request. PK samples from participants in Cohort 2b who are following the IM-only Sampling Schedule will have the assays performed in real-time up through Week 20. Samples from Wk. 28 through Wk. 44 may be assayed in batches and upon team request. PK samples collected from any Confirmation of Virologic Failure visit will be assayed as requested by the team.

10.3.1 Interim Analyses

The first interim analysis will be performed once 8 dose-evaluable participants across Weight Bands 1, 2, and 3 have completed the Wk. 12 visit with at least two dose-evaluable participants in the lowest of these weight bands (20-24.9 kg). If the observed median Wk. 12 concentrations meet the acceptance criteria for CAB and RPV (below), then the lighter Weight Bands, 4 and 5 will open to enrollment. See “Potential Dose Modification” section below for additional details.

A second interim analysis is planned to take place once Weight Bands 4 and 5 are open to accrual and 8 dose-evaluable participants across Weight Bands 3, 4, and 5 have completed the Wk. 12 visit with at least two dose-evaluable participants in the lowest weight band (10-13.9 kg). If the observed median Wk. 12 concentrations meet the acceptance criteria for CAB and RPV (below), then Cohort 2 can enroll across all weight bands. See “Potential Dose Modification” section below for additional details.

Additional evaluations of CAB and RPV pharmacokinetics may be performed for specific weight bands, for either Cohort 1 or Cohort 2, depending on the ongoing study findings, safety data, and/or any proposed changes to the initial weight-band dosing regimens (changes in dose amounts and/or dose intervals).

PK Acceptance Criteria

Oral CAB

The CAB PK acceptable criteria following oral administration is:

- A median Wk. 2 $AUC_{0-\tau}$ between 38 and 277 and mcg*h/mL (the lower bound of the 95% CI for AUC following 10mg once daily to the upper bound of the 95% CI for AUC following 60mg once daily in adults living with HIV in LAI116482 (LATTE))
- Median trough (at the end of the oral dosing interval; C_{τ}) concentrations ≥ 0.45 mcg/mL (5th percentile of the observed CAB trough concentration following the initiation injection in Phase 3 studies in adults)
- Median $C_{max} \leq 22.5$ mcg/mL that was observed in the TQT study in adults without any impact on QT interval.

Oral RPV

The RPV PK acceptable criteria following oral administration is:

- A median Wk. 2 $AUC_{0-\tau}$ between 1250 and 4166 ng*h/mL (approximately 60-200% of the geometric mean in adults, which is 2083 ng*h/mL).
- Median trough (C_{τ}) concentrations ≥ 17.3 ng/mL (5th percentile of the observed RPV trough concentration following the initiation injection in Phase 3 studies in adults)
- Median $C_{max} \leq 450$ ng/mL (determined as not posing an increased risk for QT interval prolongation based on PK/PD modeling and simulation for adult TQT studies)

For this study, AUC of a selected RPV dose under fed and steady-state conditions will be the primary PK parameter for determination of the acceptability of the RPV oral dose, but the C_{max} and C_0 of RPV will also be taken into consideration.

CAB LA

The CAB PK acceptable criteria following LA administration is:

- A median Wk. 12 (Cohort 1) or Wk. 8 (Cohort 2b) trough (prior to next LA dose; C_t) concentration between 0.71-6.7 mcg/mL

RPV LA

The RPV PK acceptable criteria following LA administration is:

- A median Wk. 12 (Cohort 1) or Wk. 8 (Cohort 2b) C_t between 25-100 ng/mL

The study team will review all of the PK parameters following oral and long-acting CAB and RPV, safety and tolerability/acceptability data to determine if dose modifications are warranted (for each drug, for each formulation and for each weight band).

Potential Dose Modification

Dose adjustments for management of individual participant PK target exposures will not occur. In the event of failure with respect to safety and/or PK criteria that are deemed potentially avoidable by lower (or higher) exposure to the study drugs, as judged by the CMC, a dose adjustment will be considered for the applicable weight band. As noted in [Section 5.1.2](#), dosing regimen modifications for each weight band may occur as needed following the Cohort 1 interim analyses and/or based on ongoing reviews of safety, PK, and all other relevant data, and will be implemented across all participants within the applicable weight band group. During the reviews of the data and based on the findings, the protocol team may decide whether to continue with Q4W dosing, move to Q8W dosing, change to a different dose on either the Q4W or Q8W schedule, or gather additional data on the initial Q4W dosing regimen for each weight band.

At the two planned interim analyses, and at any other additional relevant PK analysis, the PK parameters calculated from each individual participant will be used to predict that participant's exposure at Wk. 12 (Cohort 1) or Wk. 8 (Cohort 2b) if they were taking Q8W injections instead of Q4W (via modeling and simulation). Using the *predicted* Q8W dose interval trough concentrations from each participant, the same trough acceptance criteria will be applied as already noted in the protocol above. The same strategy will be used, if needed, during ongoing study PK analyses to assess alternate doses or dose intervals if particular weight-bands do not meet acceptance criteria for either the oral or the LA dosing. In other words, based on the observed PK data from each participant, those participants' predicted exposures on the new dose or dose regimen will be calculated, and the acceptance criteria will be applied to those individual participants' predictions on that new dose or dose interval.

When assessing whether to change the dose interval, if the median of the predicted concentrations from every 8 week dosing meets the LA dosing trough acceptance criteria, new participants in the corresponding Weight Bands may be initiated on every 8 week dosing. Ongoing study participants that enrolled on every 4 week dosing may also transition to every 8 week dosing after their week 24 visit.

10.4 Pharmacokinetic Sample Size Justification

See [Section 3](#) and [Section 9.4](#) for details regarding the sample size and accrual targets for the study, including stratification requirements. The total sample size for Cohort 1 and 2 was primarily driven by safety outcome measures, but the total number of participants, including the minimum of 6 participants required in each Weight Band in Cohort 1, and a minimum of 4 participants in each Cohort 2a and 2b are sufficient to characterize the PK profile based on [the](#) statistical precision.

The precision was estimated using PK trough concentration for the sample sizes of the minimum of 4 (Cohort 2a and Cohort 2b) and 6 (each weight band in Cohort 1), respectively, as shown in [Table 12](#). For example, with a minimum of 4 participants in Cohort 2a or 2b, the precision can be achieved with 90% CI of sample geometric mean trough concentration (C_t prior to IM doses) at Week 20/24 being 0.84 -3.06 ug/mL for CAB, and 32.11-101.74 ng/mL for RPV. Therefore, the predicted 90% CI will allow to exclude a value of 4 X PA-IC90 (0.664 ug/mL) for CAB, and rule out a value of 2 X PA-IC90 (24 ng/mL) for RPV.

Table 12.
Statistical Precision When Estimating PK Trough Concentration at Week 20 (direct to injection)/ Week 24 injection visit (oral lead-in followed by LA)

Study drugs	N	Assumption			Precision ⁺ when estimating trough Concentration 90%CI	
		Mean (LgConc.)	SD (LgConc.)	Geo. Mean*		
	Assumption 1: PK Trough data from ATLAS-2M					
CAB (ug/mL)	6	0.47	0.55	1.6	1.02	2.52
	4				0.84	3.06
RPV (ng/mL)	6	4.05	0.49	57.16	38.20	85.54
	4				32.11	101.74
	Assumption 2: 10% increase of SD (LgConc.) from Assumption 1					
CAB (ug/mL)	6	0.47	0.61	1.6	0.97	2.63
	4				0.79	3.26
RPV (ng/mL)	6	4.05	0.54	57.16	36.69	89.06
	4				30.31	107.78

	Assumption 3: 30% increase of SD (LgConc.) from Assumption 1					
CAB (ug/mL)	6	0.47	0.72	1.6	0.89	2.88
	4				0.69	3.71
RPV (ng/mL)	6	4.05	0.64	57.16	33.85	96.53
	4				27.01	120.95
	Assumption 4: 50% increase of SD (LgConc.) from Assumption 1					
CAB (ug/mL)	6	0.47	0.83	1.6	0.81	3.15
	4				0.61	4.22
RPV (ng/mL)	6	4.05	0.74	57.16	31.22	104.64
	4				24.07	135.74
+Precisions were calculated based on t-distribution. *Geometric means (1.6 ug/mL for CAB and 57.16 ng/mL for RPV PK trough) were observed at Week 24 based on a large number of adults (N=506) in ATLAS-2M study who received CAB+RPV Q8W. For the purpose of predicting precision, these values were assumed to be the true geometric mean of PK trough in this pediatric study population.						

10.5 Pharmacokinetic Analyses

Pharmacokinetic analyses will be performed on the pharmacokinetic analysis set which is defined in [Section 9.6](#).

Demographic data used in the PK analysis may include age, sex assigned at birth, race, ethnicity, study site, height, weight, weight Z score, weight band, BMI, BMI Z score and BSA. Available laboratory data will include serum creatinine, albumin, ALT, bilirubin and hemoglobin. Complete dosing information will also be utilized including dose dates, times, dose amounts, food intake (oral dosing only), oral administration method, dose quantity administered, injection site (gluteal or thigh), needle length and gauge, single vs. split injection dose administration and sample collection dates and times. Refer to the PK SAP for additional details.

10.5.1 Oral Dosing: Non-Compartmental Analyses (NCA)

A non-compartmental pharmacokinetic analysis (NCA) will be performed on the plasma CAB and RPV concentration-time data generated for each individual. Calculated pharmacokinetic parameters will include, as permitted by data:

- area-under-the-curve during the dosing interval ($AUC_{0-\tau}$),
- maximum concentration (C_{max}),
- time to C_{max} (T_{max}),
- Pre-dose concentration (C_0),
- apparent clearance (CL/F),

C_{max} and T_{max} will be taken directly from the observed concentration-time data. $AUC_{0-\tau}$ will be determined using the linear trapezoidal method and C_0 will be used as an estimate of trough concentration at the end of the dose interval C_τ (for oral), when needed, assuming steady-state conditions. In absence of adequate PK data to perform an NCA, other appropriate analyses may be undertaken to support dose recommendations. Refer to the PK SAP for more details.

For the second Other Objective, in Cohort 2, participants that opted to receive oral lead-in of CAB and RPV will have the option to take the pediatric formulation tablets (CAB dispersible tablets and RPV 2.5 mg tablets) either solubilized/dispersed in water or by swallowing or dissolving in the mouth without prior dispersal. Therefore, based on the data collected in CRAYON, we will evaluate

the differences between the oral administration methods via population PK or other quantitative approaches where feasible.

10.5.2 LA Dosing and LSFU: PK Analyses

PK analyses following LA injectable dosing will consist primarily of reporting observed concentrations at key time points (C_{\max} and C_{trough} around specific administrations). Accumulation ratios are calculated from the observed trough concentrations at specific time points. After study drug discontinuation, the terminal half-life from the injectable formulations may be calculated from the terminal slope of the concentration-time curve after the last injection, if permitted by data. Refer to the PK SAP for more details.

10.5.3 Population Pharmacokinetic Analysis

Population (POP) PK analyses for CAB and RPV may be performed where appropriate using the IMPAACT 2036 PK data alone or in combination with existing adolescent and adult PK data using appropriate nonlinear mixed effect (NLME) methodology. POP PK analysis will be considered outside of the scope of this protocol and will be reported separately along with the modelling and simulation analysis plan. Other PK analyses of collected data, including POP PK evaluations, may be performed to assist the study team with assessment of safety or dosing/regimen. Relationships between plasma PK parameters and pharmacodynamics (e.g., adverse events, virologic, immunologic) may be assessed based on emerging data.

11 DATA HANDLING AND RECORD KEEPING

11.1 Data Management Responsibilities

As described in [Section 4.8](#), data on screening and enrollment in this study will be collected using the DMC SES.

Study sites must maintain adequate and accurate research records containing all information pertinent to the study for all screened and enrolled participants and parents/caregivers, including paper-based CRFs (if used), eCRFs, and supporting source data. In maintaining these records, sites must comply with the standards of source documentation specified in the DAIDS Site Clinical Operations and Research Essentials (SCORE) Manual, which is available at: <https://www.niaid.nih.gov/research/daids-clinical-site-implementation-operations>

eCRFs and an eCRF completion guide will be made available to study sites by the DMC. Study site staff will enter required data into eCRFs, with system checks applied and data queries generated immediately upon saving the entered data. Data must be entered within timeframes specified by the DMC; queries must also be resolved in a timely manner. Selected laboratory data will be transferred electronically to the DMC through the LDMS.

The Protocol Team and/or study oversight bodies (e.g., SMC) may determine that additional source data associated with procedures or evaluations performed per protocol should be entered into eCRFs so that the data can be used for analysis or to otherwise assist with interpretation of study findings. In such cases, sites will be officially instructed to enter the additional data into eCRFs from available source documentation.

Further information on eCRFs and IMPAACT data management procedures will be provided by the DMC. A User Manual for the Study Enrollment System is available on the DMC portal at: <https://www.frontierscience.org>.

Qualitative in-depth interviews will be conducted, digitally audio-recorded, and transcribed and translated into English. Audio recordings should be stored on a secure server or CD (that has been certified as an exact copy of the original audio recording) and maintained along with finalized transcripts as source documentation per the requirements outlined in [Section 11.2](#). Personal identifiers will be removed from the transcripts prior to being electronically uploaded and transferred to the DMC portal using the File Exchange Utility.

11.2 Essential and Source Documents and Access to Source Data

Study sites must comply with requirements for essential documents and source documentation, as specified in the DAIDS SCORE Manual. This includes establishing SOPs for maintaining essential and source documents. Site SOPs should be updated and/or supplemented as needed to describe roles, responsibilities, and procedures for this study, and site SOPs should be followed throughout the study.

Per the DAIDS policy on Storage and Retention of Clinical Research Records, study records must be stored in a manner that ensures privacy, confidentiality, security, and accessibility during the conduct of the study and after the study is completed. Records must be retained for a minimum of three years after the completion of the study. Per 21 CFR 312.62, records must be maintained for two years after the date a marketing application is approved for one or more of the study products for the indication for which they are evaluated in this study; or, if no application is filed, or if the application is not approved for this indication, records must be retained two years after the study is discontinued and the FDA is notified.

All study records must be accessible for inspection, monitoring, and/or auditing during and after the conduct of the study by authorized representatives of the study sponsors and their contracted monitors, IMPAACT, ViiV Healthcare Ltd, Janssen Research & Development LLC, the US FDA, the US Office for Human Research Protections, site drug regulatory authorities, site IRBs/ECs, the sIRB (for US sites), and other US, local, and international regulatory entities. Records must be kept on-site throughout the period of study implementation; thereafter, instructions for off-site storage may be provided by NIAID or NICHD. No study records may be removed to an off-site location or destroyed prior to receiving approval from NIAID or NICHD.

11.3 Quality Control and Quality Assurance

Study sites must ensure that essential documents and participant research records are subject to continuous quality control and quality assurance procedures consistent with the DAIDS SCORE Manual.

12 CLINICAL SITE MONITORING

Under contract to NIAID or NICHD, site monitors will inspect study site facilities and review participant study records — including parental permission and informed assent forms, paper-based CRFs (if used), eCRFs, medical records, laboratory records, and pharmacy records — to ensure protection of study participants, compliance with the IRB/EC approved protocol, and accuracy and completeness of records. Monitors also will review essential document files to ensure compliance

with all applicable regulatory requirements. Site investigators will make study facilities and documents available for inspection by monitors.

Monitoring visits may be conducted on-site or remotely. Remote visits may include remote source document verification using methods specified for this purpose by NIAID or NICHD. Remote monitoring visits may be performed in place of, or in addition to, onsite visits to ensure the safety of study participants and data integrity (22). Site investigators must make available study documents for site monitors to review utilizing a secure platform that is 21 CFR Part 11 compliant and HIPAA compliant. The DMC has configured Medidata Remote Source Review (RSR) to be available to all sites. If Medidata RSR is not utilized, other potential platform options include: Veeva SiteVault, site-controlled SharePoint or cloud-based portal, direct access to Electronic Medical Record (EMR), and Medidata Rave Imaging Solution. Other secure platforms that are 21 CFR Part 11 and HIPAA compliant may be utilized, as allowed by the DAIDS Office of Clinical Site Oversight or NICHD.

13 HUMAN SUBJECTS PROTECTIONS

13.1 Institutional Review Board/Ethics Committee Review and Approval

Prior to study initiation, site investigators must obtain IRB/EC review and approval of this protocol and site-specific parental permission, informed consent, and assent forms in accordance with 45 CFR 46; subsequent to initial review and approval, IRBs/ECs must review the study at least annually. Site investigators must promptly report to the IRBs/ECs any changes in the study and must comply with the requirements of 45 CFR 46.108(a)(4) and 21 CFR 56.108(b) for promptly reporting the following: unanticipated problems involving risks to participants or others; serious or continuing noncompliance with applicable regulations or the requirements or determinations of their IRBs/ECs; and any suspension or termination of IRB approval.

Non-US sites are frequently overseen by more than one IRB/EC. US sites are overseen by an sIRB, with additional review by local IRBs if required per their agreements with the sIRB. Site investigators are responsible for awareness of and adherence to the policies and procedures of all applicable IRBs/ECs. All such policies and procedures must be followed and complete documentation of all correspondence to and from all applicable IRBs/ECs must be maintained in site essential document files. Sites must submit documentation of both initial review and approval and continuing review to the DAIDS Protocol Registration Office (PRO) in accordance with the DAIDS Protocol Registration Manual (see also [Section 14.2](#)).

13.2 Vulnerable Participants

NIH policy requires that children be included in clinical research conducted or supported by the NIH when appropriate (23). This study complies with that policy and will provide clinical research data to inform study product dosing for children. Nonetheless, the children who take part in this study are considered vulnerable participants per 45 CFR 46 Subpart D.

IRBs/ECs must determine the level of risk to children in the categories specified in 45 CFR 46.404-407. Documentation of this determination is required to complete the DAIDS protocol registration process described in [Section 14.2](#), and the risk category assigned by the IRB/EC further determines the parental permission requirements for the study at each site. Per 45 CFR 46.408 (b), the IRB/EC may find that the permission of one parent is sufficient for research to be conducted under 46.404 or 46.405. If the IRB/EC finds that the research is covered by 46.406 or 46.407, both parents must give their permission, unless one parent is deceased, unknown, incompetent, or not reasonably available or when only one parent has legal responsibility for the care and custody of the child (as determined

locally). IRBs/ECs must document their risk determination. Parental permission will be documented on site-specific parental permission forms, and study sites should adapt the signature pages of their site-specific forms as needed to accommodate the parental permission requirements associated with the IRB/EC determination.

Study sites must comply with requirements for enrolling minors in clinical research as specified in the DAIDS SCORE Manual. In addition, to the US regulations cited above, sites must also comply with all applicable local and national and international guidelines and regulations. When multiple different sets of requirements apply, the most stringent requirements must be followed.

13.3 Parental Permission, Informed Consent, and Informed Assent

Refer to [Section 4.8](#) and the study-specific MOP for further information on informed consent and assent procedures for this study. Refer to [Appendix IV](#) for sample ICFs and to [Appendix V](#) for sample assent forms.

In general, the informed consent and assent processes for participants as well as parents/caregivers will include information exchange, detailed discussion, and assessment of understanding of all required elements of informed consent, including the potential risks, benefits, and alternatives to study participation.

13.3.1 Parental Permission and Informed Assent for Child Study Participants

Written parental permission for study participation will be obtained from each participant's parent or legal guardian before any study-specific procedures are performed. It is generally expected that the permission of one parent (or legal guardian) will be sufficient for child participation in this study. However, parental permission requirements at each site will depend on the IRB/EC risk determination as described in [Section 13.3](#); all applicable IRB/EC requirements must be followed. If applicable per local regulations, the potential participant is considered a minor who is legally able to provide informed consent, written informed consent for study participation will be obtained from the potential participant instead of parental or legal guardian permission before any study-specific procedures are performed.

Permission for the child's participation will include a description of what is currently known about the safety and efficacy of the study products and the context of current local standards of care for HIV-1 care and treatment. Should the participant be unaware of their HIV-1 status, the parental permission process may be conducted with the parent or legal guardian separately and without the presence of the participant, per IRB/EC policies.

When applicable per site IRB/EC policies and procedures, written assent will also be obtained from each child before any study-specific procedures are performed. If the participant does not provide assent, or the parent or legal guardian does not provide permission, the participant will not be enrolled in the study. Minor participants who assent to a study and later withdraw that assent will not be maintained in the study against their will, even if their parent or legal guardian still wants and permits them to participate.

Should the permitting parent or legal guardian of an enrolled participant die or no longer be available for any reason, all applicable IRB/EC policies and procedures should be followed. If the participant is doing well on study drug, it is generally expected that they will stay on study drug with safety monitoring evaluations performed consistent with the local standard of care. Other study-specific evaluations (outside the standard of care) should not be performed until written permission for continued study participation is obtained from the child's new legal guardian. If a new legal guardian

cannot be identified, or if the new legal guardian does not permit continued study participation, the child must be withdrawn from the study.

The assent process will include an age-appropriate discussion of study participation. Sites should follow IRB/EC policies when determining whether the assent process should be conducted with both the parent or legal guardian and the participant present. Non-US sites may develop multiple assent forms, if desired, in anticipation of different information needs across the study age range. When preparing site-specific assent forms, sites may remove or modify the wording included in the sample assent forms in order to provide the most appropriate information and level of detail, consistent with applicable IRB/EC policies and procedures. Given the study age range, it is expected that some potential participants will be aware of their HIV status whereas others will not. To avoid unintentional disclosure of HIV status, the sample assent forms provided in [Appendix V](#) do not refer to HIV status or treatment of HIV. For potential participants who are aware of their status, study staff may provide more specific and HIV-related information when discussing the assent form.

For participants who do not meet IRB/EC criteria for providing assent or consent at the time of screening and enrollment, if such criteria are met during follow-up, assent or consent should be obtained when the criteria are met.

As part of the parental permission and informed assent processes, parents or legal guardians will be asked whether they agree to storage and future research testing of biological specimens remaining after all protocol-specified testing has been completed. This storage and future research testing is optional and may be declined with no impact on other aspects of study participation.

In accordance with the requirements for enrolling minors in clinical research as specified in the DAIDS SCORE Manual, all sites must establish and maintain written procedures describing the standards that will be followed to identify who may serve as legal guardian for an enrolled child, reflective of applicable IRB/EC guidance for conduct of human subjects research within the context of available local law, regulation, or government policy.

13.3.2 Informed Consent for Continued Product Use During Pregnancy

In the event that a pregnant participant will continue injectable study product use during pregnancy (see [Section 8.2](#)), local IRB/EC requirements must be followed regarding obtaining written parental/legal guardian permission with accompanying informed assent from the participant or informed consent from the participant (e.g., if pregnant participants are automatically granted the legal status of an emancipated minor) prior to continued study product use. A sample written parental/legal guardian permission form is provided in [Appendix IV-D](#) and a sample informed assent form is provided in [Appendix V-C](#). Either sample form can be modified to comply with local IRB/EC requirements.

13.3.3 Informed Consent for Parents/Caregivers

Parents/caregivers who will be enrolling into the study to complete assessments related to tolerability and acceptability must also provide written informed consent before any study-specific procedures are performed, in accordance with all applicable IRB/EC requirements. The informed consent process will include information exchange, detailed discussion, and assessment of understanding of all required elements of informed consent, including the potential risks, benefits, and alternatives to study participation. Parent/caregiver consent should be obtained after the child participant's eligibility has been confirmed. It will ideally be obtained at the entry visit, but may be completed at a later date, if necessary.

13.4 Potential Benefits

There may or may not be direct benefit to participants who take part in this study. Although direct benefit cannot be guaranteed, the study drugs have been demonstrated as safe, effective, and well-tolerated in adolescents and adults, and are expected to provide similar therapeutic benefits to children. There is a potential benefit for improved understanding of, and engagement in, HIV-1 care and study-specific evaluations may provide beneficial information relevant to participants' health and clinical care. Information learned in this study may benefit participants and others in the future, particularly information that may lead to more treatment options for children living with HIV-1. There may be potential benefits associated with switching from an oral ART regimen to a long-acting injectable regimen. Lastly, participants may also appreciate the opportunity to contribute to HIV-1-related research.

13.5 Potential Risks

The potential risks of participation in this study include risks associated with study procedures and risks associated with receipt of study drug.

Most study procedures are routine medical procedures that are associated with minimal to no risk. It is acknowledged, however, that the frequency at which some procedures will be performed for this study is not routine in clinical practice. As indicated above, the increased frequency of some procedures may be of potential benefit. The increased frequency of blood collection may be of potential risk, as blood collection may cause pain, bruising, swelling, or fainting. There is a very small chance of infection where the needle is inserted. Participants or parents/caregivers may feel uncomfortable or become anxious or embarrassed when responding to questionnaires or answering other questions asked by study staff.

Refer to [Section 1.2.5.1](#) and to the respective IBs for a description of the potential risks associated with the use of these drugs in adults. Although there is already a great deal of robust safety, PK and efficacy data in adults and a study with adolescents is underway, these drugs have not yet been studied in children younger than 12. The injections may cause pain, swelling, reddening of the skin, and nodule formations where the needle is inserted. There may also be additional risks associated with use of these study products in children. Risks associated with CAB and RPV use during pregnancy are unknown. Every effort will be made in the study to avoid the occurrence of pregnancies. Refer to [Section 1.2.5.1](#) and to the respective IBs for a description of the potential risks associated with the use of these drugs in adults.

The CAB LA and RPV LA injections are long-acting and may be present in the participant's blood for one year or longer, after a single injection. The amount of drug will decrease overtime and will eventually disappear.

Participants or parents/caregivers may feel uncomfortable or become anxious or embarrassed when responding to questionnaires or answering other questions asked by study staff.

Refer to [Section 1](#) and the IB for CAB and the IB for TMC278 (rilpivirine, oral and parenteral) for a description of the potential risks associated with the use of these drugs. For virologically suppressed ART-experienced children switching to use of CAB + RPV, there is a potential additional risk that the study drugs may not be as well-tolerated or as effective in maintaining viral suppression as the child's pre-study ART regimen.

Refer to [Section 13.7](#) for further information on privacy and confidentiality. Despite efforts to maintain confidentiality, participant's involvement in this study could become known to others, possibly leading to unfair treatment, discrimination, or other social impacts (e.g., because participants could become known as having HIV-1). For example, participants could be treated unfairly or discriminated against or could have problems being accepted by their families and/or communities. Every effort will be made to protect children's information, but this cannot be guaranteed.

13.6 Reimbursement/Compensation

Pending IRB/EC approval, participants will be reimbursed for costs associated with completing study visits (e.g., transport costs). Reimbursement amounts will be specified in site-specific ICFs and/or other materials per applicable IRB/EC policies and procedures.

13.7 Privacy and Confidentiality

All study procedures will be conducted in private and every effort will be made to protect participant privacy and confidentiality to the extent possible. Participant information will not be released without written permission to do so except as necessary for review, monitoring, and/or auditing as described in [Section 11.2](#).

All study-related information will be stored securely. Participant research records will be stored in locked areas with access limited to study staff. All laboratory specimens, CRFs, and other documents that may be transmitted off-site (e.g., EAE report forms, photographs of observed reactions) will be identified by PID only. Likewise, communications between study staff and Protocol Team members regarding individual participants will identify participants by PID only.

Study sites are encouraged but not required by DAIDS to store study records that bear participant names or other personal identifiers separately from records identified by PID. All local databases must be secured with password protected access systems. Lists, logbooks, appointment books, and any other documents that link PID numbers to personal identifying information should be stored in a separate, locked location in an area with limited access.

