IMPAACT 2017

Phase I/II Study of the Safety, Acceptability, Tolerability, and Pharmacokinetics of Oral and Long-Acting Injectable Cabotegravir and Long-Acting Injectable Rilpivirine in Virologically Suppressed HIV-Infected Children and Adolescents

"MOCHA"
More Options for Children and Adolescents

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

Pharmaceutical Support Provided by:
ViiV Healthcare

DAIDS ID #30070
IND #138,754 Held By DAIDS

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FINAL Version 4.0
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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

IMPAACT 2017
Phase I/II Study of the Safety, Acceptability, Tolerability, and Pharmacokinetics of Oral and Long-Acting Injectable Cabotegravir and Long-Acting Injectable Rilpivirine in Virologically Suppressed HIV-Infected Children and Adolescents

DAIDS Study ID #30070

Version 4.0
Protocol Signature Page

I will conduct this study in accordance with the provisions of this protocol amendment 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 Conference on Harmonisation Guideline for Good Clinical Practice (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.

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ABBREVIATIONS AND ACRONYMS

3TC	Lamivudine
ABC	Abacavir
ADR	Adverse drug reaction
AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine Transaminase
ARV	Antiretroviral
ART	Antiretroviral Therapy
AST	Aspartate Aminotransferase
ATV	Atazanavir
AUC	Area under the plasma concentration-time curve
BMI	Body Mass Index
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
C28D	Concentration at 28 days
CAB	Cabotegravir
CAB LA	Long-Acting Injectable Cabotegravir
cART	Combination Antiretroviral Therapy
CAR	Continued Antiretroviral Regimen
CBC	Complete Blood Count
CD4	Cluster of differentiation 4
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CHOP	Children's Hospital of Philadelphia
CI	Confidence intervals
CK	Creatine Kinase
CL/F	Apparent total body clearance
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	Maximum concentration
CM	Clarification Memorandum
CMC	Clinical Management Committee
COVID-19	Coronavirus disease 2019
CPK	Creatine phosphokinase
CrCl	Creatinine clearance
CRMS	NIAID Clinical Research Management System
CRPMC	NIAID Clinical Research Products Management Center
CT	Cohort
C_{τ}	Trough concentration
C_{NDx}	Concentration at a specified time (x) after administration of a specific dose number (ND)
CV%	Coefficient of variation
CVF	Confirmed Virologic Failure
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
DMPK	Drug Metabolism and Pharmacokinetics
DTG	Dolutegravir
EAE	Expedited Adverse Event
EC	Ethics Committee
ECG/EKG	Electrocardiogram
eCRF	Electronic Case