In addition to the above, a Certificate of Confidentiality has been deemed issued for the IMPAACT Network by the US Department of Health and Human Services. This certificate protects study staff from being compelled to disclose study-related information by any US Federal, state, or local civil, criminal, administrative, legislative, or other proceedings. It thus serves to protect the identity and privacy of study participants. Because the certificate cannot be enforced outside of the US, however, it applies only to US sites and participants.

13.8 Communicable Disease Reporting

Study staff will comply with local requirements to report communicable diseases including HIV-1 infection identified among study participants to health authorities. Parents or legal guardians will be made aware of all applicable reporting requirements as part of the parental permission process.

13.9 Management of Incidental Findings

Site clinicians will inform parents (or other authorized guardians if applicable) of all clinically meaningful physical exam findings and laboratory test results, including but not limited to results of ECGs and protocol-required laboratory evaluations. Pregnancy test results will be disclosed consistent with local standards of care and any applicable guidelines; local standard procedures will

be noted in site-specific parental permission and informed assent forms. The results of other tests that may be performed using specimens collected in this study, such as PK test results, are not planned to be provided to parents/guardians, as these are considered research tests that are not expected to be relevant to clinical care and management. If, however, new information becomes available indicating that the results of any tests are of clinical relevance, the results will be provided. When applicable, site clinicians will provide referrals to non-study sources of medical care for further evaluation and/or treatment of these findings.

13.10 Management of New Information Pertinent to Study Participation

Study staff will provide participants, and their parent (or other authorized guardians if applicable) with any new information that becomes available over the course of the study that may affect their willingness for the participant to continue receiving study product and/or remain in follow-up in the study.

13.11 Post-Trial Access to Study Drug

ViiV Healthcare Ltd and Janssen Research & Development LLC are committed to exploring all options to provide continued access to investigational product to participants deriving therapeutic benefit from CAB LA + RPV LA. Upon identification of a suitable option for access, participants who received CAB LA + RPV LA and who have successfully completed 72 weeks on study for Cohort 1, or 48 weeks/44 weeks for Cohorts 2a/2b, respectively, will be given the opportunity to continue to receive CAB LA + RPV LA. Additionally, both of the following conditions must be met for the participant to continue to receive CAB LA + RPV LA:

- there is evidence of continued clinical benefit for the participant;
- and such provision of CAB LA + RPV LA is permitted under local laws and regulations.

The investigator is responsible for ensuring that consideration has been given to the post-study care of the participant and for determining whether all parameters are met for an individual participant's post-study access to CAB LA + RPV LA or whether the participant should transition to local standard HIV care and treatment (See [Section 6.8](#)). Continued access to unapproved CAB LA + RPV LA will cease if the participant no longer exhibits a clinical benefit or if risks of continuing treatment outweigh benefits. Additionally, access will cease if the development of CAB LA + RPV LA is discontinued or market access becomes available.

The mechanism that will be used to provide post-trial access to study drug may be country-specific; additional details will be provided in the study-specific MOP.

14 ADMINISTRATIVE PROCEDURES

14.1 Regulatory Oversight

This study is sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), and National Institute of Mental Health (NIMH), which are part of the United States National Institutes of Health (NIH). ViiV Healthcare Ltd will provide funding for this study. Study products are manufactured by ViiV Healthcare Ltd and Janssen Research and Development LLC.; however, these organizations are not involved in sponsorship or regulatory oversight of this study.

Within the NIAID, DAIDS is responsible for regulatory oversight of this study. DAIDS will distribute safety-related information pertaining to the study products prior to and during the conduct of the study, in accordance with its sponsor obligations.

NIAID and NICHD provide funding to the clinical research sites at which this study will be conducted. Each institute contracts with an independent clinical site monitoring group to perform clinical site monitoring as described in [Section 12](#). As part of this activity, monitors will inspect study-related documentation to ensure compliance with applicable US, local, and international regulatory requirements.

14.2 Protocol Registration

Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the study parental permission, informed consent, and assent forms approved, as appropriate, by applicable IRBs/ECs and any other applicable regulatory entities; for US sites, this includes the sIRB. Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all of the required documents have been received.

Site-specific parental permission, informed consent, and assent forms will be reviewed and approved by the DAIDS PRO and sites will receive an Initial Registration Notification from the DAIDS PRO that indicates successful completion of the protocol registration process. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

For any future protocol amendments, upon receiving final IRB/EC and any other applicable regulatory entity approvals as well as meeting any additional study-specific requirements as determined by the protocol team, sites should implement the amendment immediately. Sites are required to submit an amendment registration packet to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all the required documents have been received. Site-specific parental permission, informed consent, and assent forms will NOT be reviewed and approved by the DAIDS PRO and sites will receive an Amendment Registration Notification when the DAIDS PRO receives a complete registration packet. A copy of the amendment Registration Notification should be retained in the site's regulatory files.

For additional information on the protocol registration process and specific documents required for initial and amendment registrations, refer to the current version of the DAIDS Protocol Registration Manual, which is available at: <https://rsc.niaid.nih.gov/clinical-research-sites/daids-protocol-registration-policy-and-procedures-manual>

14.3 Study Implementation

This study will be conducted in accordance with the protocol, international good clinical practice guidelines, and all applicable US, local, and international regulations. Study implementation will also be guided by the IMPAACT MOP, study-specific MOP, LPC, and other study implementation materials, which will be available on the study-specific IMPAACT website: <https://www.impaactnetwork.org/studies/impaact2036>

Study implementation at each site will also be guided site-specific SOPs. The DAIDS SCORE Manual specifies the minimum set of SOPs that must be established at sites conducting DAIDS funded and/or sponsored clinical trials. These SOPs should be updated and/or supplemented as needed to describe roles, responsibilities, and procedures for this study.

14.4 Protocol Deviation Reporting

Per the requirements for source documentation specified in the DAIDS SCORE Manual, all protocol deviations must be documented in participant research records. Reasons for the deviations and corrective and preventive actions taken in response to the deviations should also be documented.

Deviations should be reported to applicable IRBs/ECs and other applicable review bodies in accordance with the policies and procedures of these review bodies. Serious deviations that are associated with increased risk to one or more study participants and/or significant impacts on the integrity of study data must also be reported within IMPAACT, following procedures specified in the IMPAACT MOP.

14.5 ClinicalTrials.gov

The NIH Policy on Dissemination of NIH-funded Clinical Trial Information establishes the expectation that clinical trials funded in whole or in part by the NIH will be registered and have summary results information submitted to ClinicalTrials.gov for public posting. The Protocol Team will comply with this policy as well as the requirements of 42 CFR 11.

15 PUBLICATIONS

All presentations and publications of data collected in this study are governed by IMPAACT policies, which are available in the IMPAACT Network Manual of Procedures.

16 REFERENCES

1. Beleck A, Nachman S. Understanding Pediatric Drug Lag Time: Review of Selected Drug Package Inserts. *J Pediatric Infect Dis Soc.* 2021;10(4):509-13.
2. Swindells S, Andrade-Villanueva JF, Richmond GJ, Rizzardini G, Baumgarten A, Masiá M, et al. Long-Acting Cabotegravir and Rilpivirine for Maintenance of HIV-1 Suppression. *N Engl J Med.* 2020;382(12):1112-23.
3. Overton ET, Richmond G, Rizzardini G, Jaeger H, Orrell C, Nagimova F, et al. Long-acting cabotegravir and rilpivirine dosed every 2 months in adults with HIV-1 infection (ATLAS-2M), 48-week results: a randomised, multicentre, open-label, phase 3b, non-inferiority study. *Lancet.* 2021;396(10267):1994-2005.
4. Ford SL, Sutton K, Lou Y, Zhang Z, Tenorio A, Trezza C, et al. Effect of Rifampin on the Single-Dose Pharmacokinetics of Oral Cabotegravir in Healthy Subjects. *Antimicrob Agents Chemother.* 2017;61(10).
5. Margolis DA, Gonzalez-Garcia J, Stellbrink H-J, Eron JJ, Yazdanpanah Y, Podzamczar D, et al. Long-acting intramuscular cabotegravir and rilpivirine in adults with HIV-1 infection (LATTE-2): 96-week results of a randomised, open-label, phase 2b, non-inferiority trial. *The Lancet.* 2017;390(10101):1499-510.
6. Orkin C, Arasteh K, Gorgolas Hernandez-Mora M, Pokrovsky V, Overton ET, Girard PM, et al. Long-Acting Cabotegravir and Rilpivirine after Oral Induction for HIV-1 Infection. *N Engl J Med.* 2020;382(12):1124-35.
7. ViiV Healthcare G. Cabenuva® (cabotegravir extended-release injectable suspension; rilpivirine extended-release injectable suspension), [package insert, revised 03/2022]. GlaxoSmithKline; 2022.
8. ViiV Healthcare. Investigator's Brochure for GSK1265744 (Cabotegravir). 2019.
9. Janssen. Edurant® (rilpivirine) tablets for oral use [package insert, revised 05/2019]. Titusville, NJ, USA: Janssen Products, LP; 2019.

10. Lombaard J, Bunupuradah T, Flynn PM, Ramapuram J, Ssali F, Crauwels H, et al. Rilpivirine as a treatment for HIV-infected antiretroviral-naïve adolescents: Week 48 safety, efficacy, virology and pharmacokinetics. *Pediatr Infect Dis J*. 2016;35(11):1215-21.
11. Neyens M. CH, Perez-Ruixo JJ., Rossenu. Population pharmacokinetics of the rilpivirine long-acting formulation after intramuscular dosing in healthy subjects and people living with HIV. *The Journal of Antimicrobial Chemotherapy* 2021;76(12):3255-62.
12. Overton ET, Richmond GJ, Rizzardini G, Jaeger H, Orrell C, Nagimova F, et al. Cabotegravir + Rilpivirine every 2 months is noninferior to monthly: ATLAS-2M Study. *Conference on Retroviruses and Opportunistic Infections*; 8-11 March 2020; Boston, MA2020.
13. Moore C, Capparelli E, Calabrese K, Best B, Ward S, McCoig C, et al., editors. Safety and PK of Long-Acting Cabotegravir and Rilpivirine in Adolescents. *CROI 2022*. 2022 *Conference on Retroviruses and Opportunistic Infections* 2022.
14. Lowenthal E, Chapman J, Calabrese K, Milligan R, Agwu A, Camacho-Gonzalez A, et al. Adolescent and Parent Experiences with Long-Acting Injectables in the MOCHA Study. *CROI*. *Conference on Retroviruses and Opportunistic Infections Virtual* 2022.
15. ViiV H. Cabotegravir (GSK1265744) Investigator's Brochure January 2022.
16. Janssen. TMC278 (rilpivirine, oral and parenteral) Investigator's Brochure July 2022.
17. Janssen. Rekambys [Package insert, 2020 Dec]. Janssen Pharmaceutica December 2020.
18. ViiV Healthcare G. Vocabria [Package insert, 2020 Dec]. GlaxoSmithKline Manufacturing 2020.
19. Orkin C, Oka S, Philibert P, Brinson C, Bassa A, Gusev D, et al. Long-acting cabotegravir plus rilpivirine for treatment in adults with HIV-1 infection: 96-week results of the randomised, open-label, phase 3 FLAIR study. *Lancet HIV*. 2021;8(4):e185-e96.
20. Highlights of Prescribing Information for Tivicay [revised 2020 June]. Research Triangle Park, NC 22709: GlaxoSmithKline 2020.
21. Administration USFD. Patient-Focused Drug Development Public Workshop on Guidance 1: Collecting Comprehensive and Representative Input 2017.
22. FDA Guidance on Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency: Guidance for Industry, Investigators, and Institutional Review Boards. March 2020, Updated on January 27, 2021 [Available from: <https://www.fda.gov/media/136238/download>].
23. National Institutes of Health. NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects. 1998 March 6.

Appendix I: Schedule of Evaluations

Appendix I-A: Cohort 1 (through Week 72) and Cohort 2A (through Week 48 only) Schedule of Evaluations

Study Visit	Screen	Step 1 (oral phase)			Step 2 (injection phase)							Confirm ation of Virologic Failure
		Entry	Wk 2	Wk 4a	Wk 4b (Step 2 Entry)	Wk 5	Wk 6, Wk 9 (Rich Sampli ng Only)	Wk 8, 12, 16, 20	Wk 24	Wk 28- 72	Interim Injection	
Behavioral Evaluations												
Participant Acceptability/Tolerability assessment ¹		X	*	*	X	*	*	X ⁶	X	X ⁶	*	
Parent/Caregiver Acceptability/Tolerability assessment		X	*	*	X	*	*	Wk 8 only	X	Wk 48 and 72 only	*	
Parent/Caregiver Qualitative Interview ²									X			
Clinical Evaluations												
Medical history	X	X	X	X	X	X	X	X	X	X	X	X
Adherence assessment			X	X	X							
Complete physical examination	X			X					X	Wk 48 and 72 only		
Targeted physical examination		X	X		X	X	X	X		X ⁴	X	X
ECG	X				X				X			
Study Product												
Dispense oral study product		X	*	*								
Administer injection study product ⁵					X			X	X	X	X	
Laboratory Evaluations												
Pregnancy test (for participants of childbearing potential) ⁷	X	X	X	X	X			X	X	X ⁶	X	X
Confirmatory HIV-1 testing	0-6 mL*											
Hematology	1 mL	1 mL	1 mL	1 mL		1 mL		1 mL	1 mL	1 mL ⁶	1 mL	
Chemistries	2 mL	2 mL	2 mL	2 mL		2 mL		2 mL	2 mL	2 mL ⁶	2 mL	
Hepatitis B: HBsAg, HBcAb, HBsAb	2.5 mL											
CD4 count and percentage		1 mL							1 mL	1 mL (Wk 48 and 72 only)		

HIV-1 RNA	3 mL	3 mL	3 mL		3 mL			3 mL	3 mL	3 mL ⁶	3 mL	3 mL
Stored whole blood for genotypic resistance testing and HIV-1 subtyping		4 mL										
Stored plasma for genotypic and phenotypic resistance testing					6 mL				6 mL			6 mL
PK Sampling ³			1-3 mL		1-1.5 mL	0.5mL	0.5mL	0.5mL ³	0.5mL	0.5mL ³	0.5mL	0.5mL
Total maximum blood volume	8.5-14.5 mL	11 mL	7-9mL	3 mL	10-10.5 mL	3.5 mL	0.5 mL	6-6.5 mL	13.5 mL	0-7.5 mL	6.5 mL	9.5 mL

Notes: X – required; * - if indicated

- 1) Participant acceptability/tolerability assessment questionnaires will be administered based upon participant age, as specified in the IMPAACT 2036 MOP. See [Section 6.15](#) for further details.
- 2) Only a subset of participants and caregivers will be selected for the qualitative in-depth interview at select sites. See [Section 3.4](#) for qualitative interview window and details on participant selection.
- 3) See [Sections 6.2- 6.7](#) and 6.16 for PK sample collection timepoints and windows, including Rich and Limited PK Sampling Schedules.
- 4) Performed at Week 28, 32, 36, 40, 44, 52, 56, 60, 64, and 68 Visits.
- 5) Following the Cohort 1 interim analyses and/or based upon ongoing reviews of PK and safety data, injection dosing may be adjusted to a Q8W schedule. Participants will maintain their original visit schedule with visits occurring approximately every four weeks, but Q8W injections will only be administered at weeks 4b, 8, 16, 24, 32, 40, 48, 56, 64, and 72.
- 6) Only performed/collected at visits when participant is receiving an injection. Procedure may be omitted at non-injection visits for participants on a Q8W schedule.
- 7) Urine pregnancy testing will be required unless a blood draw is otherwise required at the visit, in which case sites may choose to use either urine or serum pregnancy testing. At visits when a blood test for hCG is conducted, the total blood volume will be 1 mL greater than shown in the table above.

Appendix I-B: Cohort 2B Schedule of Evaluations

Study Visit ¹	Screen	Entry	Day 3	Wk 2	Wk 4	Wk 8, 12, 16	Wk 20	Wk 24-44	Interim Injection	Confirmati on of Virologic Failure
Behavioral Evaluations										
Participant Acceptability/Tolerability assessment ¹		X	*	*	X	X ⁶	X	X ⁶	*	
Parent/Caregiver Acceptability/Tolerability assessment		X	*	*	X	*	X	Wk 44 only		
Parent/Caregiver Qualitative Interview ³							X			
Clinical Evaluations										
Medical history	X	X	X	X	X	X	X	X	X	X
Complete physical examination	X						X	Wk 44 only		
Targeted physical examination		X	X	X	X	X		X ⁴	X	X
ECG	X	X					X			
Study Product										
Administer injection study product ⁵		X			X	X	X	X	X	
Laboratory Evaluations										
Pregnancy test (for participants of childbearing potential) ⁷	X	X			X	X	X	X ⁶	X	X
Confirmatory HIV-1 testing	0-6 mL*									
Hematology	1 mL	1 mL	1 mL	1 mL	1 mL	1 mL	1 mL	1 mL ⁶	1 mL	
Chemistries	2 mL	2 mL	2 mL	2 mL	2 mL	2 mL	2 mL	2 mL ⁶	2 mL	
Hepatitis B: HBsAg, HBcAb, HBsAb	2.5 mL									
CD4 count and percentage		1 mL					1 mL	1 mL (Wk 44 only)		
HIV-1 RNA	3 mL	3 mL		3 mL	3 mL	3 mL	3 mL	3 mL ⁶	3 mL	3 mL
Stored whole blood for genotypic resistance testing and HIV-1 subtyping		4 mL								
Stored plasma for genotypic and phenotypic resistance testing							6 mL			6 mL
PK Sampling ³		1.5 mL	0.5mL	0.5mL	0.5mL	0.5mL ³	0.5mL	0.5mL ³	0.5mL	0.5mL
Total maximum blood volume	8.5-14.5 mL	12.5 mL	3.5 mL	6.5 mL	6.5 mL	6-6.5 mL	13.5 mL	0-7.5 mL	6.5 mL	9.5 mL

Notes: X – required; * - if indicated

- 1) Participant acceptability/tolerability assessment questionnaires will be administered based upon participant age, as specified in the IMPAACT 2036 MOP. See [Section 6.15](#) for further details.
- 2) Only a subset of participants and caregivers will be selected for the qualitative in-depth interview at select sites. See [Section 3.4](#) for qualitative interview window and details on participant selection.
- 3) See [Sections 6.2-6.7](#) and [Section 6.16](#) for PK sample collection timepoints and windows.
- 4) Performed at Week 28, 32, 36, and 40 Visits.

- 5) Following the Cohort 1 interim analyses and/or based upon ongoing reviews of PK and safety data, injection dosing may be adjusted to a Q8W schedule. Participants will maintain their original visit schedule with visits occurring approximately every four weeks, but Q8W injections will only be administered at Entry, and weeks 4, 12, 20, 28, 36, and 44.
- 6) Only performed/collected at visits when participant is receiving an injection. Procedure may be omitted at non-injection visits for participants on a Q8W schedule.
- 7) Urine pregnancy testing will be required unless a blood draw is otherwise required at the visit, in which case sites may choose to use either urine or serum pregnancy testing. At visits when a blood test for hCG is conducted, the total blood volume will be 1 mL greater than shown in the table above.

Appendix I-C: Schedule of Evaluations for Long-Term Safety and Washout PK Follow-Up (LSFU)

Study Visit ¹	LSFU Week 4, 8, 24, and 36	LSFU Week 48/Early Termination ¹	Confirmation of Virologic Failure
Behavioral Evaluations			
Participant Acceptability/Tolerability assessment		X ²	
Parent/Caregiver Acceptability/Tolerability assessment		X ²	
Clinical Evaluations			
Medical history	X	X	X
Complete physical examination		X	
Targeted physical examination	X		X
Laboratory Evaluations			
Pregnancy test (for participants of childbearing potential) ³	X	X	X
Hematology	1 mL	1 mL	
Chemistries	2 mL	2 mL	
HIV-1 RNA	3 mL	3 mL	3 mL
Resistance testing		(early term only) 4 mL ¹	6 mL
PK Sampling	0.5 mL	0.5 mL ¹	0.5 mL
Total maximum blood volume	6.5 mL	6.5-10.5 mL	9.5 mL

Notes: X – required

- 1) See [Section 6.6.2](#) for more details on conducting Early Termination visits. Participants completing an Early Termination visit will have 4 mL of whole blood collected for genotypic resistance testing and HIV-1 subtyping. Cohort 1 and 2a participants who complete an Early Termination visit during the oral lead in phase will not have a PK evaluation performed and a PK sample will not be collected.
- 2) Participant and parent/caregiver acceptability/tolerability assessments will only be conducted as part of an Early Termination visit. Assessments will be administered based upon participant age, as specified in the IMPAACT 2036 MOP.
- 3) Pregnancy testing will not be required for participants who are currently pregnant. Urine pregnancy testing will be required unless a blood draw is otherwise required at the visit, in which case sites may choose to use either urine or serum pregnancy testing. At visits when a blood test for hCG is conducted, the total blood volume will be 1 mL greater than shown in the table above.

Appendix II: Target Visit Dates and Visit Windows

Q4W: COHORT 1 (through Week 72) and COHORT 2A (through Week 48 only)			
Study Visit Name	Target Visit Date	Target Visit Window	Min/Max requirements (from previous IM)
Week 2	14 days from entry	-7/+6 days from target date	N/A
Week 4a	28 days from entry	-7/+10 days from the target date	N/A
Week 4b	As soon as lab results are available from the Week 4a visit and no later than 42 days from entry		N/A
Week 5	3 days from Week 4b	-1 day/+4 days from the target date	N/A
Week 6	12 days from Week 4b		N/A
Week 8	28 days from Week 4b	-7 days/+3 days from the target date	minimum of 3 weeks (21 days) and a maximum of 4 weeks and 3 days (31 days) apart, as counted from the previous injection
Week 9	3 days from Week 8	-1 day/+5 days from the target date	N/A
Week 12	56 days from Week 4b	-7 days/+3 days from the target date	minimum of 3 weeks (21 days) and a maximum of 5 weeks (35 days) apart, as counted from the previous injection
Week 16	84 days from Week 4b		
Week 20	112 days from Week 4b		
Week 24	140 days from Week 4b	-7/+7 days from the target date	
Week 28	168 days from Week 4b		
Week 32	196 days from Week 4b		
Week 36	224 days from Week 4b		
Week 40	252 days from Week 4b		
Week 44	280 days from Week 4b		
Week 48	308 days from Week 4b		
Week 52	336 days from Week 4b		
Week 56	364 days from Week 4b		
Week 60	392 days from Week 4b		
Week 64	420 days from Week 4b		
Week 68	448 days from Week 4b		
Week 72	476 days from Week 4b		

Q8W: COHORT 1 (through Week 72) and COHORT 2A (through Week 48 only)			
Study Visit Name	Target Visit Date	Target Visit Window	Min/Max requirements (from previous IM)
Week 2	14 days from entry	-7/+6 days from target date	N/A
Week 4a	28 days from entry	-7/+10 days from target date	N/A
Week 4b	As soon as lab results are available from the Week 4a visit and no later than 42 days from entry		N/A
Week 5	3 days from Week 4b	-1 day/+4 days from the target date	N/A
Week 6	12 days from Week 4b		N/A
Week 8	28 days from Week 4b	-7 days/+3 days from the target date	a minimum of 3 weeks (21 days) and a maximum of 4 weeks and 3 days (31 days) from the Week 4b injection
Week 9	3 days from Week 8	-1 day/+5 days from the target date	N/A
Week 12	56 days from Week 4b	-7 days/+3 days from the target date	N/A
Week 16	84 days from Week 4b		a minimum of 7 weeks (49 days) and a maximum of 8 weeks and 3 days (59 days) from the Week 8 injection
Week 20	112 days from Week 4b		N/A
Week 24	140 days from Week 4b	-7 days/+7 days from the target date	a minimum of 7 weeks (49 days) and a maximum of 9 weeks (63 days) from the previous regularly scheduled injection
Week 28	168 days from Week 4b		N/A
Week 32	196 days from Week 4b		a minimum of 7 weeks (49 days) and a maximum of 9 weeks (63 days) from the previous regularly scheduled injection
Week 36	224 days from Week 4b		N/A
Week 40	252 days from Week 4b		a minimum of 7 weeks (49 days) and a maximum of 9 weeks (63 days) from the previous regularly scheduled injection
Week 44	280 days from Week 4b		N/A
Week 48	308 days from Week 4b		a minimum of 7 weeks (49 days) and a maximum of 9 weeks (63 days) from the previous regularly scheduled injection
Week 52	336 days from Week 4b		N/A
Week 56	364 days from Week 4b		a minimum of 7 weeks (49 days) and a maximum of 9 weeks (63 days) from the previous regularly scheduled injection
Week 60	392 days from Week 4b		N/A
Week 64	420 days from Week 4b		a minimum of 7 weeks (49 days) and a maximum of 9 weeks (63 days) from the previous regularly scheduled injection
Week 68	448 days from Week 4b		N/A

Week 72	476 days from Week 4b		a minimum of 7 weeks (49 days) and a maximum of 9 weeks (63 days) from the previous regularly scheduled injection
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Q4W: COHORT 2b			
Study Visit Name	Target Visit Date	Target Visit Window	Min/Max requirements (from previous IM)
Day 3	3 days from entry	-1/+4 days from target date	N/A
Week 2	14 days from entry	-7/+6 days from the target date	N/A
Week 4	28 days from entry	-7/+3 days from the target date	A minimum of 3 weeks (21 days) and a maximum of 4 weeks and 3 days (31 days) from the previous injection.
Week 8	56 days from entry		A minimum of 3 weeks (21 days) and a maximum of 5 weeks (35 days) apart, as counted from the previous injection
Week 12	84 days from entry		
Week 16	112 days from entry		
Week 20	140 days from entry		
Week 24	168 days from entry		
Week 28	196 days from entry		
Week 32	224 days from entry		
Week 36	252 days from entry		
Week 40	280 days from entry		
Week 44	308 days from entry		

Q8W: COHORT 2b			
Study Visit Name	Target Visit Date	Target Visit Window	Min/Max requirements (from previous IM)
Day 3	3 days from entry	-1/+4 days from target date	N/A
Week 2	14 days from entry	-7/+6 days from the target date	N/A
Week 4	28 days from entry	-7/+3 days from the target date	A minimum of 3 weeks (21 days) and a maximum of 4 weeks and 3 days (31 days) from the previous injection
Week 8	56 days from entry		N/A
Week 12	84 days from entry		A minimum of 7 weeks (49 days) and a maximum of 8 weeks and 3 days (59 days) from the previous injection.
Week 16	112 days from entry		N/A
Week 20	140 days from entry	-7/ + 7 days from the target date	A minimum of 7 weeks (49 days) and a maximum of 9 weeks (63 days) from the previous regularly scheduled injection.
Week 24	168 days from entry		N/A
Week 28	196 days from entry		A minimum of 7 weeks (49 days) and a maximum of 9 weeks (63 days) from the previous regularly scheduled injection.
Week 32	224 days from entry		N/A
Week 36	252 days from entry		A minimum of 7 weeks (49 days) and a maximum of 9 weeks (63 days) from the previous regularly scheduled injection.
Week 40	280 days from entry		N/A
Week 44	308 days from entry		A minimum of 7 weeks (49 days) and a maximum of 9 weeks (63 days) from the previous regularly scheduled injection.

Appendix III: Prohibited and Precautionary Medications

The following information may not be all-inclusive. Our understanding of drug interactions continues to grow as new information becomes available. Please refer to the most up-to-date prescribing and drug interaction information in the respective Investigator's Brochures.

For any IMPAACT 2036 participant requiring a prohibited or precautionary medication, refer to protocol [Section 8](#).

The remainder of this document provides further information on medications considered prohibited or precautionary with concurrent use of each study drug agent. Note that [Section 2](#) of this document contains sub-sections listing prohibited medications for specified participants.

Appendix III-A: Precautionary Medications

IMPAACT 2036 study participants will receive both CAB and RPV. During study conduct and prior to prescribing new medications, study investigators should review drug labels, exercise caution, and exert medical judgment (in regards to risk-benefit) when prescribing a medicinal product associated with an increased risk for Torsades de Pointes (TdP), including the below medications. If questions arise when prescribing drugs associated with an increased risk of TdP, please contact the IMPAACT 2036 CMC.

- Anti-arrhythmics:
 - Amiodarone
 - Disopyramide
 - Dofetilide
 - Dronedarone
 - Flecainide
 - Ibutilide
 - Procainamide
 - Quinidine
 - Sotalol
- Antipsychotics:
 - Chlorpromazine
 - Droperidol
 - Haloperidol
 - Levomepromazine
 - Mesoridazine
 - Pimozide
 - Thioridazine
- Anti-infectives:
 - Clarithromycin
 - Erythromycin
 - Roxithromycin
 - Pentamidine
 - Sparfloxacin

Note: Consider alternatives for anti-infectives, such as azithromycin, which increases rilpivirine concentrations less than other macrolides

- Gastro-intestinal drugs:
 - Cisapride
 - Domperidone
- Opiate agonists:
 - Levomethadyl
 - Methadone
- Antimalarials:
 - Chloroquine
 - Halofantrine
- Other:
 - Arsenic trioxide
 - Bepridil
 - Probucol

Appendix III-B: Prohibited Medications

The below section contains listings of prohibited medications for **specified participants** at **specified timepoints during study participation** and **within 7 days prior to entry (per exclusion criterion 4.2.11)**. If, for any of the below medications, the participant cannot discontinue or change to an allowable alternative, refer to protocol [Section 8.5](#) for participant management due to prohibited medications.

Prohibited Medications Throughout Study Participation (Step 1, Step 2, LSFU Participants):

The following medications may not be administered at any time during study participation, including long-term safety and washout PK follow-up (LSFU) visits:

- HIV immunotherapeutic vaccines.
- Other experimental agents, antiretroviral drugs not otherwise specified in the protocol, cytotoxic chemotherapy, or radiation therapy.
- Chronic use of systemic (oral or parenteral) glucocorticoids must be avoided due to their immunosuppressive effect; however, short treatment courses with oral prednisone/prednisolone/methylprednisolone (e.g., adjunctive treatment of Pneumocystis pneumonia with 21 days of tapering prednisone) are allowed.
- While a single dose of systemic dexamethasone is permitted, more than a single dose in a treatment course may cause significant decrease in RPV plasma concentration and is prohibited. Topical, inhaled, or intranasal use of glucocorticoids are allowed.

- Systemically administered immunomodulators (such as interleukin and interferon agents). This includes topical agents with substantial systemic exposure and systemic effects. Use of topical imiquimod is permitted (see below).

Prohibited Systemically Administered Immunomodulators:

The below is a list of examples of immunomodulators prohibited in the study. Please note that the list is not exhaustive and may be updated as needed. The IoR should consider medical history of auto-immune disease and the use of potential immunomodulators not listed below. Use of other immunomodulators that directly affect immune responses will be considered in consultation with the CMC on a case by case basis.

- Calcineurin inhibitors:
 - Cyclosporine A
 - Pimecrolimus
 - Tacrolimus
- Fluorouracil (including topical)
- Imiquimod topical (use within 30 days prior to entry requires consultation with the CMC)
- Interferon
- mTOR kinase inhibitors:
 - Everolimus
 - Sirolimus
- Methotrexate purine analogues:
 - Azathioprine
 - 6-Mercaptopurine
- Targeted immune modulators (biological response modifiers):
 - Abatacept
 - Adalimumab
 - Alefacept
 - Anakinra
 - Certolizumab
 - Efalizumab
 - Etanercept
 - Golimumab
 - Infliximab
 - Natalizumab
 - Rituximab
 - Tocilizumab
 - Ustekinumab
- Aminosalicylates:
 - Sulfasalazine
- Aminoquinoline compounds/anti-malarial drugs commonly used to treat auto-immune disorders:
 - Hydroxychloroquine

Prohibited Medications During Study Treatment (Step 1 and Step 2 Participants):

For participants receiving any formulation (oral or injectable) of CAB and RPV, the following medications could significantly decrease levels of CAB and/or RPV due to enzyme induction and therefore must not be administered concurrently:

- Carbamazepine

- Oxcarbazepine
- Phenobarbital
- Phenytoin
- Rifabutin
- Rifampicin/Rifampin
- Rifapentine
- Systemic dexamethasone (more than a single dose)
- St. John's wort (*Hypericum perforatum*)

Additionally,

- Hepatitis C infection therapy is prohibited in conjunction with ongoing study drug treatment (oral or injectable) through Week 24.

Additional Prohibited Medications During Oral Lead-In (Step 1 Participants) or Oral Bridging (Step 2 Participants):

In addition, participants must discontinue the following (or change to an allowable alternative) while receiving oral RPV study product as part of the Step 1 regimen of oral CAB + oral RPV:

- Proton pump inhibitors, such as esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole

Additional Prohibited Medications While Receiving Injectables (Step 2 Participants)

For participants receiving CAB LA and RPV LA, use of anticoagulation agents for greater than 14 days is prohibited, with the exception of the use of anticoagulation for DVT prophylaxis (e.g., postoperative DVT prophylaxis) or the use of low dose acetylsalicylic acid (325 mg). Systemic anticoagulation (including prophylaxis doses) on the day of an IM injection should be avoided.

Note: Any prohibited medications that decrease CAB or RPV concentrations should be discontinued for a minimum of 4 weeks or a minimum of three half-lives (whichever is longer), prior to the first dose and any other prohibited medications should be discontinued for a minimum of 2 weeks or a minimum of three half-lives (whichever is longer) prior to the first dose.

Appendix IV: Sample Parental Permission and Informed Consent Forms

Appendix IV-A: Sample Parental Permission Form for Participation in Cohort 1 for parent/legal guardian of child participant

IMPAACT 2036

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

Version 1.0, 22 September 2022

Sponsor / Study Title: National Institutes of Health (NIH) / National Institute of Allergy and Infectious Diseases (NIAID) / National Institute of Child Health and Human Development (NICHD) / National Institute of Mental Health (NIMH) / “CRAYON”

Protocol Number: IMPAACT 2036

Principal Investigator: <<PI Full Name>>
(Study Doctor)

Telephone: <<Phone Number>>

Address: <<Location>>

Introduction

This form is for the parent or legal guardian of a child who is being asked to participate in the research study named above. Your permission is needed, and the assent of your child may also be required depending on their age. This form gives information about the study. Please read it or have it read to you. Ask any questions you may have. We will take as much time as needed for you to fully understand the study. We will ask you questions to see if we have explained the study clearly.

Here is a summary of important information about the study:

- The study is testing two anti-HIV drugs (ARVs), cabotegravir (CAB) and rilpivirine (RPV), taken as pills and given as long-acting shots in children ages 2 to less than 12.
- Some of the study drugs are already approved in some countries for use in adolescents or adults, but they have not yet been tested in younger children.
- There are two groups in this study called Cohort 1 and Cohort 2. **This form is about Cohort 1.**
- Your child will stop taking their usual ARVs when they enter the study and will start taking the CAB and RPV pills. They will take the study pills every day for about a month. At the end of that time, if they qualify, they will start getting CAB and RPV as shots. The study shots will be given every month or every 2 months for about a year and 4 months. The frequency of the shots will be based on information collected in the study. We will explain your child’s shot schedule before they enroll.

- While in the study, children will have clinic visits with physical examinations and blood draws for laboratory tests. Some visits will include a review of the child's medical records and an electrocardiogram (ECG), which is a test to look at the child's heart. You and your child will answer questions about your child's health, and the drugs being tested.
- At the end of the study, your child may have the opportunity to continue getting the CAB and RPV shots outside the study, if you wish. We will explain all the treatment options available to you and help ensure your access to continued treatment.
- Children who stop taking the CAB and RPV shots may be followed for up to 1 year for long-term safety follow-up. During this time, children will not take any study drugs (shots or pills), but will take other ARVs.
- There are possible risks for children in the study. One possible risk is that the drugs being tested could cause side effects. The most severe side effects include allergic reactions, liver problems, and mental health problems. Severe side effects are rare.
- There may or may not be benefits for children in the study. One possible benefit is not having to take a daily pill while getting the CAB and RPV shots. Another possible benefit is that the shots being tested could be better for your child's health and HIV care than the usual ARV pills.
- Your decision on your child's participation in the study will have no effect on the medical care your child receives. Your child's access to services, and the benefits and rights they normally have, will not be affected.

More information about the study is given in this form. You should feel that you understand the study before deciding whether your child will participate. If you decide that your child will participate, you will be asked to sign or make your mark on this form. You will be offered a copy to keep.

About the study

The International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) and <<site name>> are doing this study. The person in charge of the study at <<site name>> is the study doctor listed on the first page of this form.

The study is testing two anti-HIV drugs (antiretrovirals or ARVs) in children who are 2-11 years old. HIV is the virus that can lead to AIDS. The study ARVs are called cabotegravir (CAB) and rilpivirine (RPV).

The study will include up to 90 children from Brazil, Botswana, South Africa, Thailand, Uganda, and the United States. There will be two groups of children, called Cohort 1 and Cohort 2. This form is about Cohort 1.

As a separate part of this study, about 90 parents or caregivers of child participants will also enroll to complete questionnaires. Some of them will also take part in an in-depth interview. Study staff may ask you about who should participate in that part of the study.

The United States National Institutes of Health and the companies that make CAB and RPV, ViiV Healthcare and Janssen Pharmaceuticals, are paying for this study.

1. The study is testing CAB and RPV in children.

People with HIV usually take a combination of ARVs each day to stay healthy. There are not as many ARVs available for children as for adults because many ARVs have not yet been tested in children. ARVs can be made in different forms, such as liquids, pills, and injections (shots). This study will test CAB and RPV pills swallowed whole or dissolved in liquid (for the smallest children) as well as CAB and RPV

shots. The pills will be taken every day. The shots may be given every month or every two months. The frequency of the shots will be based on information collected in the study. We will explain your child's shot schedule before they enroll and during follow-up, if there are any changes.

Some countries have already approved RPV and CAB pills (swallowed whole) and shots for use in adults and in adolescents starting at 12 years of age. The approvals were possible because of studies, like this one, that showed CAB and RPV were safe and worked well to control HIV in adults.

This is the first time that all of the study drugs are being studied in younger children, and the first time the CAB pills dissolved in liquid have ever been studied. This study will look at whether these ARVs are the correct dose for children, are safe and well-tolerated, and can control HIV. The study will also look at whether any of the medications cause bad effects when given to children.

2. Only children who qualify can participate in the study.

If you decide to have your child join this study, we will first do some tests to find out if your child qualifies. More information about the tests is given in #4, below. If your child qualifies, they may enter the study. If your child does not qualify, they cannot join the study.

3. It is your decision whether to have your child participate in the study.

Deciding to have your child join the study is voluntary (your choice). You are free to have your child join or not join. If you decide to have your child join, you can change your mind and take your child off the study at any time. Your decisions will have no effect on the medical care your child receives. Your child's access to services, and the benefits and rights they normally have, will not be affected.

Your child does not need to join this study to receive medical care and ARVs. There are alternatives to participation. For example, your child can keep receiving medical care and ARVs from outside the study. Take your time and consider your decision carefully. Your child may also qualify for other studies. Please ask any questions you may have about these types of alternatives. If you wish, you can talk to other people about the study before you decide. You can bring other people here to learn about the study with you.

No matter what you decide about the study, it is important for your child to receive medical care and take ARVs. Taking ARVs is the best way for children with HIV to stay healthy.

Finding out if your child qualifies for this study

4. We will ask questions, examine your child, and test your child's blood.

To find out if your child qualifies for the study, we will:

- Review your child's medical records.
- Ask about your child's health, ARVs, and other medicines.
- Talk with you and your child about the study requirements.
- Do a physical examination.
- Give your child an electrocardiogram (ECG). This is a test of how well your child's heart is working.
- Draw up to 11.5 mL (about 2 teaspoons) of blood for tests. The tests will:
 - Check your child's blood cells, liver, and kidneys. This includes checking for an infection called hepatitis B.

- Confirm your child has HIV. If the tests that are required for joining this study are already documented in your child's medical records, we may not need to do these tests again.
- Measure the amount of HIV in your child's blood. This is called your child's "viral load."

If your child is at least 9 years old and can become pregnant, we will ask about their sexual activity and collect blood (1 mL or a few drops) or urine for a pregnancy test. If your child is pregnant, they will not qualify for the study. If your child is not pregnant, but is sexually active, they will need to be on an effective method of birth control throughout their study participation.

These procedures will take about 4 hours. <<*Here and throughout this form, sites may modify the expected visit duration as needed.*>>

Most of the blood or urine tests we do at this visit and any future visits will be done here. Some tests will be done at other laboratories. We will give you the results of any tests that might impact your child's medical care. Some tests are important for the study, but do not impact your child's medical care, and these results may not be shared with you. Some test results from this visit will be ready quickly. Others may take about 2-3 weeks. We will schedule your child to come back when the results are ready. We may ask you to bring your child back for more tests, if needed to find out if your child qualifies for the study. While waiting for the results, it is important for your child to keep taking their regular ARVs.

5. We will tell you if your child is eligible.

If your child is not eligible for the study for any reason, we will tell you this. They will not be entered in the study. They can and should continue to receive medical care and treatment outside of the study. We will tell you more about getting this care and treatment and any other services you may need. If your child does not enter the study, we will still use some information collected about them (for example, age, sex, and race). We will use this information to look at patterns or common reasons for not entering the study.

If your child is eligible for the study, they can continue to the study entry visit.

Entering the study

6. If your child qualifies, they can enter the study

On the day you bring your child to enter the study, we need to confirm they qualify. On that day, we will:

- Review your child's medical records.
- Ask about your child's health, ARVs, and other medicines.
- If your child is old enough, we will ask them some questions about what they think about the study drugs.
- Do a physical examination.
- Draw about 11mL (a little more than 2 teaspoons) of blood for tests. The tests will:
 - Check your child's blood cells, liver, and kidneys.
 - Check how much the virus has affected your child's ability to fight the virus. This is called a CD4 cell count.
 - Check your child's HIV viral load.
 - Some blood will be saved for later testing for resistance to ARVs. This test shows whether different ARVs may work against the HIV in your blood.
- If your child is at least 9 years old and can become pregnant, we will ask about their sexual activity and collect blood (1 mL or a few drops) or urine for a pregnancy test.

If these procedures confirm that that your child qualifies, your child will enter the study. They will stop taking their usual ARVs and start taking CAB and RPV pills. The pills will either be swallowed or mixed into liquid before swallowing. Your child's weight will determine which kind of pills they receive. We will give you information on which kind of pills your child will receive and explain how to take them. Your child will take their first dose of both study pills at the visit. We will also give you pills for your child to take at home.

After you go home, it is very important for your child to take the pills as instructed. We will take as much time as needed for you and your child to understand the instructions. We will talk with you about strategies to help your child take the medications as instructed.

These procedures will take about 4 hours.

During the study

7. After entering the study, your child will have two more visits in the study pills phase (Week 2, Week 4a).

Once your child is in the study, there will be 2 more visits in the study pill phase. The first visit will happen about 2 weeks after your child enters the study and the second visit will happen about 2 weeks after that. Each visit will take about 1-3 hours.

At these visits we will:

- Review your child's medical records.
- Ask about your child's health, ARVs, and other medicines.
- Do a physical exam.
- Give you more CAB and RPV pills for your child, as needed.
- Draw about 3 mL (a little less than a teaspoon) of blood for tests to check your child's blood cells, liver, and kidneys.
- If your child is at least 9 years old and can become pregnant, we will ask about their sexual activity and collect blood (1 mL or a few drops) or urine for a pregnancy test.

At the first visit (Week 2), we will draw some additional blood. We will use about 3 mL (about half a teaspoon) of blood to check your child's viral load.

We will also draw some blood for a pharmacokinetic (PK) test. This is a test to look at the amount of CAB or RPV in your child's blood over time. We will ask that you bring your child to this visit at a specified time. To prepare for the visit, your child will need to take their study drugs at a specific time each day for the three days before the visit. Your child should **not** take their study drugs the day of the visit. We will give you more information in advance of the visit to help you remember these rules. When you come for the visit, we will draw blood for the first part of the PK test and then your child can take their study pills.

After your child has taken the pills, we will draw their blood again. The number of PK samples we collect will depend on when your child enrolled in the study. If your child was one of the first children to join the study, we will draw blood 5 more times after they take the study drugs, about 1, 2, 3, 4, and 8 hours later. If your child was not one of the first to join the study, they will have 1 blood draw after taking the study drugs, about 3 hours later. We will tell you which group your child is in. In most cases, you and your child will need to stay at the clinic the whole time PK samples are being collected.

<<Sites: modify language as appropriate to indicate procedures for the PK collection.>> We will not need to stick your child with a needle each time we draw blood. Instead, a small plastic tube attached to a plastic needle will be placed in your child's arm when we draw the first sample. The tube and needle will stay in place until all the blood draws are done.

Each PK blood draw is about 0.5mL (a few drops).

At the end each visit during the pill phase, we will let you know if there are any rules about when your child should take their oral CAB and oral RPV doses at home.

8. If your child is eligible, they will enter the injection phase of the study (Week 4b).

The next visit your child has will be called the Week 4b visit. At this visit, we will determine if your child is eligible to get the CAB and RPV study shots. Your child should **not** take oral CAB and oral RPV before coming to the clinic. At this visit we will:

- Review your child's medical records.
- Ask about your child's health, ARVs, and other medicines.
- If your child is old enough, we will ask them some questions about what they think about the study drugs.
- Do a physical exam.
- Draw about 9mL (about 2 teaspoons) of blood for tests. These tests will check your child's HIV viral load. Some blood will be saved for later resistance testing.
- If your child is at least 9 years old and can become pregnant, we will ask about their sexual activity and collect blood (1 mL or a few drops) or urine for a pregnancy test.

If your child is eligible, they will enter the injection phase of the study. We may ask them to take one last dose of the study pills at the clinic before we give them the first shot of CAB and the first shot of RPV. About 2 hours after the shots, we will do an ECG. We also need to look closely at the amount of CAB and RPV in your child's blood before and after the CAB and RPV shots. To do this, we will need to draw your child's blood two times during the visit, once before the CAB and RPV shots, and once after. Each time we will draw 0.5mL (a few drops).

If your child is not eligible to enter the injection phase, they will stop taking the study pills and will start taking other non-study ARVs to treat HIV. They will complete a final study visit about 4 weeks after their last study pills. This study visit is described in #15 below.

9. The injection phase will continue for about 1 year and 4 months.

If your child enters the injection phase and starts receiving study shots, they will continue with study visits for about 1 year and 4 months. Most of these visits will take place about 4 weeks apart, but some of them in the first few months will take place only 1 or 2 weeks apart. Children who had more PK samples drawn at the Week 2 visit (6 samples drawn) will also have two additional visits at Week 6 and Week 9 for additional PK testing.

<<Sites to modify time estimates for visit length.>> Each visit during the injection phase will take about 1-3 hours. At every visit, we will:

- Review your child's medical records.
- Ask about your child's health, ARVs, and other medicines.
- Do a physical exam.

- If your child is at least 9 years old and can become pregnant, we will ask about their sexual activity and collect blood (1 mL or a few drops) or urine for a pregnancy test at every visit when they are scheduled to get the study shots.

At some visits, if your child is old enough, we will ask some questions about what they think about the study drugs.

At some visits, we will draw between 0.5 mL and 13.5mL (a few drops to about 3 teaspoons) of blood for tests. The tests will:

- Check your child's blood cells, liver, and kidneys.
- Check your child's CD4 cell count.
- Check your child's HIV viral load.
- Check the amount of CAB and RPV in your child's blood.
- Some blood will be saved for later testing for resistance to ARVs.

The tests will vary depending on which visit is being completed. At some visits, only some of the tests will be done. At other visits, all of the tests will be done. The visit that takes place after your child has been receiving injections for about 20 weeks, will also include an ECG.

10. Shots will be given once a month (every 4 weeks) or every 2 months (every 8 weeks).

One of the goals of the study is to see if the study shots will work just as well when they are given every 2 months (every 8 weeks) instead of every month (every 4 weeks). To make this decision, we first need to see how the shots work in children when given monthly. Children who enroll early in this study will get the shots every 4 weeks. When we have enough information, we will look at how well the shots are working in these children and then decide if the shots can be spaced out to every two months. Different decisions could be made for smaller children and bigger children, depending on what the study information shows.

If we decide it is safe to give the shots every two months, children who are already in the study may switch to the new study shots schedule. Children who are newly entering the study will get all of their shots on the new shots schedule. We will give you information about the current schedule before you join the study.

If your child receives shots every two months, you will still have follow-up visits every month, but the visits in between shots will have fewer procedures. For example, at the visits when your child does not get a shot, we will not need to do any blood tests or test for pregnancy, and we will not ask your child questions about the study drugs. These visits can happen at the clinic or over the phone.

11. Your child may have an extra visit if their HIV is not controlled.

While receiving the study drugs, your child's HIV viral load should remain low. If tests show that your child's viral load is higher than expected, your child will have an additional visit. At this visit we will:

- Review your child's medical records.
- Ask about your child's health, ARVs, and other medicines.
- Do a physical examination.
- Draw about 9.5 mL (about 2 teaspoons) of blood for tests. The tests will re-check your child's viral load and the amount of CAB and RPV in your child's blood.
- If your child's viral load is still high, we will test for resistance.

We will give you the results of these tests and explain them to you. If the results show that your child's ARVs may need to be changed, we will discuss that with you.

12. There are additional requirements for participants who can become pregnant.

Potential participants should not join this study if they are pregnant or want to become pregnant within the next 1½ years. If your child is at least 9 years old and can become pregnant, we will collect blood (1 mL or a few drops) or urine for a pregnancy test at all visits when they are receiving the study drugs (pills or shots). We will ask your child about sexual activity. If your child is having sex that could lead to pregnancy, they will be required to use contraception throughout study participation and for at least 30 days after their last study pills and 48 weeks after their last study shots. We will talk with you and your child about the importance of avoiding pregnancy and about the contraception methods that can be used in this study. We will help you and your child choose the best contraceptive methods for your child. At each visit, we will talk again about contraception, to check on how your child is doing. We will ask you and your child to tell us if you want to stop or change methods. We will ask you and your child to tell us if your child may be pregnant at any time.

If your child becomes pregnant while taking oral CAB and RPV, they will stop taking the pills. We will tell you about other ARVs your child can take instead. We will tell you if your child can get other ARVs here at this clinic or if you must go to another clinic. We will also tell you where you can take your child for health care related to the pregnancy. Your child will enter a different phase of the study called long-term safety follow-up. More information about this phase is provided below.

If your child becomes pregnant while receiving CAB and RPV shots, the study team will review your child's medical history and decide if they think it is safe and beneficial to your child's health to continue on the CAB and RPV shots. If so, your child can remain on their regular follow-up schedule. This will be discussed with you and your child at the time and agreement to this plan will need to be documented. The correct dose of CAB and RPV during pregnancy is not known, but we will continue doing tests to check your child's HIV viral load and the amount of CAB and RPV in your child's blood. If the study team recommends stopping the study shots, or if you do not want your child to continue receiving the shots while pregnant, your child will switch from shots to other non-study ARVs and join the long-term safety follow-up phase instead.

If your child is still pregnant after completing the study, we will stay in touch with you so we can collect information on the outcome of the pregnancy.

13. If your child stops the study shots early or decides not to continue with the shots after the study, they will enter the long-term safety follow-up phase.

Most children will continue to receive the study shots through the Week 72 visit. At the end of the study, your child may have the opportunity to continue getting the CAB and RPV shots outside the study, if you wish. If your child stops the shots of CAB and RPV early or chooses to use different ARVs after the final Week 72 visit, they will be asked to enter the long-term safety follow-up phase of the study. Participants who become pregnant may join this phase as well, as described in #12 above.

During the long-term safety follow-up phase, your child will not receive any study drugs. Their HIV will be treated with non-study ARVs. We will discuss what ARVs are available to you and whether you can get them at the study site or another clinic.

There will be 5 long-term safety follow-up visits, which will be scheduled 4, 8, 24, 36, and 48 weeks after your last CAB and RPV shots (or positive pregnancy test). *<<Sites to modify>>* Each of these visits will take about 1-3 hours. At these visits, we will:

- Review your child's medical records.
- Ask about your child's health, ARVs, and other medicines.
- Do a physical exam.
- Draw about 10.5 mL (about 2 teaspoons) of blood for tests. These tests will:
 - Check your child's blood cells, liver, and kidneys.
 - Check your child's HIV viral load.
 - Check the amount of CAB and RPV in your child's blood.
- If your child is at least 9 years old and can become pregnant (but is not currently pregnant), we will ask about their sexual activity and collect blood (1 mL or a few drops) or urine for a pregnancy test.

14. If you agree, your child's blood may be used for future research.

After your child's blood is tested for the study, there may be some samples left over. We call these extra samples. The IMPAACT Network would like to keep these extra samples and use them for other research in the future. It is your decision whether to allow extra samples to be kept and used for future research. You are free to say yes or no, and to change your mind at any time.

If you agree, your child's extra samples will be kept in a repository and used for future research on HIV, ARVs, the immune system, and other diseases. A repository is a secure facility used to store samples. The IMPAACT Network repository is in the United States.

<<Sites insert one of the following two paragraph options. US sites are expected to choose the first option. Non-US sites should select the option that applies based on whether local regulations do or do not permit specimen storage for future research in the US.>>

If you agree to have your child's extra samples stored, the samples will be kept in this repository. There is no limit on how long the samples will be kept. *<<Sites may modify the preceding sentence to specify time limits or additional site-specific requirements if required by local authorities.>>*

However, our regulations require that samples be stored in our country. Therefore, if you agree to have your child's extra samples stored, the samples will be kept here at our laboratory. There is no limit on how long the samples will be kept. *<<Sites may modify the preceding sentence to specify time limits or additional site-specific requirements if required by local authorities.>>*

If you agree, extra samples could be used for research that looks at your child's genes. Genes are passed to children from their birth parents. They affect how people look and how their bodies work. Differences in people's genes can help explain why some people get a disease while others do not. Your child's samples would only be used to look at genes related to HIV, ARVs, and the immune system. Testing of all your child's genes, which is sometimes called whole genome sequencing, will not be done. *<<For inclusion at US sites only>>* If any genetic testing is performed in the future, your child will be protected by the Genetic Information Nondiscrimination Act (GINA) of 2008, which protects from health insurance and employment discrimination based on genetic information.

Research done with extra samples must be approved by the IMPAACT Network. The research must also be approved by an institutional review board. The role of an institutional review board is to review the research plan and protect the rights and well-being of children whose samples will be used. Approved

research may be done in the United States or other locations. The samples will not be sold or used for commercial profit.

Research done with extra samples is not expected to give information relevant to your child's health. Therefore, the results will not be given you. The results will not be placed in your child's study records.

Your decision whether to allow your child's extra samples to be kept and used for future research will not affect your child's participation in the study. Your child can be in the study whether you say yes or no. If you say no, all extra samples will be destroyed. You will record your decision at the end of this form.

15. You may choose to leave the study at any time or we may need to take your child off the study early.

You are free to take your child off the study at any time for any reason. The care your child receives will not be affected, but it is important that we know your decision.

Some children may have to stop the study drugs and stop the study early. This could happen if:

- Your child is not able to come to the study visits or meet other study requirements.
- During the study pills phase:
 - Your child is not able to use the CAB and RPV pills as instructed.
 - Continuing the study pills may be harmful to your child.
 - The study drugs are not controlling the HIV in your child's blood.
 - Your child is not able to receive the study shots upon completion of the study pills phase.
- The study is stopped for any reason.
- The study doctor determines that continued participation in the study would be unsafe or otherwise not in the best interest of your child.

If your child leaves the study early, we will ask you to bring them back for one last clinic visit.

During this visit, we will:

- Review your child's medical records.
- Ask about your child's health, ARVs, and other medicines.
- Collect any study pills that your child has not taken.
- If your child is old enough, we will ask them some questions about what they think about the study drugs.
- Do a physical exam.
- Draw about 10.5 mL (about 2 teaspoons) of blood for tests. These tests will:
 - Check your child's blood cells, liver, and kidneys.
 - Check your child's HIV viral load.
 - Some blood will also be saved for future resistance testing.
- If your child is at least 9 years old and can become pregnant, we will ask about their sexual activity and collect blood (1 mL or a few drops) or urine for a pregnancy test.
- If your child has received a study shot, then we will also draw about 0.5 mL (a few drops) of blood to check the amount of CAB and RPV in your child's blood.

If your child leaves the study early for any reason, we will tell you where you can go for any care or treatment your child may need. It is very important for your child to keep taking ARVs after leaving the study. We will talk with you about your child's options and help make sure your child can get ARVs from

outside the study. We will answer any questions you may have and tell you how to contact us in the future, if you wish.

Risks of the study

16. There are several possible risks of the study.

Taking part in this study may involve some risks and discomfort. Most procedures done in this study are routine medical procedures, with little risk to your child. Study risks include risks from blood draw, risks from receiving shots, risks from the study drugs, and risks to your child's privacy. Your child may feel nervous or embarrassed when answering questions for the study or talking about their answers with you.

17. There are risks from blood draws and receiving shots.

Drawing blood can cause pain, swelling, bruising, or bleeding where the needle is inserted. Rarely, drawing blood can cause fainting or infection.

Receiving shots can cause some people to feel light-headed or feel like they might faint. Some people in other studies who have received CAB and RPV shots have experienced injection site reactions such as:

- pain and discomfort, or a hardened mass or lump (very common);
- swelling, redness, itching, bruising, warmth or discoloration, which may include a collection of blood under the skin (common);
- or cellulitis (heat, swelling or redness), abscess (collection of pus), numbness, minor bleeding, or discoloration (uncommon).

Some reactions may happen quickly, but others may happen a day or two later. Most reactions go away in a week or less, but sometimes they can last longer. Most people do well with them and can continue the study drugs.

A vasovagal reaction, with symptoms like feeling lightheaded or fainting, may sometimes occur. Such reactions have also been reported with other injectable medicines. This reaction usually resolves quickly and is generally not a threat to your child's health.

Post-injection reaction symptoms have happened within minutes in some people after receiving their rilpivirine shot. Most symptoms resolved within a few minutes after the RPV shot. Symptoms of post-injection reactions may include: difficulty breathing, stomach cramps, rash, sweating, numbness of the mouth, blood pressure changes, and pain (back and chest), feeling anxious, feeling warm, or feeling lightheaded or faint. These cases may be due to an accidental injection of part of the medication into a blood vessel instead of the muscle. Not all patients in whom an accidental injection in a blood vessel was suspected reported such symptoms. Most of the symptoms resolved within minutes. Your child's study doctor may need to administer treatment to help resolve these symptoms. Your child will be observed briefly (approximately 10 minutes) after each injection.

Another risk is that the shot could be given too deeply, not deeply enough, or part of the shot may accidentally be injected into the skin only, a blood vessel, or a nerve instead of a muscle. The risks of this are not well understood but could make the CAB or RPV levels in your child's body too high or too low. If too low, the study drug may not work against your child's HIV. If the RPV levels are too high, there could be side effects such as a change in your child's heart beat due to an increase in the QTc interval (change in electrical activity). Very rarely, in severe cases this can be life-threatening and could lead to sudden death; however, no such severe changes in electrical activity or sudden deaths have been observed

in clinical studies with RPV. If your study doctor thinks that the shot was not given in the right way, we may need your child to stay in the clinic for extra time for observation or for additional treatment and tests to make sure they are safe.

18. There are risks from the study ARVs

All ARVs can cause side effects. This includes ARVs your child is currently taking and any other ARVs they would receive outside the study. Some side effects are minor, others can be severe. Some side effects are common, others are rare. Some people have some of the side effects. Other people have no side effects.

The most common and most serious side effects of CAB and RPV are listed below. There may be other side effects that we do not know about now. This may be especially true for children, because this is the first study of the CAB and RPV combination for HIV treatment in children under 12 years of age.

If you join the study, we will tell you more about the study drugs you will be taking. At each study visit, we will check on whether the study drugs may be causing side effects. We will also tell you what to do if you have side effects. If you have questions or concerns at any time, please tell us.

19. Side effects from the CAB pills and the CAB shot.

Many adults and a small number of adolescents have received CAB pills or CAB shots in other studies. The table below lists side effects identified from other studies of CAB in people who have HIV.

Common and Uncommon Side Effects of CAB*

Very Common Side Effects of CAB	Common Side Effects of CAB	Uncommon Side Effects of CAB
<ul style="list-style-type: none">• Headache• Pyrexia (fever), feeling hot, body temperature increase	<ul style="list-style-type: none">• Rash• Vomiting (being sick)• Nausea (feeling sick to the stomach)• Abdominal pain, upper abdominal pain (stomach pain and discomfort)• Insomnia (problems sleeping)• Abnormal dreams/nightmares• Anxiety (feeling anxious)• Feeling lightheaded (dizziness)• Depression (feelings of deep sadness and unworthiness)• Flatulence (passing gas or wind)• Diarrhea or loose stools• Myalgia (muscle pain)• Fatigue (lack of energy)• Asthenia (feeling weak)• Malaise (feeling generally unwell)• Weight increase	<ul style="list-style-type: none">• Somnolence (sleepiness or drowsiness)• Hepatotoxicity (liver problems)• Transaminase increase (blood tests may show increase in the level of liver enzymes)

*in addition to risks from receiving shots, as outlined in Section 17.

The following effects have also been seen in some of the people who received CAB in other studies:

Abnormal liver tests:

A small number of people across all studies (just over 1%) had abnormal liver tests requiring them to stop CAB. Some abnormal liver tests were explained by other health conditions such as a new virus infection, like Hepatitis A, B or C. A small number of people did not have health conditions that could explain the abnormal test, so it is possible that a mild form of liver damage happened from taking CAB. The liver tests got better after stopping CAB, showing that any damage was temporary.

Blood tests to check the health of your child's liver will be done during the study. Your study doctor will tell you if your child needs to stop taking the study drugs or if other actions are needed. If your child stops taking the study drug, your child may be able to re-start the study drug or may need to switch to non-study ARVs.

Seizures/convulsions:

Seizures have been seen (rarely) in people with and without HIV who have taken CAB. They are not thought to be caused by CAB, but the study staff will ask you and your child about their occurrence in your child.

If your child has a history of seizures, please let your study doctor know.

20. Side effects from the RPV pills and RPV shot

Oral RPV is a drug that many people throughout the world have received to manage HIV, so we know a lot about it. The following side effects have been seen in people with HIV taking RPV.

Common and Uncommon Side Effects of RPV*

Very common side effects of RPV	Common Side Effects of RPV	Uncommon Side Effects of RPV
<ul style="list-style-type: none"> • Headache • Fever (pyrexia) • Feeling hot • Body temperature increase 	<ul style="list-style-type: none"> • Feeling less hungry (decreased appetite) • Sleep disorders, insomnia (sleeplessness) • Abnormal dreams • Dizziness • Fatigue (lack of energy) • Asthenia • Malaise • Myalgia (muscle pain) • Rash • Depression • Diarrhea • Nausea, vomiting abdominal pain or discomfort (belly ache) • Upper abdominal (belly) pain 	<ul style="list-style-type: none"> • Immune reconstitution syndrome (this can be an overreaction of the body's recovering defense system to a previously present infection, or problems in the immune system) • Depressed mood • Sleepiness (somnolence) • Abdominal (belly) discomfort • Dry mouth • Transaminases increased (increased levels in the blood of certain liver function tests)

*in addition to risks from receiving shots, as outlined in Section 17.

Abnormal blood tests:

Changes in blood tests have been observed. People with Hepatitis B or C, or who have possible liver damage before starting RPV, may have worse liver tests while taking RPV. A few cases of liver problems were found in people taking RPV who did not already have any liver problems.

Sometimes allergic reactions can affect body organs. For example, an allergic reaction can cause liver problems which can lead to liver failure. Contact your study doctor right away if your child has any of the following signs or symptoms of liver problems:

- Yellowing of the skin or whites of the eyes
- Dark or tea colored urine
- Pale colored stools/bowel movements
- Nausea/vomiting
- Loss of appetite
- Pain, aching or tenderness on the right side below the ribs
- Itchy skin

Skin Rash:

Most rashes were mild or moderate, and happened within the first 4 weeks of taking RPV. Most rashes got better after one week, and the people did not need to stop taking RPV. However, the study ARVs will need to be stopped for some types of moderate rash and all types of severe rash, which can be life-threatening. If this happens to your child, your child will need to come for extra study visits to monitor their health. Some people with rash may also have other signs and symptoms of allergic reaction.

If your child has any type of rash or other skin problems during the study you must tell your child's study doctor right away, and the doctor may tell your child to stop taking the study drugs.

21. There may be other possible risks.

The study ARV shots stay in your child's body for a long time

The shots your child gets in this study are long acting, meaning they stay in the body for a long time. In most people, the drugs will no longer be in the body one year after an injection, but in some people, low levels of CAB and RPV may still be in the body.

If your child develops a side effect to the study drug after the shot, there will be no way to remove the drug from their body. If your child develops a symptom from these drugs while the drugs are still in their body, every effort will be made to treat the side effects. The amount of drug will decrease overtime and will eventually disappear.

If your child stops getting the study shots, the study drugs will stop working to treat HIV, as the amount of medicine in the body decreases slowly over time. When stopping these drugs, it will be very important for your child to start taking other HIV medications, as directed by their doctor.

Risk of switching ARVs

If your child joins this study, they will stop taking their current ARVs and start taking ARVs given by the study. Any time a person switches to ARVs, there is a chance that they could experience new side effects. There is also a chance that the new ARVs may not work as well. For example, the study ARVs may not work as well to control the amount of HIV in your child's body. This is why we test the HIV viral load at most study visits. If your child's viral load is higher than expected, they will have repeat testing, and may need to stop using the study ARVs.

Risk of resistance

By stopping their previous ARVs and switching to the study ARVs, your child could develop resistance. This could happen if the study ARVs don't work as well to control the amount of HIV in your child's body. Resistance means that if these ARVs are taken again in the future, they may not work against HIV. To prevent resistance, it is important that your child takes and/or receives the ARVs as instructed, and does not miss any doses.

Mental illness or depression

Some people with HIV sometimes have feelings of depression or may feel sad or hopeless, feel anxious or restless, or may have thoughts of hurting or killing themselves (suicide). A small number of people being treated with drugs that work the same way as CAB (called integrase inhibitors), have had suicidal thoughts and actions. This is more common in people with a prior history of depression or mental health illness.

Tell the study doctor if your child has a history of mental health illness. If your child is worrying more often, experiencing low mood, having sleep problems, has thoughts of hurting or killing themselves, or has any other unusual or uncomfortable thoughts during this study, you should tell the study doctor or go to the nearest hospital right away.

Possible effects on pregnancy

HIV and ARVs may lead to some pregnancy complications, like early delivery or a low birth weight for the baby. We do not yet know if CAB is safe in pregnancy. There is little information from humans on the effects of CAB in pregnancy, but CAB LA and RPV LA have been detected in the body for up to 12 months or longer after an injection and the effects of the drugs on an unborn baby are currently unknown. The unborn baby would be exposed to CAB and RPV even if injections stop as soon as pregnancy is identified. Most of the information we have is from animal studies. RPV does not appear to be a risk to pregnancy and the developing baby from what we know now, but additional information is still being collected.

Participants who are able to become pregnant and are sexually active must agree to use certain effective methods of birth control to be in this study. If your child becomes pregnant during the study, please let us know right away. We will give you and your child more information about ARV options in pregnancy, including whether it is possible to stay on the study ARVs or not.

Immune reconstitution syndrome

In some people with advanced HIV, signs and symptoms from other infections or certain diseases (for example a liver condition called autoimmune hepatitis) may occur soon after starting combination ARVs or later into treatment. Some of these symptoms may be life threatening. If your child starts having new symptoms, or if you notice that any existing symptoms are getting worse after starting the study drugs, tell your doctor immediately.

Abnormal distribution of body fat and wasting

The use of potent antiretroviral drug combinations may be associated with other body changes, especially related to body fat distribution. Body changes could include an increase in fat around the waist and stomach area or on the back of the neck. There could also be breast enlargement and/or thinning of the face, legs, and arms.

Risks of disclosure of your child's information.

In addition to the risks of study procedures and the study drugs, there is a risk of disclosure of your child's information. We will make every effort to keep your child's information private and confidential. Study records and blood samples will be kept in secure locations. All samples and most records will be labeled only with a code number. However, your and your child's name will be written on some records.

<<To be included at US sites>> U.S. Federal laws protect the privacy of your protected health information ("personal/private information"). However, there are exceptions to these laws. The Researchers will ask you to sign a form ("HIPAA Authorization") to give your permission for certain uses and sharing of your personal (private) information for the study. That form provides more details about the types of information that may be used and shared, and how it will be protected.

<<To be included at South African sites>> In addition, the Protection of Personal Information Act (POPIA) ensures that all South African institutions conduct themselves in a responsible manner when collecting, processing, storing and sharing your personal information by holding them accountable should they abuse or compromise your personal information in any way.

<<All sites to include any other relevant country-specific data-sharing requirements, as applicable>>

<<To be included at US sites>> Your child's privacy may also be protected by a Certificate of Confidentiality that helps us avoid being forced to release information that may identify your child, such as by the courts or police. The certificate cannot be used in all situations, but it can be used to resist demands for information that would identify your child. The certificate does not protect against requests for information from the United States federal government or from the United States Food and Drug Administration. Regardless of the certificate, you can release information about your child's participation in the study to others, if you wish.

The information we collect about your child for this study will be combined with information collected about all other children in the study. This will be done at an organization called a statistical and data management center. The IMPAACT Network statistical and data management center is in the United States. We will send your child's information to this center, but your child's name and other information that could personally identify your child will not be sent. The information will be sent securely, following applicable laws and policies.

Information collected for this study may be used for other research in the future. For example, researchers may use information from this study to try to answer different questions about children with HIV. Any future research done with the information from this study must be approved by the IMPAACT Network. If any future research is done, information about your child may be used. Your child's information will be labeled with a code number, and the only link between the code number and your child's name will be kept here at this clinic.

Despite our best efforts to keep your child's information private, it is possible that your child's information, could be obtained by someone who should not have it. If this were to happen, your child could be treated badly or unfairly.

Benefits of the study

22. There may or may not be benefits to your child from being in the study.

By joining the study, your child will be part of the search for new treatments for children with HIV. There may be a direct benefit to your child by taking part in the study, but we cannot guarantee that being in the study will benefit your child in any way. One possible benefit is that you or your child might prefer getting CAB and RPV as a monthly (or every two months) shot instead of taking pills every day. The study drugs could have fewer side effects than the previous ARVs your child was taking. There may also be benefit if the results from this study lead to a safe and effective dose of the study drugs for children. If your child likes the shots, and they are working well, your child will be able to continue getting them after the study is over. Information learned from this study may help other children who have HIV.

Your child will have regular visits here and frequent checks on their health, including their HIV viral load. It is possible the study ARVs will slow the progress of HIV in your child.

Other information about the study

23. There are no costs to you for your child being in the study.

There are no costs to you or your child for study visits or procedures, or the study drugs.

<<Sites insert information about compensation/reimbursement here.>> You will be reimbursed for the cost of transport to study visits and your time spent here. For each visit, you will be given <<specify amount>>.

24. Your child's records may be reviewed by study staff and groups that oversee the study.

Groups that oversee the study include:

- <<U.S. sites insert sIRB>>
- <<Sites insert local IRBs/ECs as applicable>>
- <<Sites insert applicable drug regulatory authorities and other regulatory entities>>
- The United States National Institutes of Health and its study monitors
- The United States Food and Drug Administration
- The United States Office for Human Research Protections
- Other United States, local, and international regulatory entities
- The IMPAACT Network that is coordinating the study
- The companies that make the study drugs, ViiV Healthcare and Janssen Research and Development

Like the study staff, these groups are required to make efforts to keep study records private and confidential.

The results of the study may be presented publicly or published. However, no presentation or publication will use your child's name or identify your child personally.

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov> as required by US Law. This Web site will not include information that can identify your child. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Your child's study information may be disclosed to other authorities if required by law. <<Sites may add more specific detail here describing local laws that may be applicable.>>

25. If your child gets sick or injured, contact us immediately.

Your child's health is important to us. We will make every effort to protect your child's well-being and minimize risks. It is possible, however, that your child could have an illness or injury that is study-related. This means that the illness or injury occurred as a direct result of being in the study.

<<Sites may modify this paragraph to reflect local institutional policies; information regarding coverage available through clinical trial insurance obtained by the site should be included if applicable; the statement regarding no program for compensation through the NIH may not be removed.>> If a study-related illness or injury occurs, we will treat your child or tell you where you can get the treatment your child needs. The cost for this treatment may be charged to you or your health insurance. There is no program to pay money or give other forms of compensation for study-related illness or injury through *<<site name>>* or the United States National Institutes of Health.

Who to contact

26. If you have questions, concerns, or problems at any time, use these contacts.

If you have questions, concerns, or problems at any time, use these contacts.

- If you have questions about the study or your child's health, or if you want your child to leave the study:
<<Name, phone number, and other relevant contact details of investigator or other study staff>>
- If you have questions about your child's rights as a study participant, or problems or concerns about how your child is being treated in the study:
<<Name, phone number, and other relevant contact details of IRB contact person or other appropriate person or organization; US sites to include sIRB contact information>>

Permission for Long Term Specimen Storage and Future Use

Please write your initials or make your mark next to your choice for whether your child's extra samples can be kept and used for future research.

- _____ I allow my child's extra samples to be used for research on HIV, ARVs, the immune system, and other diseases. I also allow my child's samples to be used for tests of their genes.
- _____ I allow my child's extra samples to be used for research on HIV, ARVs, the immune system, and other diseases. I do not allow my child's samples to be used for tests of their genes.
- _____ I do not allow my child's extra samples to be used for any research.

Permission for Off-Site Visits

On rare occasions, members of the research team may be able to schedule visit activities off-site at your home or at another location. Before any visits take place off-site, the study staff will discuss the location

and time so that the visit is conducted at a convenient time and done in a place you and your child feel comfortable and where confidentiality can be maintained. To conduct visits outside of the clinic, we will also need you to give us your written permission to do so.

Please read the following statements carefully and write your initials or make your mark next to the option you prefer.

_____ I do agree to have study visits at a location other than the study clinic, when necessary.

_____ I do not agree to have study visits at a location other than the study clinic, when necessary.

Signatures

If you decide to have your child join this study, please sign or make your mark below.

Before deciding whether to have your child join this study, make sure you have read this form or had it read to you. Make sure all your questions have been answered. You should feel that you understand the study, its risks and benefits, and what is expected of you and your child.

We will tell you any new information from this study or other studies that may affect your willingness to keep your child in the study. You are welcome to ask questions or request more information at any time.

You do not give up any rights by signing this form.

<<Sites insert signature blocks as required by IRB and institutional policies.>>

Name of Child
(print)

Name of Parent or Legal Guardian
(print)

Parent or Legal Guardian Signature

Date

Name of Witness
(if applicable, print)

Witness Signature

Date

Study Staff Conducting
Permission Process Name (print)

Study Staff Signature

Date

**Appendix IV-B: Sample Parental Permission Form for Participation in Cohort 2
for parent/legal guardian of child participant**

IMPAACT 2036

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

Version 1.0, 22 September 2022

Sponsor / Study Title: National Institutes of Health (NIH) / National Institute of Allergy and Infectious Diseases (NIAID) / National Institute of Child Health and Human Development (NICHD) / National Institute of Mental Health (NIMH) / “CRAYON”

Protocol Number: IMPAACT 2036

Principal Investigator: <<PI Full Name>>
(Study Doctor)

Telephone: <<Phone Number>>

Address: <<Location>>

Introduction

This form is for the parent or legal guardian of a child who is being asked to participate in the research study named above. Your permission is needed, and the assent of your child may also be required depending on their age. This form gives information about the study. Please read it or have it read to you. Ask any questions you may have. We will take as much time as needed for you to fully understand the study. We will ask you questions to see if we have explained the study clearly.

Here is a summary of important information about the study:

- The study is testing two anti-HIV drugs (ARVs), cabotegravir (CAB) and rilpivirine (RPV), taken as pills and given as long-acting shots in children ages 2 to less than 12.
- Some of the study drugs are already approved in some countries for use in adolescents or adults, but they have not yet been tested in younger children.
- There are two groups in this study called Cohort 1 and Cohort 2. **This form is about Cohort 2.**
- All children in Cohort 2 will stop taking their usual ARVs when they enter the study.
- Cohort 2 has two sub-groups: Cohort 2a and Cohort 2b. You will decide together with your child’s doctor whether your child will be in Cohort 2a or Cohort 2b. Your child will stay in the group you choose for the whole study. Cohort 2a and Cohort 2b are explained below.
- If you decide for your child to join Cohort 2a, your child will start taking CAB and RPV pills when they enter the study. They will take the study pills every day for about a month. At the end of that time, if they qualify, they will start getting CAB and RPV as shots.
- If you decide for your child to join Cohort 2b, your child will not take the CAB and RPV pills and instead will start getting the CAB and RPV shots when they enter the study.

- For both Cohort 2a and 2b, the study shots will be given every month or every 2 months for about a year. The frequency of the shots will be based on information collected in the study. We will explain your child's shot schedule before they enroll.
- While in the study, children will have clinic visits with physical examinations and blood draws for laboratory tests. Some visits will include a review of the child's medical records and an electrocardiogram (ECG), which is a test to look at the child's heart. You and your child will answer questions about your child's health, and the drugs being tested.
- At the end of the study, your child may have the opportunity to continue getting the CAB and RPV shots outside the study, if you wish. We will explain all the treatment options available to you and help ensure your access to continued treatment.
- Children who stop taking the CAB and RPV shots may be followed for up to 1 year for long-term safety follow-up. During this time, children will not take any study drugs (shots or pills), but will take other ARVs.
- There are possible risks for children in the study. One possible risk is that the drugs being tested could cause side effects. The most severe side effects include allergic reactions, liver problems, and mental health problems. Severe side effects are rare.
- There may or may not be possible benefits for children in the study. One possible benefit is not having to take a daily pill while getting the CAB and RPV shots. Another possible benefit is that the shots being tested could be better for your child's health and HIV care than the usual ARV pills.
- Your decision on your child's participation in the study will have no effect on the medical care your child receives. Your child's access to services, and the benefits and rights they normally have, will not be affected.

More information about the study is given in this form. You should feel that you understand the study before deciding whether your child will participate. If you decide that your child will participate, you will be asked to sign or make your mark on this form. You will be offered a copy to keep.

About the study

The International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) and <<site name>> are doing this study. The person in charge of the study at <<site name>> is the study doctor listed on the first page of this form.

The study is testing two anti-HIV drugs (antiretrovirals or ARVs) in children who are 2-11 years old. HIV is the virus that can lead to AIDS. The study ARVs are called cabotegravir (CAB) and rilpivirine (RPV).

The study will include up to 90 children from Brazil, Botswana, South Africa, Thailand, Uganda, and the United States. There will be two groups of children, called Cohort 1 and Cohort 2. This form is about Cohort 2.

As a separate part of this study, about 90 parents or caregivers of child participants will also enroll to complete questionnaires. Some of them will also take part in an in-depth interview. Study staff may ask you about who should participate in that part of the study.

The United States National Institutes of Health and the companies that make CAB and RPV, ViiV Healthcare and Janssen Pharmaceuticals, are paying for this study.

1. The study is testing CAB and RPV in children.

People with HIV usually take a combination of ARVs each day to stay healthy. There are not as many ARVs available for children as for adults because many ARVs have not yet been tested in children. ARVs can be made in different forms, such as liquids, pills, and injections (shots). This study will test CAB and RPV pills swallowed whole or dissolved in liquid (for the smallest children) as well as CAB and RPV shots. The pills will be taken every day, if your child takes the study pills. The shots may be given every month or every two months. The frequency of the shots will be based on information collected in the study. We will explain your child's shot schedule before they enroll and during follow-up, if there are any changes.

Some countries have already approved RPV and CAB pills (swallowed whole) and shots for use in adults and in adolescents starting at 12 years of age. The approvals were possible because of studies, like this one, that showed CAB and RPV were safe and worked well to control HIV in adults.

This is the first time that all of the study drugs are being studied in younger children, and the first time the CAB pills dissolved in liquid have ever been studied. This study will look at whether these ARVs are the correct dose for children, are safe and well-tolerated, and can control HIV. The study will also look at whether any of the medications cause bad effects when given to children.

2. Only children who qualify can participate in the study.

If you decide to have your child join this study, we will first do some tests to find out if your child qualifies. More information about the tests is given in #4, below. If your child qualifies, they may enter the study. If your child does not qualify, they cannot join the study.

3. It is your decision whether to have your child participate in the study.

Deciding to have your child join the study is voluntary (your choice). You are free to have your child join or not join. If you decide to have your child join, you can change your mind and take your child off the study at any time. Your decisions will have no effect on the medical care your child receives. Your child's access to services, and the benefits and rights they normally have, will not be affected.

If you decide to have your child join the study, you will need to decide whether they will be in Cohort 2a or Cohort 2b. If you decide for your child to join Cohort 2a, your child will start taking CAB and RPV pills when they enter the study. They will take the study pills every day for about a month. At the end of that time, if they qualify, they will start getting CAB and RPV as shots. If you decide for your child to join Cohort 2b, your child will not take the CAB and RPV pills and instead will start getting the CAB and RPV shots when they enter the study. You and your child's doctors will decide together whether Cohort 2a or Cohort 2b is a better fit for your child based on factors like personal preferences and medical history. Once your child is enrolled in Cohort 2a or Cohort 2b, your child will stay in that group throughout the study and will not be able to switch to the other group.

Your child does not need to join this study to receive medical care and ARVs. There are alternatives to participation. For example, your child can keep receiving medical care and ARVs from outside the study. Take your time and consider your decision carefully. Your child may also qualify for other studies. Please ask any questions you may have about these types of alternatives. If you wish, you can talk to other people about the study before you decide. You can bring other people here to learn about the study with you.

No matter what you decide about the study, it is important for your child to receive medical care and take ARVs. Taking ARVs is the best way for children with HIV to stay healthy.

Finding out if your child qualifies for this study

4. We will ask questions, examine your child, and test your child's blood.

To find out if your child qualifies for the study, we will:

- Review your child's medical records.
- Ask about your child's health, ARVs, and other medicines.
- Talk with you and your child about the study requirements.
- Do a physical examination.
- Give your child an electrocardiogram (ECG). This is a test of how well your child's heart is working.
- Draw up to 11.5 mL (about 2 teaspoons) of blood for tests. The tests will:
 - Check your child's blood cells, liver, and kidneys. This includes checking for an infection called hepatitis B.
 - Confirm your child has HIV. If the tests that are required for joining this study are already documented in your child's medical records, we may not need to do these tests again.
 - Measure the amount of HIV in your child's blood. This is called your child's "viral load."

If your child is at least 9 years old and can become pregnant, we will ask about their sexual activity and collect blood (1 mL or a few drops) or urine for a pregnancy test. If your child is pregnant, they will not qualify for the study. If your child is not pregnant, but is sexually active, they will need to be on an effective method of birth control throughout their study participation.

These procedures will take about 4 hours. <<*Here and throughout this form, sites may modify the expected visit duration as needed.*>>

Most of the blood or urine tests we do at this visit and any future visits will be done here. Some tests will be done at other laboratories. We will give you the results of any tests that might impact your child's medical care. Some tests are important for the study, but do not impact your child's medical care, and these results may not be shared with you. Some test results from this visit will be ready quickly. Others may take about 2-3 weeks. We will schedule your child to come back when the results are ready. We may ask you to bring your child back for more tests, if needed to find out if your child qualifies for the study. While waiting for the results, it is important for your child to keep taking their regular ARVs.

5. We will tell you if your child is eligible.

If your child is not eligible for the study for any reason, we will tell you this. They will not be entered in the study. They can and should continue to receive medical care and treatment outside of the study. We will tell you more about getting this care and treatment and any other services you may need. If your child does not enter the study, we will still use some information collected about them (for example, age, sex, and race). We will use this information to look at patterns or common reasons for not entering the study.

If your child is eligible for the study, they can continue to the study entry visit.

Entering the study

6. If your child qualifies, they can enter the study

On the day you bring your child to enter the study, we need to confirm they qualify. On that day, we will:

- Review your child's medical records.
- Ask about your child's health, ARVs, and other medicines.
- If your child is old enough, we will ask them some questions about what they think about the study drugs.
- Do a physical examination.
- Draw about 11mL (a little more than 2 teaspoons) of blood for tests. The tests will:
 - Check your child's blood cells, liver, and kidneys.
 - Check how much the virus has affected your child's ability to fight the virus. This is called a CD4 cell count.
 - Check your child's HIV viral load.
 - Some blood will be saved for later testing for resistance to ARVs. This test shows whether different ARVs may work against the HIV in your blood.
- If your child is at least 9 years old and can become pregnant, we will ask about their sexual activity and collect blood (1 mL or a few drops) or urine for a pregnancy test.

If these procedures confirm that that your child qualifies, your child will enter the study. If your child is in Cohort 2a, they will stop taking their usual ARVs and start taking the CAB and RPV pills. If your child is in Cohort 2b, they will stop taking their usual ARVs and receive their first CAB and RPV shots during the visit.

These procedures will take about 4 hours.

During the study

7. Study Pills Phase: This part is only for children in Cohort 2a. When they enter the study, your child will begin taking the study pills and will have two more visits in the study pills phase (Week 2, Week 4a).

Your child will take their first dose of both study pills at the visit when they enter the study. The pills will either be swallowed or mixed into liquid before swallowing. Your child's weight will determine which kind of pills they receive. We will give you information on which kind of pills your child will receive and explain how to take them. We will also give you pills for your child to take at home.

After you go home, it is very important for your child to take the pills as instructed. We will take as much time as needed for you and your child to understand the instructions. We will talk with you about strategies to help your child take the medications as instructed.

Once your child is in the study, there will be 2 more visits in the study pill phase. The first visit will happen about 2 weeks after your child enters the study and the second visit will happen about 2 weeks after that. Each visit will take about 1-3 hours.

At these visits we will:

- Review your child's medical records.
- Ask about your child's health, ARVs, and other medicines.
- Do a physical exam.
- Give you more CAB and RPV pills for your child, as needed.
- Draw about 3 mL (a little less than a teaspoon) of blood for tests to check your child's blood cells, liver, and kidneys.
- If your child is at least 9 years old and can become pregnant, we will ask about their sexual activity and collect blood (1 mL or a few drops) or urine for a pregnancy test.

At the first visit (Week 2), we will draw some additional blood. We will use about 3 mL (about half a teaspoon) of blood to check your child's viral load.

We will also draw some blood for a pharmacokinetic (PK) test. This is a test to look at the amount of CAB or RPV in your child's blood over time. We will ask that you bring your child to this visit at a specified time. To prepare for the visit, your child will need to take their study drugs at a specific time each day for the three days before the visit. Your child should **not** take their study drugs the day of the visit. We will give you more information in advance of the visit to help you remember these rules. When you come for the visit, we will draw blood for the first part of the PK test and then your child can take their study pills. After your child has taken the pills, we will draw their blood again about 3 hours later.

<<Sites: modify language as appropriate to indicate procedures for the PK collection.>> We will not need to stick your child with a needle each time we draw blood. Instead, a small plastic tube attached to a plastic needle will be placed in your child's arm when we draw the first sample. The tube and needle will stay in place until all the blood draws are done.

Each PK blood draw is about 0.5 mL (a few drops).

At the end each visit during the pill phase, we will let you know if there are any rules about when your child should take their oral CAB and oral RPV doses at home.

8. This part is only for children in Cohort 2a. If your child is eligible, they will enter the injection phase of the study (Week 4b).

The next visit your child has will be called the Week 4b visit. At this visit, we will determine if your child is eligible to get the CAB and RPV study shots. Your child should **not** take oral CAB and oral RPV before coming to the clinic. At this visit we will:

- Review your child's medical records.
- Ask about your child's health, ARVs, and other medicines.
- If your child is old enough, we will ask them some questions about what they think about the study drugs.
- Do a physical exam.
- Draw about 9mL (about 2 teaspoons) of blood for tests. These tests will check your child's HIV viral load. Some blood will be saved for later resistance testing.
- If your child is at least 9 years old and can become pregnant, we will ask about their sexual activity and collect blood (1 mL or a few drops) or urine for a pregnancy test.

If your child is eligible they will enter the injection phase of the study. We may ask them to take one last dose of the study pills at the clinic before we give them the first shot of CAB and the first shot of RPV.

If your child is not eligible to enter the injection phase, they will stop taking the study pills and will start taking other non-study ARVs to treat HIV. They will complete a final study visit about 4 weeks after their last study pills. This study visit is described in #16 below.

9. Injection Phase: This part is for children in both Cohort 2a and 2b. When your child gets their first CAB and RPV shots, your child will have a few tests done.

Participants in Cohort 2a will have their first study shots when they finish the study pills phase (Week 4b visit). Participants in Cohort 2b will not take part in the study pills phase so they will have their first study shots when they enter the study (Entry visit).

About 2 hours after your child receives their first study shots, we will do an ECG. We also need to look closely at the amount of CAB and RPV in your child's blood before and after the CAB and RPV shots. To do this, we will need to draw your blood two times during the visit, once before the CAB and RPV shots, and once after. Each time we will draw 0.5mL (a few drops).

10. The injection phase will continue for about 1 year.

Once your child starts receiving study shots, they will continue with study visits for about 1 year. Most of these visits will take place about 4 weeks apart, but some of them in the first few months will take place only 1 or 2 weeks apart. Children who join Cohort 2b will also have a visit a few days after their first study shot to make sure they are tolerating medication well.

<<*Sites to modify time estimates for visit length.*>> Each visit during the injection phase will take about 1-3 hours. At every visit, we will:

- Review your child's medical records.
- Ask about your child's health, ARVs, and other medicines.
- Do a physical exam.
- If your child is at least 9 years old and can become pregnant, we will ask about their sexual activity and collect blood (1 mL or a few drops) or urine for a pregnancy test at every visit when they are scheduled to get the study shots.

At some visits, if your child is old enough, we will ask some questions about what they think about the study drugs.

At some visits, we will draw between 0.5 mL and 13.5mL (a few drops to about 3 teaspoons) of blood for tests. The tests will:

- Check your child's blood cells, liver, and kidneys.
- Check your child's CD4 cell count.
- Check your child's HIV viral load.
- Check the amount of CAB and RPV in your child's blood.
- Some blood will be saved for later testing for resistance to ARVs.

The tests will vary depending on which visit is being completed. At some visits, only some of the tests will be done. At other visits, all of the tests will be done. The visit that takes place after your child has been receiving injections for about 20 weeks, will also include an ECG.

11. Shots will be given once a month (every 4 weeks) or every 2 months (every 8 weeks).

One of the goals of the study is to see if the study shots will work just as well when they are given every 2 months (every 8 weeks) instead of every month (every 4 weeks). To make this decision, we first need to see how the shots work in children when given monthly. Children who enroll early in this study will get the shots every 4 weeks. When we have enough information, we will look at how well the shots are working in these children and then decide if the shots can be spaced out to every two months. Different decisions could be made for smaller children and bigger children, depending on what the study information shows.

If we decide it is safe to give the shots every two months, children who are already in the study may switch to the new study shots schedule. Children who are newly entering the study will get all of their shots on the new shots schedule. We will give you information about the current schedule before you join the study.

If your child receives shots every two months, you will still have follow-up visits every month, but the visits in between shots will have fewer procedures. For example, at the visits when your child does not get a shot, we will not need to do any blood tests or test for pregnancy, and we will not ask your child questions about the study drugs. These visits can happen at the clinic or over the phone.

12. Your child may have an extra visit if their HIV is not controlled.

While receiving the study drugs, your child's HIV viral load should remain low. If tests show that your child's viral load is higher than expected, your child will have an additional visit. At this visit we will:

- Review your child's medical records.
- Ask about your child's health, ARVs, and other medicines.
- Do a physical examination.
- Draw about 9.5 mL (about 2 teaspoons) of blood for tests. The tests will re-check your child's viral load and the amount of CAB and RPV in your child's blood. If your child's viral load is still high, we will test for resistance.

We will give you the results of these tests and explain them to you. If the results show that your child's ARVs may need to be changed, we will discuss that with you.

13. There are additional requirements for participants who can become pregnant.

Potential participants should not join this study if they are pregnant or want to become pregnant within the next 1½ years. If your child is at least 9 years old and can become pregnant, we will collect blood (1 mL or a few drops) or urine for a pregnancy test at all visits when they are receiving the study drugs (pills or shots). We will ask your child about sexual activity. If your child is having sex that could lead to pregnancy, they will be required to use contraception throughout study participation and for at least 30 days after their last study pills and 48 weeks after their last study shots. We will talk with you and your child about the importance of avoiding pregnancy and about the contraception methods that can be used in this study. We will help you and your child choose the best contraceptive methods for your child. At each visit, we will talk again about contraception, to check on how your child is doing. We will ask you and your child to tell us if you want to stop or change methods. We will ask you and your child to tell us if your child may be pregnant at any time.

If your child becomes pregnant while taking oral CAB and RPV, they will stop taking the pills. We will tell you about other ARVs your child can take instead. We will tell you if your child can get other ARVs here at this clinic or if you must go to another clinic. We will also tell you where you can take your child for health care related to the pregnancy. Your child will enter a different phase of the study called long-term safety follow-up. More information about this phase is provided below.

If your child becomes pregnant while receiving CAB and RPV shots, the study team will review your child's medical history and decide if they think it is safe and beneficial to your child's health to continue on the CAB and RPV shots. If so, your child can remain on their regular follow-up schedule. This will be discussed with you and your child at the time and your agreement to this plan will need to be documented. The correct dose of CAB and RPV during pregnancy is not known, but we will continue doing tests to check your child's HIV viral load and the amount of CAB and RPV in your child's blood. If the study team recommends stopping the study shots, or if you do not want your child to continue receiving the shots while pregnant, your child will switch from shots to other non-study ARVs and join the long-term safety follow-up phase instead.

If your child is still pregnant after completing the study, we will stay in touch with you so we can collect information on the outcome of the pregnancy.

14. If your child stops the study shots early or decides not to continue with the shots after the study, they will enter the long-term safety follow-up phase.

Most children will continue to receive the study shots through the end of their study participation. At the end of the study, your child may have the opportunity to continue getting the CAB and RPV shots outside the study, if you wish. If your child stops the shots of CAB and RPV early or chooses to use different ARVs after the final study visit, they will be asked to enter the long-term safety follow-up phase of the study. Participants who become pregnant may join this phase as well, as described in #13 above.

During the long-term safety follow-up phase, your child will not receive any study drugs. Their HIV will be treated with non-study ARVs. We will discuss what ARVs are available to you and whether you can get them at the study site or another clinic.

There will be 5 long-term safety follow-up visits, which will be scheduled 4, 8, 24, 36, and 48 weeks after your last CAB and RPV shots (or positive pregnancy test). *<<Sites to modify>>* Each of these visits will take about 1-3 hours. At these visits, we will:

- Review your child's medical records.
- Ask about your child's health, ARVs, and other medicines.
- Do a physical exam.
- Draw about 10.5 mL (about 2 teaspoons) of blood for tests. These tests will:
 - Check your child's blood cells, liver, and kidneys.
 - Check your child's HIV viral load.
 - Check the amount of CAB and RPV in your child's blood.
- If your child is at least 9 years old and can become pregnant (but is not currently pregnant), we will ask about their sexual activity and collect blood (1 mL or a few drops) or urine for a pregnancy test.

15. If you agree, your child's blood may be used for future research.

After your child's blood is tested for the study, there may be some samples left over. We call these extra samples. The IMPAACT Network would like to keep these extra samples and use them for other research in the future. It is your decision whether to allow extra samples to be kept and used for future research. You are free to say yes or no, and to change your mind at any time.

If you agree, your child's extra samples will be kept in a repository and used for future research on HIV, ARVs, the immune system, and other diseases. A repository is a secure facility used to store samples. *<<Sites insert one of the following two paragraph options. US sites are expected to choose the first*

option. Non-US sites should select the option that applies based on whether local regulations do or do not permit specimen storage for future research in the US.>>

If you agree to have your child's extra samples stored, the samples will be kept in this repository. There is no limit on how long the samples will be kept. <<*Sites may modify the preceding sentence to specify time limits or additional site-specific requirements if required by local authorities.*>>

However, our regulations require that samples be stored in our country. Therefore, if you agree to have your child's extra samples stored, the samples will be kept here at our laboratory. There is no limit on how long the samples will be kept. <<*Sites may modify the preceding sentence to specify time limits or additional site-specific requirements if required by local authorities.*>>

If you agree, extra samples could be used for research that looks at your child's genes. Genes are passed to children from their birth parents. They affect how people look and how their bodies work. Differences in people's genes can help explain why some people get a disease while others do not. Your child's samples would only be used to look at genes related to HIV, ARVs, and the immune system. Testing of all your child's genes, which is sometimes called whole genome sequencing, will not be done. <<*For inclusion at US sites only*>> If any genetic testing is performed in the future, your child will be protected by the Genetic Information Nondiscrimination Act (GINA) of 2008, which protects from health insurance and employment discrimination based on genetic information.

Research done with extra samples must be approved by the IMPAACT Network. The research must also be approved by an institutional review board. The role of an institutional review board is to review the research plan and protect the rights and well-being of children whose samples will be used. Approved research may be done in the United States or other locations. The samples will not be sold or used for commercial profit.

Research done with extra samples is not expected to give information relevant to your child's health. Therefore, the results will not be given you. The results will not be placed in your child's study records.

Your decision whether to allow your child's extra samples to be kept and used for future research will not affect your child's participation in the study. Your child can be in the study whether you say yes or no. If you say no, all extra samples will be destroyed. You will record your decision at the end of this form.

16. You may choose to leave the study at any time or we may need to take your child off the study early.

You are free to take your child off the study at any time for any reason. The care your child receives will not be affected, but it is important that we know your decision.

Some children may have to stop the study drugs and stop the study early. This could happen if:

- Your child is not able to come to the study visits or meet other study requirements.
- During the study pills phase:
 - Your child is not able to use the CAB and RPV pills as instructed.
 - Continuing the study pills may be harmful to your child.
 - The study drugs are not controlling the HIV in your child's blood.
 - Your child is not able to receive the study shots upon completion of the study pills phase.
- The study is stopped for any reason.

- The study doctor determines that continued participation in the study would be unsafe or otherwise not in the best interest of your child.

If your child leaves the study early, we will ask you to bring them back for one last clinic visit.

During this visit, we will:

- Review your child's medical records.
- Ask about your child's health, ARVs, and other medicines.
- Collect any study pills that your child has not taken.
- If your child is old enough, we will ask them some questions about what they think about the study drugs.
- Do a physical exam.
- Draw about 10.5 mL (about 2 teaspoons) of blood for tests. These tests will:
 - Check your child's blood cells, liver, and kidneys.
 - Check your child's HIV viral load.
 - Some blood will also be saved for future resistance testing.
- If your child is at least 9 years old and can become pregnant, we will ask about their sexual activity and collect blood (1 mL or a few drops) or urine for a pregnancy test.
- If your child has received a study shot, then we will also draw about 0.5 mL (a few drops) of blood to check the amount of CAB and RPV in your child's blood.

If your child leaves the study early for any reason, we will tell you where you can go for any care or treatment your child may need. It is very important for your child to keep taking ARVs after leaving the study. We will talk with you about your child's options and help make sure your child can get ARVs from outside the study. We will answer any questions you may have and tell you how to contact us in the future, if you wish.

Risks of the study

17. There are several possible risks of the study.

Taking part in this study may involve some risks and discomfort. Most procedures done in this study are routine medical procedures, with little risk to your child. Study risks include risks from blood draw, risks from receiving shots, risks from the study drugs, and risks to your child's privacy. Your child may feel nervous or embarrassed when answering questions for the study or talking about their answers with you.

18. There are risks from blood draws and receiving shots.

Drawing blood can cause pain, swelling, bruising, or bleeding where the needle is inserted. Rarely, drawing blood can cause fainting or infection.

Receiving shots can cause some people to feel light-headed or feel like they might faint. Some people in other studies who have received CAB and RPV shots have experienced injection site reactions such as:

- pain and discomfort, or a hardened mass or lump (very common);
- swelling, redness, itching, bruising, warmth or discoloration, which may include a collection of blood under the skin (common);
- or cellulitis (heat, swelling or redness), abscess (collection of pus), numbness, minor bleeding, or discoloration (uncommon).

Some reactions may happen quickly, but others may happen a day or two later. Most reactions go away in a week or less, but sometimes they can last longer. Most people do well with them and can continue the study drugs.

A vasovagal reaction, with symptoms like feeling lightheaded or fainting, may sometimes occur. Such reactions have also been reported with other injectable medicines. This reaction usually resolves quickly and is generally not a threat to your child's health.

Post-injection reaction symptoms have happened within minutes in some people after receiving their rilpivirine shot. Most symptoms resolved within a few minutes after the RPV shot. Symptoms of post-injection reactions may include: difficulty breathing, stomach cramps, rash, sweating, numbness of the mouth, blood pressure changes, and pain (back and chest), feeling anxious, feeling warm, or feeling lightheaded or faint. These cases may be due to an accidental injection of part of the medication into a blood vessel instead of the muscle. Not all patients in whom an accidental injection in a blood vessel was suspected reported such symptoms. Most of the symptoms resolved within minutes. Your child's study doctor may need to administer treatment to help resolve these symptoms. Your child will be observed briefly (approximately 10 minutes) after each injection.

Another risk is that the shot could be given too deeply, not deeply enough, or part of the shot may accidentally be injected into the skin only, a blood vessel, or a nerve instead of a muscle. The risks of this are not well understood but could make the CAB or RPV levels in your child's body too high or too low. If too low, the study drug may not work against your child's HIV. If the RPV levels are too high, there could be side effects such as a change in your child's heart beat due to an increase in the QTc interval (change in electrical activity). Very rarely, in severe cases this can be life-threatening and could lead to sudden death; however, no such severe changes in electrical activity or sudden deaths have been observed in clinical studies with RPV. If your study doctor thinks that the shot was not given in the right way, we may need your child to stay in the clinic for extra time for observation or for additional treatment and tests to make sure they are safe.

19. There are risks from the study ARVs

All ARVs can cause side effects. This includes ARVs your child is currently taking and any other ARVs they would receive outside the study. Some side effects are minor, others can be severe. Some side effects are common, others are rare. Some people have some of the side effects. Other people have no side effects.

The most common and most serious side effects of CAB and RPV are listed below. There may be other side effects that we do not know about now. This may be especially true for children, because this is the first study of the CAB and RPV combination for HIV treatment in children under 12 years of age.

If you join the study, we will tell you more about the study drugs you will be taking. At each study visit, we will check on whether the study drugs may be causing side effects. We will also tell you what to do if you have side effects. If you have questions or concerns at any time, please tell us.

20. Side effects from the CAB pills and the CAB shot.

Many adults and a small number of adolescents have received CAB pills or CAB shots in other studies. The table below lists side effects identified from other studies of CAB in people who have HIV.

Common and Uncommon Side Effects of CAB*

Very Common Side Effects of CAB	Common Side Effects of CAB	Uncommon Side Effects of CAB
<ul style="list-style-type: none">• Headache• Pyrexia (fever), feeling hot, body temperature increase	<ul style="list-style-type: none">• Rash• Vomiting (being sick)• Nausea (feeling sick to the stomach)• Abdominal pain, upper abdominal pain (stomach pain and discomfort)• Insomnia (problems sleeping)• Abnormal dreams/nightmares• Anxiety (feeling anxious)• Feeling lightheaded (dizziness)• Depression (feelings of deep sadness and unworthiness)• Flatulence (passing gas or wind)• Diarrhea or loose stools• Myalgia (muscle pain)• Fatigue (lack of energy)• Asthenia (feeling weak)• Malaise (feeling generally unwell)• Weight increase	<ul style="list-style-type: none">• Somnolence (sleepiness or drowsiness)• Hepatotoxicity (liver problems)• Transaminase increase (blood tests may show increase in the level of liver enzymes)

*in addition to risks from receiving shots, as outlined in Section 18.

The following effects have also been seen in some of the people who received CAB in other studies:

Abnormal liver tests:

A small number of people across all studies (just over 1%) had abnormal liver tests requiring them to stop CAB. Some abnormal liver tests were explained by other health conditions such as a new virus infection, like Hepatitis A, B or C. A small number of people did not have health conditions that could explain the abnormal test, so it is possible that a mild form of liver damage happened from taking CAB. The liver tests got better after stopping CAB, showing that any damage was temporary.

Blood tests to check the health of your child's liver will be done during the study. Your study doctor will tell you if your child needs to stop taking the study drugs or if other actions are needed. If your child stops taking the study drug, your child may be able to re-start the study drug or may need to switch to non-study ARVs.

Seizures/convulsions:

Seizures have been seen (rarely) in people with and without HIV who have taken CAB. They are not thought to be caused by CAB, but the study staff will ask you and your child about their occurrence in your child.

If your child has a history of seizures, please let your study doctor know.

21. Side effects from the RPV pills and RPV shot

Oral RPV is a drug that many people throughout the world have received to manage HIV, so we know a lot about it. The following side effects have been seen in people with HIV taking RPV.

Common and Uncommon Side Effects of RPV*

Very common side effects of RPV	Common Side Effects of RPV	Uncommon Side Effects of RPV
<ul style="list-style-type: none"> • Headache • Fever (pyrexia) • Feeling hot • Body temperature increase 	<ul style="list-style-type: none"> • Feeling less hungry (decreased appetite) • Sleep disorders, insomnia (sleeplessness) • Abnormal dreams • Dizziness • Fatigue (lack of energy) • Asthenia • Malaise • Myalgia (muscle pain) • Rash • Depression • Diarrhea • Nausea, vomiting abdominal pain or discomfort (belly ache) • Upper abdominal (belly) pain 	<ul style="list-style-type: none"> • Immune reconstitution syndrome (this can be an overreaction of the body's recovering defense system to a previously present infection, or problems in the immune system) • Depressed mood • Sleepiness (somnolence) • Abdominal (belly) discomfort • Dry mouth • Transaminases increased (increased levels in the blood of certain liver function tests)

*in addition to risks from receiving shots, as outlined in Section 18.

Abnormal blood tests:

Changes in blood tests have been observed. People with Hepatitis B or C, or who have possible liver damage before starting RPV, may have worse liver tests while taking RPV. A few cases of liver problems were found in people taking RPV who did not already have any liver problems.

Sometimes allergic reactions can affect body organs. For example, an allergic reaction can cause liver problems which can lead to liver failure. Contact your study doctor right away if your child has any of the following signs or symptoms of liver problems:

- Yellowing of the skin or whites of the eyes
- Dark or tea colored urine
- Pale colored stools/bowel movements
- Nausea/vomiting
- Loss of appetite
- Pain, aching or tenderness on the right side below the ribs
- Itchy skin

Skin Rash:

Most rashes were mild or moderate, and happened within the first 4 weeks of taking RPV. Most rashes got better after one week, and the people did not need to stop taking RPV. However, the study ARVs will need to be stopped for some types of moderate rash and all types of severe rash, which can be life-threatening. If this happens to your child, your child will need to come for extra study visits to monitor their health. Some people with rash may also have other signs and symptoms of allergic reaction.

If your child has any type of rash or other skin problems during the study you must tell your child's study doctor right away, and the doctor may tell your child to stop taking the study drugs.

22. There may be other possible risks.

The study ARV shots stay in your child's body for a long time

The shots your child gets in this study are long acting, meaning they stay in the body for a long time. In most people, the drugs will no longer be in the body one year after an injection, but in some people, low levels of CAB and RPV may still be in the body.

Children in Cohort 2b will start receiving the study shots when they enter the study and **will not** get exposure to the CAB and RPV pills before getting the first set of study shots. Without having exposure to the CAB and RPV pills, we will not know of any potential reactions or side-effects to CAB and RPV for your child before they receive their first study shots.

If your child develops a side effect to the study drug after the shot, there will be no way to remove the drug from their body. If your child develops a symptom from these drugs while the drugs are still in their body, every effort will be made to treat the side effects. The amount of drug will decrease overtime and will eventually disappear.

If your child stops getting the study shots, the study drugs will stop working to treat HIV, as the amount of medicine in the body decreases slowly over time. When stopping these drugs, it will be very important for your child to start taking other HIV medications, as directed by their doctor.

Risk of switching ARVs

If your child joins this study, they will stop taking their current ARVs and start taking ARVs given by the study. Any time a person switches to ARVs, there is a chance that they could experience new side effects. There is also a chance that the new ARVs may not work as well. For example, the study ARVs may not work as well to control the amount of HIV in your child's body. This is why we test the HIV viral load at

most study visits. If your child's viral load is higher than expected, they will have repeat testing, and may need to stop using the study ARVs.

Risk of resistance

By stopping their previous ARVs and switching to the study ARVs, your child could develop resistance. This could happen if the study ARVs don't work as well to control the amount of HIV in your child's body. Resistance means that if these ARVs are taken again in the future, they may not work against HIV. To prevent resistance, it is important that your child takes and/or receives the ARVs as instructed and does not miss any doses.

Mental illness or depression

Some people with HIV sometimes have feelings of depression or may feel sad or hopeless, feel anxious or restless, or may have thoughts of hurting or killing themselves (suicide). A small number of people being treated with drugs that work the same way as CAB (called integrase inhibitors), have had suicidal thoughts and actions. This is more common in people with a prior history of depression or mental health illness.

Tell the study doctor if your child has a history of mental health illness. If your child is worrying more often, experiencing low mood, having sleep problems, has thoughts of hurting or killing themselves, or has any other unusual or uncomfortable thoughts during this study, you should tell the study doctor or go to the nearest hospital right away.

Possible effects on pregnancy

HIV and ARVs may lead to some pregnancy complications, like early delivery or a low birth weight for the baby. We do not yet know if CAB is safe in pregnancy. There is little information from humans on the effects of CAB in pregnancy, but CAB LA and RPV LA have been detected in the body for up to 12 months or longer after an injection and the effects of the drugs on an unborn baby are currently unknown. The unborn baby would be exposed to CAB and RPV even if injections stop as soon as pregnancy is identified. Most of the information we have is from animal studies. RPV does not appear to be a risk to pregnancy and the developing baby from what we know now, but additional information is still being collected.

Participants who are able to become pregnant and are sexually active must agree to use certain effective methods of birth control to be in this study. If your child becomes pregnant during the study, please let us know right away. We will give you and your child more information about ARV options in pregnancy, including whether it is possible to stay on the study ARVs or not.

Immune reconstitution syndrome

In some people with advanced HIV, signs and symptoms from other infections or certain diseases (for example a liver condition called autoimmune hepatitis) may occur soon after starting combination ARVs or later into treatment. Some of these symptoms may be life threatening. If your child starts having new symptoms, or if you notice that any existing symptoms are getting worse after starting the study drugs, tell your doctor immediately.

Abnormal distribution of body fat and wasting

The use of potent antiretroviral drug combinations may be associated with other body changes, especially related to body fat distribution. Body changes could include an increase in fat around the waist and stomach area or on the back of the neck. There could also be breast enlargement and/or thinning of the face, legs, and arms.

Risks of disclosure of your child's information.

In addition to the risks of study procedures and the study drugs, there is a risk of disclosure of your child's information. We will make every effort to keep your child's information private and confidential. Study records and blood samples will be kept in secure locations. All samples and most records will be labeled only with a code number. However, your and your child's name will be written on some records.

<<To be included at US sites>> U.S. Federal laws protect the privacy of your protected health information ("personal/private information"). However, there are exceptions to these laws. The Researchers will ask you to sign a form ("HIPAA Authorization") to give your permission for certain uses and sharing of your personal (private) information for the study. That form provides more details about the types of information that may be used and shared, and how it will be protected.

<<To be included at South African sites>> In addition, the Protection of Personal Information Act (POPIA) ensures that all South African institutions conduct themselves in a responsible manner when collecting, processing, storing and sharing your personal information by holding them accountable should they abuse or compromise your personal information in any way.

<<All sites to include any other relevant country-specific data-sharing requirements, as applicable>>

<<To be included at US sites>> Your child's privacy may also be protected by a Certificate of Confidentiality that helps us avoid being forced to release information that may identify your child, such as by the courts or police. The certificate cannot be used in all situations, but it can be used to resist demands for information that would identify your child. The certificate does not protect against requests for information from the United States federal government or from the United States Food and Drug Administration. Regardless of the certificate, you can release information about your child's participation in the study to others, if you wish.

The information we collect about your child for this study will be combined with information collected about all other children in the study. This will be done at an organization called a statistical and data management center. The IMPAACT Network statistical and data management center is in the United States. We will send your child's information to this center, but your child's name and other information that could personally identify your child will not be sent. The information will be sent securely, following applicable laws and policies.

Information collected for this study may be used for other research in the future. For example, researchers may use information from this study to try to answer different questions about children with HIV. Any future research done with the information from this study must be approved by the IMPAACT Network. If any future research is done, information about your child may be used. Your child's information will be labeled with a code number, and the only link between the code number and your child's name will be kept here at this clinic.

Despite our best efforts to keep your child's information private, it is possible that your child's information, could be obtained by someone who should not have it. If this were to happen, your child could be treated badly or unfairly.

Benefits of the study

23. There may or may not be benefits to your child from being in the study.

By joining the study, your child will be part of the search for new treatments for children with HIV. There may be a direct benefit to your child by taking part in the study, but we cannot guarantee that being in the study will benefit your child in any way. One possible benefit is that you or your child might prefer getting CAB and RPV as a monthly (or every two months) shot instead of taking pills every day. The study drugs could have fewer side effects than the previous ARVs your child was taking. There may also be benefit if the results from this study lead to a safe and effective dose of the study drugs for children. If your child likes the shots, and they are working well, your child will be able to continue getting them after the study is over. Information learned from this study may help other children who have HIV.

Your child will have regular visits here and frequent checks on their health, including their HIV viral load. It is possible the study ARVs will slow the progress of HIV in your child.

Other information about the study

24. There are no costs to you for your child being in the study.

There are no costs to you or your child for study visits or procedures, or the study drugs.

<<Sites insert information about compensation/reimbursement here.>> You will be reimbursed for the cost of transport to study visits and your time spent here. For each visit, you will be given <<specify amount>>.

25. Your child's records may be reviewed by study staff and groups that oversee the study.

Groups that oversee the study include:

- <<U.S. sites insert sIRB>>
- <<Sites insert local IRBs/ECs as applicable>>
- <<Sites insert applicable drug regulatory authorities and other regulatory entities>>
- The United States National Institutes of Health and its study monitors
- The United States Food and Drug Administration
- The United States Office for Human Research Protections
- Other United States, local, and international regulatory entities
- The IMPAACT Network that is coordinating the study
- The companies that make the study drugs, ViiV Healthcare and Janssen Research and Development

Like the study staff, these groups are required to make efforts to keep study records private and confidential.

The results of the study may be presented publicly or published. However, no presentation or publication will use your child's name or identify your child personally.

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov> as required by US Law. This Web site will not include information that can identify your child. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Your child's study information may be disclosed to other authorities if required by law. <<Sites may add more specific detail here describing local laws that may be applicable.>>

26. If your child gets sick or injured, contact us immediately.

Your child's health is important to us. We will make every effort to protect your child's well-being and minimize risks. It is possible, however, that your child could have an illness or injury that is study-related. This means that the illness or injury occurred as a direct result of being in the study.

<<Sites may modify this paragraph to reflect local institutional policies; information regarding coverage available through clinical trial insurance obtained by the site should be included if applicable; the statement regarding no program for compensation through the NIH may not be removed.>> If a study-related illness or injury occurs, we will treat your child or tell you where you can get the treatment your child needs. The cost for this treatment may be charged to you or your health insurance. There is no program to pay money or give other forms of compensation for study-related illness or injury through <<site name>> or the United States National Institutes of Health.

Who to contact

27. If you have questions, concerns, or problems at any time, use these contacts.

If you have questions, concerns, or problems at any time, use these contacts.

- If you have questions about the study or your child's health, or if you want your child to leave the study:
<<Name, phone number, and other relevant contact details of investigator or other study staff>>
- If you have questions about your child's rights as a study participant, or problems or concerns about how your child is being treated in the study:
<<Name, phone number, and other relevant contact details of IRB contact person or other appropriate person or organization; US sites to include sIRB contact information>>

Permission for Long Term Specimen Storage and Future Use

Please write your initials or make your mark next to your choice for whether your child's extra samples can be kept and used for future research.

_____ I allow my child's extra samples to be used for research on HIV, ARVs, the immune system, and other diseases. I also allow my child's samples to be used for tests of their genes.

_____ I allow my child's extra samples to be used for research on HIV, ARVs, the immune system, and other diseases. I do not allow my child's samples to be used for tests of their genes.

_____ I do not allow my child's extra samples to be used for any research.

Permission for Off-Site Visits

On rare occasions, members of the research team may be able to schedule visit activities off-site at your home or at another location. Before any visits take place off-site, the study staff will discuss the location and time so that the visit is conducted at a convenient time and done in a place you and your child feel comfortable and where confidentiality can be maintained. To conduct visits outside of the clinic, we will also need you to give us your written permission to do so.

Please read the following statements carefully and write your initials or make your mark next to the option you prefer.

_____ I do agree to have study visits at a location other than the study clinic, when necessary.

_____ I do not agree to have study visits at a location other than the study clinic, when necessary.

Signatures

If you decide to have your child join this study, please write your initials or make your mark next to the group you choose for your child, Cohort 2a or Cohort 2b. Then, sign or make your mark below.

Before deciding whether to have your child join this study, make sure you have read this form or had it read to you. Make sure all your questions have been answered. You should feel that you understand the study, its risks and benefits, and what is expected of you and your child.

We will tell you any new information from this study or other studies that may affect your willingness to keep your child in the study. You are welcome to ask questions or request more information at any time.

You do not give up any rights by signing this form.

<<Sites insert signature blocks as required by IRB and institutional policies.>>

_____ I agree for my child to join the Cohort 2a group. I understand that this group will have the study pills first and then the study shots. I understand that my child cannot switch groups after entering the study.

_____ I agree for my child to join the Cohort 2b group. I understand that this group will have the study shots and skip the study pills phase. I understand that my child cannot switch groups after entering the study.

Name of Child
(print)

Name of Parent or Legal Guardian
(print)

Parent or Legal Guardian Signature

Date

Name of Witness
(if applicable, print)

Witness Signature

Date

Study Staff Conducting
Permission Process Name (print)

Study Staff Signature

Date

**Appendix IV-C: Parent/Caregiver Behavioral Assessment Sample Informed Consent Form
for parent/caregiver enrollment into**

IMPAACT 2036

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

Version 1.0, 22 September 2022

Sponsor / Study Title: National Institutes of Health (NIH) / National Institute of Allergy and Infectious Diseases (NIAID) / National Institute of Child Health and Human Development (NICHD) / National Institute of Mental Health (NIMH) / “CRAYON”

Protocol Number: IMPAACT 2036

Principal Investigator: <<PI Full Name>>
(Study Doctor)

Telephone: <<Phone Number>>

Address: <<Location>>

Introduction

You are being asked to take part in the research study named above. This is a separate process from the request to have your child participate in the study.

This form gives information about your role in the study. Please read it, or have it read to you, and ask any questions you may have. We will take as much time as needed for you to fully understand your role in the study. At the end, we will ask you questions to see if we have explained everything clearly.

Here is a summary of important information about this part of the study:

- If you participate in this part of the study, we will ask you questions about your experience and your child’s experience with the study drugs. You may also be asked to complete one longer interview, either in person or over the phone.
- Your participation is voluntary. You do not have to participate for your child to be in the study and your child’s medical care will not be affected by your choice.
- There may be risks to participating in the study, like risks of disclosure of your information. We will make every effort to avoid this.
- There may be no direct benefit to you from taking part in the study.

After you understand your role in the study, and if you decide that you will participate, you will be asked to sign or make your mark on this form. You will be offered a copy to keep.

It is your decision whether or not you join the study.

Deciding to join the study is voluntary. You may choose to join or not join. If you choose to join, you can change your mind and stop the study at any time. You do not have to be in this study for your child to participate in the study. Your child's medical care will not be affected by your choice. You may also qualify for other studies. Please ask any questions you may have about these alternatives.

Your role in the study

Approximately 90 parents/caregivers of child participants will participate in this study. If you agree to join the study, you will be asked to complete several questionnaires throughout your child's study participation. The questions will mostly focus on how you think your child felt about the study drugs (CAB and RPV pills and/or study shots). Some questions will also ask about your opinions of the study drugs. This information will help us understand what people do or do not like about the study drugs, how children feel about getting the study drugs as a shot, and if there are any side effects for children who receive them. For most parents/caregivers, there will be 5 or 6 visits when we ask these questions. Answer the questions should take less than an hour. These visits will happen at the same time as your child's study visits. However, if you are unable to come to one of these visits, then you can come at a separate time or complete the questions over the phone.

Approximately 30 parents/caregivers will also complete a longer interview, either in person or over the phone. This may happen after your child has been in the study for about 5 or 6 months. Not all parents/caregivers will be asked to complete an interview. If you are selected, you will only complete one interview. It will take about 1-2 hours. We will schedule the interview at a time that works for you. During the interview, we will ask you about topics that are similar to the topics on the study questionnaires, like how you felt about your child receiving study shots. The interview will be audio recorded and written down.

There are no costs to you for being in the study.

There are no costs to you for any of the questionnaires or the interview, if you are selected.

<<Sites to insert information about compensation/reimbursement here, e.g., You will be reimbursed for your time, and given (specify amount).>>

Possible Risks

There could be risks of disclosure of your information. We will make every effort to keep your information private and confidential. Your and your child's names will not be included in any of the questionnaires or in the recording of the interview. Most study records and the interview will only be labeled with a code number.

<<To be included at US sites>> U.S. Federal laws protect the privacy of your protected health information ("personal/private information"). However, there are exceptions to these laws. The Researchers will ask you to sign a form ("HIPAA Authorization") to give your permission for certain uses and sharing of your personal (private) information for the study. That form provides more details about the types of information that may be used and shared, and how it will be protected.

<<To be included at South African sites>> In addition, the Protection of Personal Information Act (POPIA) ensures that all South African institutions conduct themselves in a responsible manner when collecting, processing, storing and sharing your personal information by holding them accountable should they abuse or compromise your personal information in any way.

<<All sites to include any other relevant country-specific data-sharing requirements, as applicable>>

<<To be included at US sites>> Your privacy may also be protected by a Certificate of Confidentiality that helps us avoid being forced to release information that may identify you, such as by the courts or police. The certificate cannot be used in all situations, but it can be used to resist demands for information that would identify you. The certificate does not protect against requests for information from the United States federal government or from the United States Food and Drug Administration. Regardless of the certificate, you can release information about your participation in the study to others, if you wish.

It is unlikely that you will get sick or injured as a result of your study participation. <<Non-US sites may modify this paragraph to reflect local institutional policies; information regarding coverage available through clinical trial insurance obtained by the site should be included if applicable; the statement regarding no program for compensation through the NIH may not be removed.>> If a study-related illness or injury occurs, we will treat you or tell you where you can get the treatment you need. The cost for this treatment may be charged to you or your health insurance. There is no program to pay money or give other forms of compensation for study-related illness or injury through <<site name or>> the United States National Institutes of Health.

Possible Benefits

By joining the study, you will be part of the search for HIV medication that may be better for children. There may be no direct benefit to you from taking part in this study. There may be a benefit if the results from this study lead to a safe and effective dose of the study drugs for children. Information learned from this study may help other children who have HIV.

Other information about the study

Study records may be reviewed by study staff and groups that oversee the study. Groups that oversee the study include:

- <<U.S. sites insert sIRB>>
- <<Sites insert local IRBs/ECs as applicable>>
- <<Sites insert applicable drug regulatory authorities and other regulatory entities>>
- The United States National Institutes of Health and its study monitors
- The United States Food and Drug Administration
- The United States Office for Human Research Protections
- Other U.S., local, and international regulatory entities
- The IMPAACT Network that is coordinating the study
- The companies that make the study drugs, ViiV Healthcare and Janssen Research and Development

Like the study staff, these groups are required to make efforts to keep study records private and confidential.

The results of the study may be presented publicly or published. However, no presentation or publication will use your name or identify you.

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov> as required by US Law. This Web site will not include information that can identify your child. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Your study information may be disclosed to other authorities if required by law. <<*Sites may add more specific detail here describing local laws that may be applicable.*>>

Who to Contact

During the study, if you have questions, concerns, or complaints about the study, please contact the study doctor at the telephone number listed on the first page of this consent document.

An institutional review board (IRB) is an independent committee established to help protect the rights of research participants. If you have any questions about your rights as a research participant, and/or concerns or complaints regarding this research study, contact the IRB:

<<*Name, phone number, and other relevant contact details of IRB/EC contact person or other appropriate person or organization*>>

Consent for Off-Site Visits

On rare occasions, members of the research team may be able to schedule visit activities off-site at your home or at another location. Before any visits take place off-site, the study staff will discuss the location and time so that the visit is conducted at a convenient time and done in a place you feel comfortable and where confidentiality can be maintained. To conduct visits outside of the clinic, we will also need you to give us your written permission to do so.

Please read the following statements carefully and write your initials or make your mark next to the option you prefer.

_____ I do agree to have study visits at a location other than the study clinic, when necessary.

_____ I do not agree to have study visits at a location other than the study clinic, when necessary.

Signatures

If you agree to participate in this study, please sign or make your mark below.

Before deciding whether to participate in this study, make sure you have read this form, or had it read to you, and that all of your questions have been answered. You should feel that you understand the study, its risks and benefits, and what is expected of you if you decide to join. You are welcome to ask questions or request more information at any time.

You do not give up any rights by signing this form.

Name of Parent/Caregiver
(print)

Signature of Parent/Caregiver

Date

Name of Study Staff Conducting
Consent Process Name (print)

Signature of Study Staff

Date

Name of Witness
(as appropriate; print)

Signature of Witness

Date

**Appendix IV-D: Sample Parental Permission Form for Continued Study Product Use During
Pregnancy
for parent/legal guardian of child participant**

**IMPAACT 2036
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Acting Injectable Cabotegravir and Rilpivirine in Virologically Suppressed Children Living with
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Sponsor / Study Title: National Institutes of Health (NIH) / National Institute of Allergy and Infectious Diseases (NIAID) / National Institute of Child Health and Human Development (NICHD) / National Institute of Mental Health (NIMH) / “CRAYON”

Protocol Number: IMPAACT 2036

Principal Investigator: <<PI Full Name>>
(Study Doctor)

Telephone: <<Phone Number>>

Address: <<Location>>

Introduction

<<Sites to modify form, as needed, based upon whether the pregnant participant or parent/legal guardian is required to provide consent per local laws and regulations>>

You are being asked to review and sign this form because you previously signed a form permitting your child to participate in IMPAACT 2036. Everything in the main study permission form still applies to your child's participation in this study unless otherwise noted in this form.

Now that your child has become pregnant while in the study, we wanted to provide some additional information about using the study products, Cabotegravir (CAB) and Rilpivirine (RPV) during pregnancy. When your child became pregnant, the study team reviewed their medical history and determined that you and your child could decide whether to continue receiving CAB and RPV shots or not. Please read this form and ask any questions that you have. When your questions have been answered, sign the page at the end of this form to indicate whether you would like your child to continue receiving CAB and RPV shots while pregnant. Your child's care provider may enter information about their pregnancy and the medications you take in the Antiretroviral Pregnancy Registry: <http://www.apregistry.com/>. The registry helps doctors learn more about the effects of antiretroviral use during pregnancy. No identifying information will be included.

There may be benefits to continuing CAB and RPV shots during pregnancy.

Receiving the study shots may be more convenient than taking pills every day or may be a better option for pregnant people who have trouble taking medications by mouth due to morning sickness (nausea during pregnancy).

There may also be risks to continuing CAB and RPV shots during pregnancy.

HIV and ARVs may lead to some pregnancy complications, like early delivery or a low birth weight for the baby. RPV does not appear to be a risk to pregnancy and the developing baby from what we know now, but additional information is still being collected. We do not yet know if CAB is safe in pregnancy. Most of the information we have is from animal studies. There is little information from humans on the effects of CAB in pregnancy, but long-acting CAB and RPV have been detected in the body for up to 12 months or longer after an injection and the effects of the drugs on an unborn baby are currently unknown. Since CAB and RPV will still be in your child's body for some time, the unborn baby may have some exposure to the study drugs even if injections stop as soon as pregnancy is identified. There is currently no data on whether the study drugs pass into breast milk and, if so, whether this may produce bad effects in the infant. It is also unknown whether taking study drugs will reduce the risk of passing HIV to the baby while breast feeding.

It is important to know that the correct dose of CAB and RPV during pregnancy is not known, but if you and your child decide to continue receiving the shots, we will continue doing tests to check the amount of HIV virus in your child's body and the amount of CAB and RPV in your child's blood to make sure the medication is working well for them.

Your visit schedule may be impacted by your decision

If you and your child decide to continue receiving CAB and RPV shots, there will not be any changes to your child's study visit schedule or the procedures we perform at each visit, but your child will remain in the study throughout their entire pregnancy. We will ask your child some questions about their delivery and the health of their baby.

If you or your child decide not to continue receiving the shots while pregnant, your child will switch from shots to other non-study ARVs and join the long-term safety follow-up phase instead. As a reminder, participants who are in the long-term safety follow-up phase will not receive any study drugs, but will have 5 follow-up visits, scheduled 4, 8, 24, 36, and 48 weeks after a positive pregnancy test. [<<Sites to modify>>](#) Each of these visits will take about 1-3 hours. At these visits, we will:

- Review your child's medical records.
- Ask about your child's health, ARVs, and other medicines.
- Do a physical exam.
- Draw about 10.5 mL (about 2 teaspoons) of blood for tests. These tests will:
 - Check your child's blood cells, liver, and kidneys.
 - Check your child's HIV viral load.
 - Check the amount of CAB and RPV in your child's blood.

No matter what you or your child decide, it is important that your child takes ARVs during their new pregnancy. Taking ARVs is the best-known way to stay healthy and avoid passing HIV to their baby.

Who to contact

If you have questions, concerns, or problems at any time, use these contacts.

If you have questions, concerns, or problems at any time, use these contacts.

- If you have questions about the study or your child's health, or if you want your child to leave the study:
<<Name, phone number, and other relevant contact details of investigator or other study staff>>
- If you have questions about your child's rights as a study participant, or problems or concerns about how your child is being treated in the study:
<<Name, phone number, and other relevant contact details of IRB contact person or other appropriate person or organization; US sites to include sIRB contact information>>

Signatures

Please write your initials or make your mark next to the option that represents your decision about continued CAB and RPV use during your child's pregnancy. Then, sign or make your mark below.

Before making your decision, make sure you have read this form or had it read to you. Make sure all your questions have been answered. You should feel that you understand the options, their risks and benefits, and what is expected of you and your child.

We will tell you any new information from this study or other studies that may affect your decision. You are welcome to ask questions or request more information at any time.

You do not give up any rights by signing this form.

<<Sites insert signature blocks as required by IRB and institutional policies.>>

_____ I agree for my child to continue receiving CAB and RPV shots during pregnancy.

_____ I do not agree for my child to continue receiving CAB and RPV shots during pregnancy and prefer for my child to switch to non-study ARVs.

Name of Child
(print)

Name of Parent or Legal Guardian
(print)

Parent or Legal Guardian Signature

Date

Name of Witness
(if applicable, print)

Witness Signature

Date

Study Staff Conducting
Consent Process Name (print)

Study Staff Signature

Date

Appendix V: Sample Informed Assent Forms

Appendix V-A: Sample Informed Assent Form for Study Participation in Cohort 1 for children who cannot provide independent informed consent for study participation

IMPAACT 2036

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

Version 1.0, 22 September 2022

FOR CHILD PARTICIPANTS

You are being asked to take part in a research study. For you to take part, you must give your permission. Your caregiver/legal guardian must also give permission.

This form gives information about the study. Please read it or have it read to you. Ask any questions you may have. After we talk about the study with you, we will ask if you want to take part. You can say yes or no. If you say yes, you will sign your name on this form. You can take a copy home with you.

It is okay to say no if you do not want to be in the study. It is also okay to say yes now but change your mind later and leave the study. Please talk this over with your caregiver/legal guardian. Even if your caregiver/legal guardian gives permission for you to be in the study, you can still say no. No one here will be upset with you no matter what you decide.

Why we are doing the study

The study is to learn about how certain drugs work in children. The drugs you will take in this study will replace some of the drugs you are already taking. Studies of these drugs have been done in the past, but not in children your age. We want to study these drugs to learn the right amount to give children, and to understand if they are safe. Up to 90 children will be part of this study.

What happens in the study

We will first ask some questions, review your health records, and examine you (check your body) to see if you can join the study.

If you join the study, you will come here about once or twice a month for a little less than a year and a half. Most of the visits will take 1-3 hours, but some of the visits may be longer. At the beginning of the study, you will take some pills at the clinic and at home. The pills might be swallowed whole or dissolved in a drink first. After a month or two, you will stop taking the pills and get the medicine as a shot instead. The shots will be given once a month or once every other month.

At each visit, we will ask questions about your health and the drugs you take. We will examine you and see how much you have grown. We will take some blood from your arm with a needle. At some visits we will do a test to look at your heart. When you are taking the pills, you may be asked to have a visit when you stay at the clinic for a full day and have your blood drawn several times. This is done to very closely measure the amount of medicine in your blood over time. Participants who can become pregnant must agree to use certain methods of birth control to take part in the study. If you become pregnant during the study, you may have to stop the study drugs.

Please tell us if anything bothers you or scares you. We will do our best to explain the study and help you feel more comfortable.

What good and bad things could happen

There may not be any good things that happen to you from being in the study. But, the study drugs may work well to keep you healthy or you may like getting a shot instead of having to take pills every day. Information learned in the study may help other children in the future.

It may hurt when we give you a shot or take your blood. The study drugs may not work well for you. They could cause bad effects. For example, they could make you feel sick. We will ask you to tell your parent/legal guardian any time you do not feel well. You and your parent/legal guardian should also tell us if you do not feel well. We will ask you to come here so we can check on you and try to make you feel better. You also may feel nervous or embarrassed when answering questions for the study.

Other people could find out that you are in the study or learn other information about you. We will make every effort to avoid this. For example, most of the records we keep here for the study will be labeled with a code number (not your name). We will not share your information with other people unless you or your parent/guardian ask us to.

If you have questions

Please ask any questions you may have. You can ask now or later. You may talk to the doctor or someone else. We will tell you if we learn any new information about the study medicines or other things that may be important for you to know.

Signatures

Name of Participant (print)

Signature of Participant

Date

Name of Study Staff Conducting
Assent Process Name (print)

Signature of Study Staff

Date

Name of Witness
(as appropriate; print)

Signature of Witness

Date

**Appendix V-B: Sample Informed Assent Form for Study Participation in Cohort 2
for children who cannot provide independent informed consent for study participation**

IMPAACT 2036

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

Version 1.0, 22 September 2022

FOR CHILD PARTICIPANTS

You are being asked to take part in a research study. For you to take part, you must give your permission. Your caregiver/legal guardian must also give permission.

This form gives information about the study. Please read it or have it read to you. Ask any questions you may have. After we talk about the study with you, we will ask if you want to take part. You can say yes or no. If you say yes, you will sign your name on this form. You can take a copy home with you.

It is okay to say no if you do not want to be in the study. It is also okay to say yes now but change your mind later and leave the study. Please talk this over with your caregiver/legal guardian. Even if your caregiver/legal guardian gives permission for you to be in the study, you can still say no. No one here will be upset with you no matter what you decide.

Why we are doing the study

The study is to learn about how certain drugs work in children. The drugs you will take in this study will replace some of the drugs you are already taking. Studies of these drugs have been done in the past, but not in children your age. We want to study these drugs to learn the right amount to give children, and to understand if they are safe. Up to 90 children will be part of this study.

What happens in the study

We will first ask some questions, review your health records, and examine you (check your body) to see if you can join the study. If you can join the study, you will be able to choose between two different groups. If you join the first group, you will begin the study by taking pills. The pills might be swallowed whole or dissolved in a drink first. You will take some pills at the clinic and some at home. After a month or two, you will stop taking the pills and get the medicine as a shot instead. The shots will be given once a month or once every other month. If you join the second group, you will skip the pills phase and start receiving the study shots right away. Both groups will get the same number of study shots.

You will decide with your caregiver/legal guardian and doctor which group is best for you. After you join one group, you will stay in that group until the end of the study, and you will not be able to switch to the other group.

If you join the study, you will come here about once or twice a month about a year. For both groups, most of the visits will take 1-3 hours, but some of the visits may be longer.

At each visit, we will ask questions about your health and the drugs you take. We will examine you and see how much you have grown. We will take some blood from your arm with a needle. At some visits we will do a test to look at your heart. Participants who can become pregnant must agree to use certain methods of birth control to take part in the study. If you become pregnant during the study, you may have to stop the study drugs.

Please tell us if anything bothers you or scares you. We will do our best to explain the study and help you feel more comfortable.

What good and bad things could happen

There may not be any good things that happen to you from being in the study. But, the study drugs may work well to keep you healthy or you may like getting a shot instead of having to take pills every day. Information learned in the study may help other children in the future.

It may hurt when we give you a shot or take your blood. The study drugs may not work well for you. They could cause bad effects. For example, they could make you feel sick. We will ask you to tell your parent/legal guardian any time you do not feel well. You and your parent/legal guardian should also tell us if you do not feel well. We will ask you to come here so we can check on you and try to make you feel better. You also may feel nervous or embarrassed when answering questions for the study.

Other people could find out that you are in the study or learn other information about you. We will make every effort to avoid this. For example, most of the records we keep here for the study will be labeled with a code number (not your name). We will not share your information with other people unless you or your parent/guardian ask us to.

If you have questions

Please ask any questions you may have. You can ask now or later. You may talk to the doctor or someone else. We will tell you if we learn any new information about the study medicines or other things that may be important for you to know.

Signatures

_____ Name of Participant (print)	_____ Signature of Participant	_____ Date
_____ Name of Study Staff Conducting Assent Process Name (print)	_____ Signature of Study Staff	_____ Date
_____ Name of Witness (as appropriate; print)	_____ Signature of Witness	_____ Date

**Appendix: V-C: Sample Inform Assent Form for Continued Study Product Use during Pregnancy
for children who cannot provide independent informed consent for study participation**

IMPAACT 2036

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

Version 1.0, 22 September 2022

FOR CHILD PARTICIPANTS

You are being asked to review this form because you (or your parent/legal guardian) previously gave your permission to take part in a research study. Everything you agreed to before is still true for your participation in the study unless the information given here says otherwise.

Now that you are pregnant, we want to give you more information about getting the study drugs while pregnant. When we found out you were pregnant, the study doctors reviewed your health records and decided that you may continue to get the study drugs if you want to. For you to continue to get the study drugs while pregnant, you must give your permission. Your caregiver/legal guardian must also give permission.

This form gives more information about continuing to get the drugs for this research study while you are pregnant. Please read this form or have it read to you. Ask any questions you may have. When you finish reviewing this form, we will ask you if you want to continue getting the study drugs while you are pregnant. You can say yes or no. If you say yes, you will sign your name on this form. You can take a copy home with you.

It is okay to say no if you do not want to continue getting the study drugs now that you are pregnant. It is also okay to say yes now but change your mind later. Please talk this over with your caregiver/legal guardian. Even if your caregiver/legal guardian gives permission for you to continue to get the study drugs, you can still say no. No one here will be upset with you no matter what you decide.

What happens if you continue to be in the study while pregnant

If you decide to continue getting the study drugs now that you are pregnant, you will continue to come here about once a month or once every other month to get the shots and other tests you have been receiving. The study shots will end when they were supposed to end if you were not pregnant, but you will stay in the study during your entire pregnancy.

If you decide to not continue getting the study drugs now that you are pregnant, you will stop getting the shots. You and your parent/legal guardian will talk with your doctor to decide what medicine to take during your pregnancy. You will have five more visits here that take about 1-3 hours. At these visits, we will take blood and do other tests to make sure the medicine you are taking is keeping you healthy.

What good and bad things could happen

There may not be any good things that happen to you if you continue to get the study drugs while you are pregnant. But, continuing to get the shots may be easier than taking pills every day.

We do not have a lot of information on how these shots may affect your pregnancy or your baby. We also do not know how much of the drugs in each shot is needed for you now that you are pregnant. We will continue to draw your blood to measure the amount of medicine in your blood and do other tests to make sure the shots are working well for you.

If you have questions

Please ask any questions you may have. You can ask now or later. You may talk to the doctor or someone else. We will tell you if we learn any new information about the study medicines or other things that may be important for you to know.

Signatures

Name of Participant (print)

Signature of Participant

Date

Name of Study Staff Conducting
Assent Process Name (print)

Signature of Study Staff

Date

Name of Witness
(as appropriate; print)

Signature of Witness

Date

Appendix VI: Study Product Preparation Requirements for the CAB DT, RPV 2.5mg tablets, and Long-Acting Injectables

This appendix provides requirements for the CAB dispersible tablets (DT), RPV 2.5mg tablets, and long-acting (LA) injectable study product preparation for both CAB and RPV. The study product regimen, administration, formulation, storage requirements, supply and other relevant information is described in protocol [Section 5](#) Study Product. The IMPAACT 2036 MOP provides additional details and guidance regarding study product ordering, prescribing, short-term storage, and administration.

The investigational pharmacist(s) must be proficient in the preparation of injectable study products using aseptic technique under a pharmacy biological safety cabinet (BSC) Class II or better isolator. Local regulations and site institutional policies and procedures for use of personal protective equipment, such as gloves, gowns, masks, and safety glasses, must be followed.

Suggested supplies for CAB LA and RPV LA:

- BD 5-mL syringe, Luer-Lok Tip, Reference No.: 309646, or equivalent
- BD 3-mL syringe, Luer-Lok Tip, Reorder No.: 309585, 309657, or equivalent
- Needle for aspiration: BD Precision Glide Needle, 21G 1 inch, Reference No.: 305165, or equivalent
- Needle for intramuscular injection:
 - 23G x 1.5" SurGuard Safety Hypodermic Needle CE MARKED Mfg Catalog Number: SG3-2338 (Central Supply as applicable per country)
 - BD Precision Glide Needle, 23G 1.5", Reference No.: 305194, or equivalent

Variable needle lengths (e.g., 1.5 inch, 2 inch) and/or needles with different gauge (CAB LA: 21 to 25 gauge; RPV LA: 21 to 23 gauge) are permitted if needed to accommodate individual body types. Needle size and gauge appropriate for IM injections in children should be used.

NOTE: 25G needle is not permitted for administration of RPV LA.

Appendix VI-A: CAB 5mg Dispersible Tablet Preparation Requirements

NOTE: Instructions below must be followed by participants in Cohort 1. Cohort 2a participants who will be using CAB dispersible tablets (DT) may disperse the tablets in liquid before ingesting, as described below, or may swallow the tablets whole (the tablets should not be chewed), followed by swallowing liquid to push the medications to the stomach. See protocol [Section 5.3.1](#) for more information.

Instructions for dispersing CAB 5mg DT:

Pour the amount of clean drinking water into the study provided dosing cup needed for the prescribed dose:

- 10 mg (2 tablets) = 5 mL of drinking water
- In the event of a dose modification, instructions for preparing potential alternative dosing for CAB 5 mg DT are as follows:
 - 5 mg (1 tablet) = 5 mL of drinking water
 - 15 mg (3 tablets) = 10 mL of drinking water
 - 20 mg (4 tablets) = 10 mL of drinking water
 - 25 mg (5 tablets) = Split dose: 2 tablets in 5 mL, then 3 tablets in 10 mL

Use clean drinking water only, **do not** use any other drink or food to prepare the dose.

Add the prescribed number of tablets to the water. Do not cut or crush the tablets before adding them to the water.

Swirl the dosing cup gently for a minimum of 2 minutes to disperse the tablets. The medicine will become cloudy. Take care not to spill any of the medicine.

Check that the medicine is ready. If there are any lumps of tablet remaining, swirl the cup until they are all gone.

If any medicine is spilled, throw away the rest of the prepared medicine and make a new dose.

The dose of medicine must be given within 30 minutes of preparing the dose. If it has been more than 30 minutes wash the dose away and prepare a new dose of medicine.

Make sure that the child is upright. Give all the prepared medicine to the child.

Add another 5 mL or less of drinking water to the dosing cup, swirl and give it all to the child.

Repeat if any medicine remains to make sure the child gets the full dose.

Wash the dosing cup with water. The dosing cup will need to be clean before preparing the next dose.

Storage information

Keep the tablets in the bottle. Keep the bottle tightly closed.

The bottle contains a desiccant canister which helps to keep the tablets dry.

Do not eat the desiccant canister.

Do not remove the desiccant canister from the bottle.

Keep all medicine out of the reach of children.

Appendix VI-B: RPV 2.5mg Tablet Preparation Requirements

NOTE: Instructions below must be followed by participants in Cohort 1. Cohort 2a participants who will be using RPV 2.5mg tablets may disperse the tablets in liquid before ingesting, as described below, or may swallow the tablets whole, followed by swallowing liquid to push the medications to the stomach. See protocol [Section 5.3.1](#) for more information.

Instructions for dispersing RPV 2.5mg tablets:

What you need to prepare the study drug

- Rilpivirine 2.5mg tablets
- A drinking glass or cup
- Spoon or plastic stirrer (no wooden spoon)
- Approximately 50 ml of water or other drink (see below what drinks are allowed) to disperse the tablets according to the following tables.

Visit	Drinks (room temperature recommended)
<i>All doses through Week 2 Visit</i>	Non-fizzy clean drinking water ONLY
<i>After Week 2 visit</i>	Non-fizzy clean drinking water
	Apple juice; orange juice
	Low fat milk (about 2-3% fat)
	Fizzy water

How to prepare and take the study mixture:

Prepare the study mixture on a clean countertop.

Prepare the study mixture as per the instructions given below:

1. Take the required number of tablets from the package. Place them into a glass or cup.
 - 12.5 mg = 5 tablets
 - 15mg = 6 tablets
 - In the event of a dose modification, instructions for preparing potential alternative dosing for RPV 2.5mg tablets are as follows:
 - 2.5 mg = 1 tablet
 - 5 mg = 2 tablets
 - 7.5 mg = 3 tablets
 - 10 mg = 4 tablets
 - 20 mg = 8 tablets
2. Add two tablespoons (~30ml) of water/drink mentioned above to the glass or cup. You can use a larger amount if you wish to.
3. Let the tablet(s) sit in the water/drink for about 5 minutes.
4. Swirl the water/drink in the glass or cup gently for about 30-40 seconds or until the tablets have dispersed (fallen apart) and are fully mixed. Use the spoon or plastic stirrer to stir the mixture. If any large tablet pieces are seen, gently press those against the inner wall of the glass or cup to break them. Ensure the tablet/s have dispersed completely.
5. The child should drink all the mixture within 30 minutes of preparing the dose.

If there is any residue still visible in the glass or cup, follow Steps 6 to 8 to ensure the child takes the full dose of the medication:

6. Rinse the glass or cup with a small amount (two tablespoons) of water/drink.
7. Your child should drink all the mixture within 30 minutes of preparing the dose.
8. Check that no study drug is left in the glass or cup.

Appendix VI-C: CAB LA Injectable Preparation Requirements

I. Preparation of CAB LA 600mg/3mL (using one 600 mg/3mL vial or two 400 mg/2 mL vials)

One syringe containing 3 mL (600 mg) of CAB LA study product must be prepared using aseptic technique under a pharmacy BSC/isolator.

1. Remove one 3-mL CAB LA vial or two 2-mL CAB LA vials (as available) from storage. If CAB LA vials are stored in the refrigerator (2°C to 8°C), remove vial(s) from the refrigerator and wait at least 15 minutes to equilibrate to room temperature. Record the time when vial(s) were removed from the refrigerator.
2. Remove vial(s) from the carton and vigorously shake the vial for a full 10 seconds by shaking the vial with long arm movements.
3. Invert the vial(s) and inspect to ensure complete re-suspension. If sediments are observed, repeat Steps 2-3 until all material is uniformly suspended. After re-suspending, it is recommended to use the suspension immediately.
4. Using aseptic technique under a pharmacy biological safety cabinet, flip off the plastic cap from the vial(s). Wipe the top of the vial(s) with disinfecting tissue of isopropyl alcohol 70% or similar and allow the alcohol to dry.
5. Remove one 5-mL syringe and aspiration needles from the blister pouch (see suggested supplies). Take one aspiration needle and attach the needle to the Luer-Lok connection of the syringe.
6. If using one 3-mL CAB LA vial:
 - With the sheath on the needle, pull back on the syringe plunger to allow approximately 1 mL of air into the syringe. Pull the needle sheath off the needle with a straight pull.
 - Push the needle through the stopper of the vial and inject 1mL of air into the vial by putting the vial in the inverted position while the needle and syringe are in the upright position.
 - Withdraw the entire contents (3 mL) of the vial into the syringe. Because the suspension can contain some air after having shaken the vial, take out enough suspension in order to be able to de-aerate the syringe properly (Step 9).
 - Record the time withdrawn into the syringe.
7. If using two 2-mL CAB LA vials:
 - With the sheath on the needle, pull back on the syringe plunger to allow approximately 1 mL of air into the syringe. Pull the needle sheath off the needle with a straight pull.
 - Push the needle through the stopper of the first vial and inject 1 mL of air into the vial by putting the vial in the inverted position while the needle and syringe are in the upright position.
 - Withdraw 1.5 mL of suspension from the first vial and put vial aside.
 - Remove the needle from the syringe and attach a new aspiration needle. Repeat the steps above to withdraw 1.5 mL of suspension from the second vial, for a total of 3 mL from two vials. Because the suspension can contain some air after having shaken the vial, take out enough suspension in order to be able to de-aerate the syringe properly (Step 9).
 - Record for each individual vial the time withdrawn into the syringe.

8. Keep the syringe with the needle in the upright position and remove the needle that was used to withdraw the suspension and discard it appropriately. Attach the needle for intramuscular administration to the Luer-Lok connection of the syringe or attach a syringe cap (per site's SOP). Consult with clinic staff regarding the recommended needle for IM administration (see suggested supplies).
9. De-aerate the syringe by first tapping with a finger against the syringe and then by moving the plunger rod carefully forward with the needle in upright position until a drop of suspension appears. Remove the excess suspension in order to administer the correct volume (3 mL).
10. Label the syringe appropriately.

After withdrawal of the suspension from the vial(s) into a syringe, it is recommended to administer the suspension immediately. **Do not exceed 2 hours between the time the vial(s) were removed from refrigerated storage (if applicable) or withdrawing the contents of the vial(s) into a syringe, whichever occurs first, and time of administration to the study participant.**

The prepared CAB LA suspension in a syringe must be stored at controlled room temperature between 20°C to 25°C from the time it is withdrawn into a syringe to the time it is administered.

Any entered vials or expired filled syringes should be disposed of in accordance with institutional or pharmacy policy.

II. Preparation of CAB LA 500 mg/2.5 mL (using one 600 mg/3mL vial or two 400 mg/2 mL vials)

One syringe containing 2.5 mL (500 mg) of CAB LA study product must be prepared using aseptic technique under a pharmacy BSC/isolator.

1. Remove one 3-mL CAB LA vial or two 2-mL CAB LA vials (as available) from storage. If CAB LA vials are stored in the refrigerator (2°C to 8°C), remove vial(s) from the refrigerator and wait at least 15 minutes to equilibrate to room temperature. Record the time when vial(s) were removed from the refrigerator.
2. Remove vial(s) from the carton and vigorously shake the vial for a full 10 seconds by shaking the vial with long arm movements.
3. Invert the vial(s) and inspect to ensure complete re-suspension. If sediments are observed, repeat Steps 2-3 until all material is uniformly suspended. After re-suspending, it is recommended to use the suspension immediately.
4. Using aseptic technique under a pharmacy biological safety cabinet, flip off the plastic cap from the vial(s). Wipe the top of the vial(s) with disinfecting tissue of isopropyl alcohol 70% or similar and allow the alcohol to dry.
5. Remove one 5-mL syringe and aspiration needles from the blister pouch (see suggested supplies). Take one aspiration needle and attach the needle to the Luer-Lok connection of the syringe.

6. If using one 3-mL CAB LA vial:
 - With the sheath on the needle, pull back on the syringe plunger to allow approximately 1 mL of air into the syringe. Pull the needle sheath off the needle with a straight pull.
 - Push the needle through the stopper of the vial and inject 1mL of air into the vial by putting the vial in the inverted position while the needle and syringe are in the upright position.
 - Withdraw 2.5 mL of suspension from the vial into the syringe. Because the suspension can contain some air after having shaken the vial, take out enough suspension in order to be able to de-aerate the syringe properly (Step 9).
 - Record the time withdrawn into the syringe.
7. If using two 2-mL CAB LA vials:
 - With the sheath on the needle, pull back on the syringe plunger to allow approximately 1 mL of air into the syringe. Pull the needle sheath off the needle with a straight pull.
 - Push the needle through the stopper of the first vial and inject 1 mL of air into the vial by putting the vial in the inverted position while the needle and syringe are in the upright position.
 - Withdraw 1.5 mL of suspension from the first vial and put vial aside.
 - Remove the needle from the syringe and attach a new aspiration needle. Repeat the steps above to withdraw 1 mL of suspension from the second vial, for a total of 2.5 mL from two vials. Because the suspension can contain some air after having shaken the vial, take out enough suspension in order to be able to de-aerate the syringe properly (Step 9).
 - Record for each individual vial the time withdrawn into the syringe.
8. Keep the syringe with the needle in the upright position and remove the needle that was used to withdraw the suspension and discard it appropriately. Attach the needle for intramuscular administration to the Luer-Lok connection of the syringe or attach a syringe cap (per site's SOP). Consult with clinic staff regarding the recommended needle for IM administration (see suggested supplies).
9. De-aerate the syringe by first tapping with a finger against the syringe and then by moving the plunger rod carefully forward with the needle in upright position until a drop of suspension appears. Remove the excess suspension in order to administer the correct volume (2.5 mL).
10. Label the syringe appropriately.

After withdrawal of the suspension from the vial(s) into a syringe, it is recommended to administer the suspension immediately. **Do not exceed 2 hours between the time the vial(s) were removed from refrigerated storage (if applicable) or withdrawing the contents of the vial(s) into a syringe, whichever occurs first, and time of administration to the study participant.**

The prepared CAB LA suspension in a syringe must be stored at controlled room temperature between 20°C to 25°C from the time it is withdrawn into a syringe to the time it is administered.

Any entered vials or expired filled syringes should be disposed of in accordance with institutional or pharmacy policy.

III. Preparation of CAB LA 400mg/2mL (using one 400 mg/2 mL vial [or one 600 mg/3 mL vial if 400 mg/2 mL vial is not available])

One syringe containing 2 mL (400 mg) of CAB LA study product must be prepared using aseptic technique under a pharmacy BSC/isolator.

1. Remove one 2 mL CAB LA vial (or one 3-mL CAB LA vial if 2-mL CAB LA vial is not available) from storage. If CAB LA vials are stored in the refrigerator (2°C to 8°C), remove vial from the refrigerator and wait at least 15 minutes to equilibrate to room temperature. Record the time when vial was removed from the refrigerator.
2. Remove vial from the carton and vigorously shake the vial for 10 seconds by shaking the vial with long arm movements.
3. Invert the vial and inspect the vial to ensure complete re-suspension. If sediments are observed, repeat Steps 2-3 until all material is uniformly suspended. After re-suspending, it is recommended to use the suspension immediately.
4. Using aseptic technique under a pharmacy biological safety cabinet, flip off the plastic cap from the vial. Wipe the top of the vial with a 70% isopropyl alcohol pad or similar and allow the alcohol to dry.
5. Remove one 3-mL syringe and one aspiration needle from the blister pouch (see suggested supplies). Attach the needle to the Luer-Lok connection of the syringe.
6. With the sheath on the needle, pull back on the syringe plunger rod to allow approximately 1 mL of air into the syringe. Pull the needle sheath off the needle with a straight pull.
7. Push the needle through the stopper of the vial and inject 1 mL of air into the vial by putting the vial in the inverted position while the needle and syringe are in the upright position.
8. Withdraw 2 mL from the vial. Since the suspension can contain some air after shaking, take out all suspension in order to be able to de-aerate the syringe properly (Step 11).
9. Record the time that the suspension is withdrawn into the syringe.
10. Keep the syringe with the needle in the upright position and remove the needle that was used to withdraw the suspension and discard it appropriately. Attach the needle for intramuscular administration to the Luer-Lok connection of the syringe or attach a syringe cap (per site's SOP). Consult with clinic staff regarding the recommended needle for IM administration (see suggested supplies).
11. De-aerate the syringe by first tapping with a finger against the syringe and then by moving the plunger rod carefully forward with the needle in upright position until a drop of suspension appears. Remove the excess suspension in order to administer the correct volume (2 mL).

12. Label the syringe appropriately.

After withdrawal of the suspension from the vial into a syringe, it is recommended to administer the suspension immediately. **Do not exceed 2 hours between the time the vial was removed from refrigerated storage (if applicable) or withdrawing the contents of the vial into a syringe, whichever occurs first, and time of administration to the study participant.**

The prepared CAB LA suspension in a syringe must be stored at controlled room temperature between 20°C to 25°C from the time it is withdrawn into a syringe to the time it is administered.

Any entered vials or expired filled syringes should be disposed of in accordance with institutional or pharmacy policy.

IV. Preparation of CAB LA 300mg/1.5mL (using one 400 mg/2 mL vial [or one 600 mg/3 mL vial if 400 mg/2 mL vial is not available])

One syringe containing 1.5 mL (300 mg) of CAB LA study product must be prepared using aseptic technique under a pharmacy BSC/isolator.

1. Remove one 2-mL CAB LA vial (or one 3-mL CAB LA vial if 2-mL CAB LA vial is not available) from storage. If CAB LA vials are stored in the refrigerator (2°C to 8°C), remove vial from the refrigerator and wait at least 15 minutes to equilibrate to room temperature. Record the time when vial was removed from the refrigerator.
2. Remove vial from the carton and vigorously shake the vial for 10 seconds by shaking the vial with long arm movements.
3. Invert the vial and inspect the vial to ensure complete re-suspension. If sediments are observed, repeat Steps 2-3 until all material is uniformly suspended. After re-suspending, it is recommended to use the suspension immediately.
4. Using aseptic technique under a pharmacy biological safety cabinet, flip off the plastic cap from the vial. Wipe the top of the vial with a 70% isopropyl alcohol pad or similar and allow the alcohol to dry.
5. Remove one 3-mL syringe and one aspiration needle from the blister pouch (see suggested supplies). Attach the needle to the Luer-Lok connection of the syringe.
6. With the sheath on the needle, pull back on the syringe plunger rod to allow approximately 1 mL of air into the syringe. Pull the needle sheath off the needle with a straight pull.
7. Push the needle through the stopper of the vial and inject 1 mL of air into the vial by putting the vial in the inverted position while the needle and syringe are in the upright position.

8. Withdraw 1.5 mL from the vial. Since the suspension can contain some air after shaking, take out all suspension in order to be able to de-aerate the syringe properly (Step 11).
9. Record the time that the suspension is withdrawn into the syringe.
10. Keep the syringe with the needle in the upright position and remove the needle that was used to withdraw the suspension and discard it appropriately. Attach the needle for intramuscular administration to the Luer-Lok connection of the syringe or attach a syringe cap (per site's SOP). Consult with clinic staff regarding the recommended needle for IM administration (see suggested supplies).
11. De-aerate the syringe by first tapping with a finger against the syringe and then by moving the plunger rod carefully forward with the needle in upright position until a drop of suspension appears. Remove the excess suspension in order to administer the correct volume (1.5 mL).
12. Label the syringe appropriately.

After withdrawal of the suspension from the vial into a syringe, it is recommended to administer the suspension immediately. **Do not exceed 2 hours between the time the vial was removed from refrigerated storage (if applicable) or withdrawing the contents of the vial into a syringe, whichever occurs first, and time of administration to the study participant.**

The prepared CAB LA suspension in a syringe must be stored at controlled room temperature between 20°C to 25°C from the time it is withdrawn into a syringe to the time it is administered.

Any entered vials or expired filled syringes should be disposed of in accordance with institutional or pharmacy policy.

V. Preparation of CAB LA 200mg/1mL (using one 400 mg/2 mL vial [or one 600 mg/3 mL vial if 400 mg/2 mL vial is not available])

One syringe containing 1 mL (200 mg) of CAB LA study product must be prepared using aseptic technique under a pharmacy BSC/isolator.

1. Remove one 2-mL CAB LA vial (or one 3-mL CAB LA vial if 2-mL CAB LA vial is not available) from storage. If CAB LA vials are stored in the refrigerator (2°C to 8°C), remove vial from the refrigerator and wait at least 15 minutes to equilibrate to room temperature. Record the time when vial was removed from the refrigerator.
2. Remove vial from the carton and vigorously shake the vial for 10 seconds by shaking the vial with long arm movements.
3. Invert the vial and inspect the vial to ensure complete re-suspension. If sediments are observed, repeat Steps 2-3 until all material is uniformly suspended. After re-suspending, it is recommended to use the suspension immediately.

4. Using aseptic technique under a pharmacy biological safety cabinet, flip off the plastic cap from the vial. Wipe the top of the vial with a 70% isopropyl alcohol pad or similar and allow the alcohol to dry.
5. Remove one 3-mL syringe and one aspiration needle from the blister pouch (see suggested supplies). Attach the needle to the Luer-Lok connection of the syringe.
6. With the sheath on the needle, pull back on the syringe plunger rod to allow approximately 1 mL of air into the syringe. Pull the needle sheath off the needle with a straight pull.
7. Push the needle through the stopper of the vial and inject 1 mL of air into the vial by putting the vial in the inverted position while the needle and syringe are in the upright position.
8. Withdraw 1 mL from the vial. Since the suspension can contain some air after shaking, take out all suspension in order to be able to de-aerate the syringe properly (Step 11).
9. Record the time that the suspension is withdrawn into the syringe.
10. Keep the syringe with the needle in the upright position and remove the needle that was used to withdraw the suspension and discard it appropriately. Attach the needle for intramuscular administration to the Luer-Lok connection of the syringe or attach a syringe cap (per site's SOP). Consult with clinic staff regarding the recommended needle for IM administration (see suggested supplies).
11. De-aerate the syringe by first tapping with a finger against the syringe and then by moving the plunger rod carefully forward with the needle in upright position until a drop of suspension appears. Remove the excess suspension in order to administer the correct volume (1 mL).
12. Label the syringe appropriately.

After withdrawal of the suspension from the vial into a syringe, it is recommended to administer the suspension immediately. **Do not exceed 2 hours between the time the vial was removed from refrigerated storage (if applicable) or withdrawing the contents of the vial into a syringe, whichever occurs first, and time of administration to the study participant.**

The prepared CAB LA suspension in a syringe must be stored at controlled room temperature between 20°C to 25°C from the time it is withdrawn into a syringe to the time it is administered.

Any entered vials or expired filled syringes should be disposed of in accordance with institutional or pharmacy policy.

VI. Preparation of CAB LA 100 mg/0.5 mL (using one 400 mg/2 mL vial [or one 600 mg/3 mL vial if 400 mg/2 mL vial is not available])

One syringe containing 0.5 mL (100 mg) of CAB LA study product must be prepared using aseptic technique under a pharmacy BSC/isolator.

1. Remove one 2-mL CAB LA vial (or one 3-mL CAB LA vial if 2-mL CAB LA vial is not available) from storage. If CAB LA vials are stored in the refrigerator (2°C to 8°C), remove vial from the refrigerator and wait at least 15 minutes to equilibrate to room temperature. Record the time when vial was removed from the refrigerator.
2. Remove vial from the carton and vigorously shake the vial for 10 seconds by shaking the vial with long arm movements.
3. Invert the vial and inspect the vial to ensure complete re-suspension. If sediments are observed, repeat Steps 2-3 until all material is uniformly suspended. After re-suspending, it is recommended to use the suspension immediately.
4. Using aseptic technique under a pharmacy biological safety cabinet, flip off the plastic cap from the vial. Wipe the top of the vial with a 70% isopropyl alcohol pad or similar and allow the alcohol to dry.
5. Remove one 1-mL syringe and one aspiration needle from the blister pouch (see suggested supplies). Attach the needle to the Luer-Lok connection of the syringe.
6. With the sheath on the needle, pull back on the syringe plunger rod to allow approximately 0.5 mL of air into the syringe. Pull the needle sheath off the needle with a straight pull.
7. Push the needle through the stopper of the vial and inject 0.5 mL of air into the vial by putting the vial in the inverted position while the needle and syringe are in the upright position.
8. Withdraw 0.5 mL from the vial. Since the suspension can contain some air after shaking, take out all suspension in order to be able to de-aerate the syringe properly (Step 11).
9. Record the time that the suspension is withdrawn into the syringe.
10. Keep the syringe with the needle in the upright position and remove the needle that was used to withdraw the suspension and discard it appropriately. Attach the needle for intramuscular administration to the Luer-Lok connection of the syringe or attach a syringe cap (per site's SOP). Consult with clinic staff regarding the recommended needle for IM administration (see suggested supplies).
11. De-aerate the syringe by first tapping with a finger against the syringe and then by moving the plunger rod carefully forward with the needle in upright position until a drop of suspension appears. Remove the excess suspension in order to administer the correct volume (0.5 mL).
12. Label the syringe appropriately.

After withdrawal of the suspension from the vial into a syringe, it is recommended to administer the suspension immediately. **Do not exceed 2 hours between the time the vial was removed from refrigerated storage (if applicable) or withdrawing the contents of the vial into a syringe, whichever occurs first, and time of administration to the study participant.**

The prepared CAB LA suspension in a syringe must be stored at controlled room temperature between 20°C to 25°C from the time it is withdrawn into a syringe to the time it is administered.

Any entered vials or expired filled syringes should be disposed of in accordance with institutional or pharmacy policy.

Appendix VI-D: RPV LA Injectable Preparation Requirements

I. Preparation of RPV LA 900mg/3mL (using one 900mg/3 mL vial or two 600 mg/2 mL vials)

One syringe containing 3 mL (900 mg) of RPV LA study product must be prepared using aseptic technique under a pharmacy BSC/isolator.

1. Remove one 3-mL RPV LA vial or two 2-mL RPV vials (as available) from the refrigerator and allow the vial(s) to sit for 15 minutes to come to room temperature (keep vial in the carton while coming to room temperature). RPV LA may sit at room temperature for a maximum of 6 hours at 25°C. During this period, excursions are allowed up to 30°C for a maximum of 2 hours. Record the time when vial(s) were removed from the refrigerator.
2. Remove the vial(s) from the carton and vigorously shake the vial(s) a full 10 seconds by shaking the vial with long arm movements.
3. Invert the vial(s) and inspect to ensure complete re-suspension. If sediments are observed, repeat Steps 2-3 until all material is uniformly suspended. After re-suspending, it is recommended to use the suspension immediately.
4. Using aseptic technique under a pharmacy biological safety cabinet, flip off the plastic cap from the vial(s). Wipe the top of the vial(s) with a 70% isopropyl alcohol pad or similar and allow the alcohol to dry.
5. Remove one 5-mL syringe and one aspiration needle from the blister pouch (see suggested supplies). Remove 2 needles if using two 2-mL vials. Attach one needle to the Luer connection of the syringe.
6. If using one 3-mL RPV vial:
 - With the sheath on the needle, pull back on the syringe plunger to allow approximately 1 mL of air into the syringe. Pull the needle sheath off the needle with a straight pull.
 - Push the needle through the stopper of the vial and inject 1 mL of air into the vial by putting the vial in the inverted position while the needle and syringe are in the upright position.
 - Withdraw the entire contents (3 mL) of the vial into the syringe. Because the suspension can contain some air after having shaken the vial, take out enough suspension in order to be able to de-aerate the syringe properly (Step 9).
 - Record the time the vial was withdrawn into the syringe.
7. If using two 2-mL RPV vials:
 - With the sheath on the needle, pull the syringe plunger rod slowly to allow approximately 1 mL of air into the syringe. Pull the needle sheath off of the needle with a straight pull.
 - Push the needle through the stopper of the first vial and inject 1 mL of air into the vial by putting the vial in the inverted position while the needle and syringe are in the upright position.
 - Withdraw approximately 1.5 mL of suspension from the vial into the syringe.

- Remove the needle from the syringe and attach a new aspiration needle. Repeat the steps above to withdraw 1.5 mL of suspension from the second vial, for a total of 3 mL from two vials. Because the suspension can contain some air after having shaken the vial, take out enough suspension in order to be able to de-aerate the syringe properly (Step 9).
 - Record for each individual vial the time withdrawn into the syringe.
8. Keep the syringe with the needle in the upright position and remove the needle that was used to withdraw the suspension and discard it appropriately. Attach the needle for intramuscular administration to the Luer-Lok connection of the syringe or attach a syringe cap (per site's SOP). Consult with clinic staff regarding the recommended needle for IM administration (see suggested supplies).
 9. De-aerate the syringe by first tapping with a finger against the syringe and then by moving the plunger rod carefully forward with the needle in upright position until first drop appear. Remove the excess suspension in order to administer the correct volume (3 mL).
 10. Label the syringe appropriately.

After withdrawal of the suspension from the vial into a syringe, it is recommended to administer the suspension immediately. If required, the prepared syringe containing RPV LA may remain at room temperature for **a maximum period of 2 hours between the time the vial(s) were removed from the refrigerator and time of administration** to the study participant. The prepared RPV-LA syringe must be protected from light (e.g., syringe covered or enclosed within an amber bag) until ready to administer.

Any entered vials or expired filled syringes should be disposed of in accordance with institutional or pharmacy policy.

II. **Preparation of RPV LA 750 mg/2.5 mL (using one 900mg/3 mL vial or two 600 mg/2 mL vials)**

One syringe containing 2.5 mL (750 mg) of RPV LA study product must be prepared using aseptic technique under a pharmacy BSC/isolator.

1. Remove one 3-mL RPV LA vial or two 2-mL RPV vials (as available) from the refrigerator and allow the vial(s) to sit for 15 minutes to come to room temperature (keep vial in the carton while coming to room temperature). RPV LA may sit at room temperature for a maximum of 6 hours at 25°C. During this period, excursions are allowed up to 30°C for a maximum of 2 hours. Record the time when vial(s) were removed from the refrigerator.
2. Remove the vial(s) from the carton and vigorously shake the vial(s) a full 10 seconds by shaking the vial with long arm movements.
3. Invert the vial(s) and inspect to ensure complete re-suspension. If sediments are observed, repeat Steps 2-3 until all material is uniformly suspended. After re-suspending, it is recommended to use the suspension immediately.
4. Using aseptic technique under a pharmacy biological safety cabinet, flip off the plastic cap from the vial(s). Wipe the top of the vial(s) with a 70% isopropyl alcohol pad or similar and allow the alcohol to dry.

5. Remove one 5-mL syringe and one aspiration needle from the blister pouch (see suggested supplies). Remove 2 needles if using two 2-mL vials. Attach one needle to the Luer connection of the syringe.
6. If using one 3-mL RPV vial:
 - With the sheath on the needle, pull back on the syringe plunger to allow approximately 1 mL of air into the syringe. Pull the needle sheath off the needle with a straight pull.
 - Push the needle through the stopper of the vial and inject 1 mL of air into the vial by putting the vial in the inverted position while the needle and syringe are in the upright position.
 - Withdraw 2.5 mL of the vial into the syringe. Because the suspension can contain some air after having shaken the vial, take out enough suspension in order to be able to de-aerate the syringe properly (Step 9).
 - Record the time the vial was withdrawn into the syringe.
7. If using two 2-mL RPV vials:
 - With the sheath on the needle, pull the syringe plunger rod slowly to allow approximately 1 mL of air into the syringe. Pull the needle sheath off of the needle with a straight pull.
 - Push the needle through the stopper of the first vial and inject 1 mL of air into the vial by putting the vial in the inverted position while the needle and syringe are in the upright position.
 - Withdraw approximately 1.5 mL of suspension from the vial into the syringe.
 - Remove the needle from the syringe and attach a new aspiration needle. Repeat the steps above to withdraw 1 mL of suspension from the second vial, for a total of 2.5 mL from two vials. Because the suspension can contain some air after having shaken the vial, take out enough suspension in order to be able to de-aerate the syringe properly (Step 9).
 - Record for each individual vial the time withdrawn into the syringe.
8. Keep the syringe with the needle in the upright position and remove the needle that was used to withdraw the suspension and discard it appropriately. Attach the needle for intramuscular administration to the Luer-Lok connection of the syringe or attach a syringe cap (per site's SOP). Consult with clinic staff regarding the recommended needle for IM administration (see suggested supplies).
9. De-aerate the syringe by first tapping with a finger against the syringe and then by moving the plunger rod carefully forward with the needle in upright position until first drop appear. Remove the excess suspension in order to administer the correct volume (2.5 mL).
10. Label the syringe appropriately.

After withdrawal of the suspension from the vial into a syringe, it is recommended to administer the suspension immediately. If required, the prepared syringe containing RPV LA may remain at room temperature for **a maximum period of 2 hours between the time the vial(s) were removed from the refrigerator and time of administration** to the study participant. The prepared RPV-LA syringe must be protected from light (e.g., syringe covered or enclosed within an amber bag) until ready to administer.

Any entered vials or expired filled syringes should be disposed of in accordance with institutional or pharmacy policy.

III. Preparation of RPV LA 600mg/2mL (using one 600mg/2 mL vial [or one 900 mg/3 mL vial if 600 mg/2 mL vial is not available])

One syringe containing 2 ml (600 mg) of RPV LA study product must be prepared using aseptic technique under a pharmacy BSC/isolator.

1. Remove one 2-mL RPV LA vial (or one 3-mL RPV LA vial if 2-mL RPV LA vial is not available) from the refrigerator. Document the time at which the vial was removed from the refrigerator. Allow the vial to sit for 15 minutes to come to room temperature (keep vial in the carton while coming to room temperature). RPV LA may sit at room temperature for a maximum of 6 hours at 25°C. During this period, excursions are allowed up to 30°C for a maximum of 2 hours.
2. Remove the vial from the carton and vigorously shake the vial for a full 10 seconds by shaking the vial with long arm movements.
3. Invert the vial and inspect the vial to ensure complete re-suspension. If sediments are observed, repeat Steps 2-3 until all material is uniformly suspended. After re-suspending, it is recommended to use the suspension immediately.
4. Using aseptic technique under a pharmacy biological safety cabinet, flip off the plastic cap from the vial. Wipe the top of the vial with a 70% isopropyl alcohol pad or similar and allow the alcohol to dry.
5. Remove one 3-mL syringe and one aspiration needle from the blister pouch (see suggested supplies). Attach the aspiration needle to the Luer connection of the syringe.
6. With the sheath on the needle, pull the syringe plunger rod to allow approximately 1 mL of air into the syringe. Pull the needle sheath off the needle with a straight pull.
7. Push the needle through the stopper of the vial and inject 1 mL of air into the vial by putting the vial in the inverted position while the needle and syringe are in the upright position.
8. Withdraw (2 mL) from the vial. Since the suspension can contain some air after shaking, take out all suspension in order to be able to de-aerate the syringe properly (Step 12).
9. Keep the syringe with the needle in the upright position and remove vial from the needle.
10. Record the time withdrawn from the vial.
11. Remove the needle that was used to withdraw the suspension and discard it appropriately. Attach the needle for intramuscular administration to the Luer-Lok connection of the syringe

or attach a syringe cap (per site's SOP). Consult with clinic staff regarding the recommended needle for IM administration (see suggested supplies).

12. De-aerate the syringe by first tapping with a finger against the syringe and then by moving the plunger rod carefully forward with the needle in upright position until the first drop appears. Remove the excess suspension in order to administer the correct volume (2 mL).
13. Label the syringe appropriately.

After withdrawal of the suspension from the vial into a syringe, it is recommended to administer the suspension immediately. If required, the prepared syringe containing RPV LA may remain at room temperature for **a maximum period of 2 hours between the time the vial was removed from the refrigerator and time of administration to the study participant. The prepared RPV-LA syringe** must be protected from light (e.g., syringe covered or enclosed within an amber bag) until ready to administer.

Any entered vials or expired filled syringes should be disposed of in accordance with institutional or pharmacy policy.

IV. Preparation of RPV LA 450 mg/1.5 mL (using one 600mg/2 mL vial [or one 900 mg/3 mL vial if 600 mg/2 mL vial is not available])

One syringe containing 1.5 mL (450 mg) of RPV LA study product must be prepared using aseptic technique under a pharmacy BSC/isolator.

1. Remove one 2-mL RPV LA vial (or one 3-mL RPV LA vial if 2-mL RPV LA vial is not available) from the refrigerator. Document the time at which the vial was removed from the refrigerator. Allow the vial to sit for 15 minutes to come to room temperature (keep vial in the carton while coming to room temperature). RPV LA may sit at room temperature for a maximum of 6 hours at 25°C. During this period, excursions are allowed up to 30°C for a maximum of 2 hours.
2. Remove the vial from the carton and vigorously shake the vial for a full 10 seconds by shaking the vial with long arm movements.
3. Invert the vial and inspect the vial to ensure complete re-suspension. If sediments are observed, repeat Steps 2-3 until all material is uniformly suspended. After re-suspending, it is recommended to use the suspension immediately.
4. Using aseptic technique under a pharmacy biological safety cabinet, flip off the plastic cap from the vial. Wipe the top of the vial with a 70% isopropyl alcohol pad or similar and allow the alcohol to dry.
5. Remove one 3-mL syringe and one aspiration needle from the blister pouch (see suggested supplies). Attach the aspiration needle to the Luer connection of the syringe.

6. With the sheath on the needle, pull the syringe plunger rod to allow approximately 1 mL of air into the syringe. Pull the needle sheath off the needle with a straight pull.
7. Push the needle through the stopper of the vial and inject 1 mL of air into the vial by putting the vial in the inverted position while the needle and syringe are in the upright position.
8. Withdraw 1.5 mL from the vial. Since the suspension can contain some air after shaking, take out all suspension in order to be able to de-aerate the syringe properly (Step 12).
9. Keep the syringe with the needle in the upright position and remove vial from the needle.
10. Record the time withdrawn from the vial.
11. Remove the needle that was used to withdraw the suspension and discard it appropriately. Attach the needle for intramuscular administration to the Luer-Lok connection of the syringe or attach a syringe cap (per site's SOP). Consult with clinic staff regarding the recommended needle for IM administration (see suggested supplies).
12. De-aerate the syringe by first tapping with a finger against the syringe and then by moving the plunger rod carefully forward with the needle in upright position until the first drop appears. Remove the excess suspension in order to administer the correct volume (1.5 mL).
13. Label the syringe appropriately.

After withdrawal of the suspension from the vial into a syringe, it is recommended to administer the suspension immediately. If required, the prepared syringe containing RPV LA may remain at room temperature for **a maximum period of 2 hours between the time the vial was removed from the refrigerator and time of administration to the study participant. The prepared RPV-LA syringe** must be protected from light (e.g., syringe covered or enclosed within an amber bag) until ready to administer.

Any entered vials or expired filled syringes should be disposed of in accordance with institutional or pharmacy policy.

V. Preparation of RPV LA 300 mg/1 mL (using one 600mg/2 mL vial [or one 900 mg/3 mL vial if 600 mg/2 mL vial is not available])

One syringe containing 1 mL (300 mg) of RPV LA study product must be prepared using aseptic technique under a pharmacy BSC/isolator.

1. Remove one 2-mL RPV LA vial (or one 3-mL RPV LA vial if 2-mL RPV LA vial is not available) from the refrigerator. Document the time at which the vial was removed from the refrigerator. Allow the vial to sit for 15 minutes to come to room temperature (keep vial in the carton while coming to room temperature). RPV LA may sit at room temperature for a maximum of 6 hours at 25°C. During this period, excursions are allowed up to 30°C for a maximum of 2 hours.

2. Remove the vial from the carton and vigorously shake the vial for a full 10 seconds by shaking the vial with long arm movements.
3. Invert the vial and inspect the vial to ensure complete re-suspension. If sediments are observed, repeat Steps 2-3 until all material is uniformly suspended. After re-suspending, it is recommended to use the suspension immediately.
4. Using aseptic technique under a pharmacy biological safety cabinet, flip off the plastic cap from the vial. Wipe the top of the vial with a 70% isopropyl alcohol pad or similar and allow the alcohol to dry.
5. Remove one 3-mL syringe and one aspiration needle from the blister pouch (see suggested supplies). Attach the aspiration needle to the Luer connection of the syringe.
6. With the sheath on the needle, pull the syringe plunger rod to allow approximately 1 mL of air into the syringe. Pull the needle sheath off the needle with a straight pull.
7. Push the needle through the stopper of the vial and inject 1 mL of air into the vial by putting the vial in the inverted position while the needle and syringe are in the upright position.
8. Withdraw 1 mL from the vial. Since the suspension can contain some air after shaking, take out all suspension in order to be able to de-aerate the syringe properly (Step 12).
9. Keep the syringe with the needle in the upright position and remove vial from the needle.
10. Record the time withdrawn from the vial.
11. Remove the needle that was used to withdraw the suspension and discard it appropriately. Attach the needle for intramuscular administration to the Luer-Lok connection of the syringe or attach a syringe cap (per site's SOP). Consult with clinic staff regarding the recommended needle for IM administration (see suggested supplies).
12. De-aerate the syringe by first tapping with a finger against the syringe and then by moving the plunger rod carefully forward with the needle in upright position until the first drop appears. Remove the excess suspension in order to administer the correct volume (1 mL).
13. Label the syringe appropriately.

After withdrawal of the suspension from the vial into a syringe, it is recommended to administer the suspension immediately. If required, the prepared syringe containing RPV LA may remain at room temperature for **a maximum period of 2 hours between the time the vial was removed from the refrigerator and time of administration to the study participant. The prepared RPV-LA syringe** must be protected from light (e.g., syringe covered or enclosed within an amber bag) until ready to administer.

Any entered vials or expired filled syringes should be disposed of in accordance with institutional or pharmacy policy.

VI. Preparation of RPV LA 150 mg/0.5 mL (using one 600mg/2 mL vial [or one 900 mg/3 mL vial if 600 mg/2 mL vial is not available])

One syringe containing 0.5 mL (150 mg) of RPV LA study product must be prepared using aseptic technique under a pharmacy BSC/isolator.

1. Remove one 2-mL RPV LA vial (or one 3-mL RPV LA vial if 2-mL RPV LA vial is not available) from the refrigerator. Document the time at which the vial was removed from the refrigerator. Allow the vial to sit for 15 minutes to come to room temperature (keep vial in the carton while coming to room temperature). RPV LA may sit at room temperature for a maximum of 6 hours at 25°C. During this period, excursions are allowed up to 30°C for a maximum of 2 hours.
2. Remove the vial from the carton and vigorously shake the vial for a full 10 seconds by shaking the vial with long arm movements.
3. Invert the vial and inspect the vial to ensure complete re-suspension. If sediments are observed, repeat Steps 2-3 until all material is uniformly suspended. After re-suspending, it is recommended to use the suspension immediately.
4. Using aseptic technique under a pharmacy biological safety cabinet, flip off the plastic cap from the vial. Wipe the top of the vial with a 70% isopropyl alcohol pad or similar and allow the alcohol to dry.
5. Remove one 1-mL syringe and one aspiration needle from the blister pouch (see suggested supplies). Attach the aspiration needle to the Luer connection of the syringe.
6. With the sheath on the needle, pull the syringe plunger rod to allow approximately 0.5 mL of air into the syringe. Pull the needle sheath off the needle with a straight pull.
7. Push the needle through the stopper of the vial and inject 0.5 mL of air into the vial by putting the vial in the inverted position while the needle and syringe are in the upright position.
8. Withdraw 0.5 mL from the vial. Since the suspension can contain some air after shaking, take out all suspension in order to be able to de-aerate the syringe properly (Step 12).
9. Keep the syringe with the needle in the upright position and remove vial from the needle.
10. Record the time withdrawn from the vial.
11. Remove the needle that was used to withdraw the suspension and discard it appropriately. Attach the needle for intramuscular administration to the Luer-Lok connection of the syringe

or attach a syringe cap (per site's SOP). Consult with clinic staff regarding the recommended needle for IM administration (see suggested supplies).

12. De-aerate the syringe by first tapping with a finger against the syringe and then by moving the plunger rod carefully forward with the needle in upright position until the first drop appears. Remove the excess suspension in order to administer the correct volume (0.5 mL).

13. Label the syringe appropriately.

After withdrawal of the suspension from the vial into a syringe, it is recommended to administer the suspension immediately. If required, the prepared syringe containing RPV LA may remain at room temperature for **a maximum period of 2 hours between the time the vial was removed from the refrigerator and time of administration to the study participant. The prepared RPV-LA syringe** must be protected from light (e.g., syringe covered or enclosed within an amber bag) until ready to administer.

Any entered vials or expired filled syringes should be disposed of in accordance with institutional or pharmacy policy.

Appendix VII: IMPAACT 2036 Alternative Dosing Regimens

Dose regimen modifications for each weight band may occur as needed based on ongoing reviews of safety and PK and/or following the Cohort 1 interim analyses. Modified regimens for each weight band will be established by selecting from the dose options included in the tables below and will be communicated to sites by a Memorandum of Operational Instruction, approved by the CMC. For each weight band, the dosing regimen will include daily oral doses of CAB + RPV (Tables I and II, Cohort 1 and 2a only) as well as injectable CAB LA + RPV LA (Tables IV, V, VI, and VII) with an assigned injection interval from Table III.

Oral Dosing:

Table I: CAB Oral Dose

I.A	30 mg	Administered as one 30 mg CAB tablet
I.B	25 mg	Administered as five 5 mg CAB DT in a split dose as instructed in Appendix VI-A
I.C	20 mg	Administered as four 5 mg CAB DT
I.D	15 mg	Administered as three 5 mg CAB DT
I.E	10 mg	Administered as two 5 mg CAB DT
I.F	5 mg	Administered as one 5 mg CAB DT

Table II: RPV Oral Dose

II.A	25 mg	Administered as one 25 mg RPV tablet
II.B	20 mg	Administered as eight 2.5 mg RPV tablets
II.C	15 mg	Administered as six 2.5 mg RPV tablets
II.D	12.5 mg	Administered as five 2.5 mg RPV tablets
II.E	10 mg	Administered as four 2.5 mg RPV tablets
II.F	7.5 mg	Administered as three 2.5 mg RPV tablets
II.G	5 mg	Administered as two 2.5 mg RPV tablets
II.H	2.5 mg	Administered as one 2.5 mg RPV tablets

Injectable Dosing:

Table III: Injection Interval

III.A	Q. 4 weeks
III.B	Doses 1 and 2, 4 weeks apart, then Q. 8 weeks

Table IV: CAB LA First Injection Dose

IV.A	600 mg
IV.B	500 mg
IV.C	400 mg
IV.D	300 mg
IV.E	200 mg
IV.F	100 mg

Table V: CAB LA Subsequent Injections

V.A	600 mg
V.B	500 mg
V.C	400 mg
V.D	300 mg
V.E	200 mg
V.F	100 mg

Table VI: RPV LA First Injection Dose

VI.A	900 mg
VI.B	750 mg
VI.C	600 mg
VI.D	450 mg
VI.E	300 mg
VI.F	150 mg

Table VII: RPV LA Subsequent Injection Dose

VI.A	900 mg
VI.B	750 mg
VI.C	600 mg
VI.D	450 mg
VI.E	300 mg
VI.F	150 mg

Appendix VIII: Operational Guidance for Study Implementation at Sites Experiencing Operational Disruptions Due to COVID-19

To safeguard the health and well-being of study participants and study staff in the context of circulating SARS-CoV-2 and the associated coronavirus disease 2019 (COVID-19), the guidance provided in this appendix may be implemented at sites experiencing disruptions due to COVID-19.

The extent to which site operations may be disrupted by COVID-19 may vary across sites and over time. **All sites should follow applicable government, health authority, and institutional policies with respect to conduct of study visits and procedures, with utmost importance placed on the health and well-being of study participants and study staff.** All sites must also comply with any directives received from the study sponsor, the IMPAACT Network, and/or the IMPAACT 2036 Protocol Team. Should a determination be made in the future that the guidance provided in this appendix is no longer applicable, sites will be formally notified and instructed to inform their IRBs/ECs and other applicable regulatory entities.

Visit Scheduling

- Sites are advised that potential participants who are screened for the study should only be enrolled if the site investigator has reasonable confidence that local conditions will allow for uninterrupted administration of both oral and injectable study products, collection and storage of PK samples, and completion of clinical and laboratory safety evaluations. In the absence of such confidence, screening and enrollment should not proceed.
- Sites are advised to make use of the visit windows when scheduling study visits during periods of operational disruption. In the event that a visit may need to be conducted outside of the visit window, the CMC should be contacted for guidance on visit completion on a case-by-case basis.
- When visits must be delayed or missed, sites should make every effort to avoid gaps in study drug access. See further guidance for study drug supply below.

Prioritization of Study Visit Procedures

- Injections and blood draws must occur at the clinical research site. However, when capacity to conduct study visits in person at the clinical research site is limited, other procedures may be conducted off-site or virtually (e.g., by telephone or other IRB-approved method) if permitted by applicable government, health authority, and institutional policies. Site investigators must ensure that SOPs are in place for off-site and virtual procedures.
 - Prior to conducting off-site or virtual study visits, site staff should communicate with participants/parents/guardians to determine how and when such visits will take place with adequate protections for safety, privacy, and confidentiality. Visit procedures should be conducted by site staff who are adequately qualified and trained to conduct the procedures, as determined by the site IoR. At least one staff member who participates in the off-site or virtual visit should be adequately trained and qualified to assess and/or manage adverse events or social impacts that may be reported during the visit. If adverse events requiring further evaluations or management are identified during the visit, staff conducting the visit should arrange for appropriate clinical management, in consultation with the site investigator, as needed.

- When capacity to conduct study visits is limited, procedures should be prioritized in the following order:
 - Clinical procedures, as guided by local standards of care, to ensure participant safety.
 - Study product provision and/or administration
 - Laboratory procedures (see protocol [Section 6.16.1](#) for specimen prioritization).
 - Contraceptive counseling, if applicable
 - Acceptability/tolerability questionnaires
- If laboratory tests cannot be performed consistent with a site's Protocol Analyte List, the tests may be performed in alternate laboratories using alternate assays (alternate laboratories must adhere to local regulations for clinical laboratory testing). Sites should identify feasible options for performing pregnancy testing for participants of childbearing potential, including use of home test kits.

Study Drug Supply

- As indicated above, new participants should only be enrolled if the site investigator has confidence that local conditions will allow for provision of study product, with additional guidance listed below.
- Oral study product may be dispensed off-site at the Week 2 or Week 4a visits in accordance with [Section 6.1.3](#).
- For participants receiving injectable study products (CAB LA, RPV LA), injections must be administered on-site. Sites should carefully assess their capacity to monitor participant safety and only consider administering injectable study products if there is adequate assurance that safety can be monitored through the conduct of on-site, off-site, or virtual visits. At sites where these conditions can be met, administration of injectable study products may continue. At sites where these conditions cannot be met, sites should consult the IMPAACT 2036 CMC for additional guidance.

Documentation

- Site-specific contingency plans, and the implementation thereof, should be documented in essential document files for IMPAACT 2036.
- Documentation should be entered in participant study charts in real-time (or close to real-time) should any of the following occur:
 - Missed visits
 - Out-of-window visits
 - Off-site or virtual visits (document the location of the visit)
 - Incomplete or partial visits (document which procedures were performed, and which were not)
 - Virtual visits performed in lieu of in-person visits (document method used to complete the contact and which procedures were performed)
 - Any other participant contacts
 - Use of alternate laboratories or alternate laboratory assays
- In consultation with the Division of AIDS, the IMPAACT Network has developed and disseminated guidance for documenting and/or reporting protocol deviations that may occur due to limited site capacity to conduct study visits or procedures due to COVID-19.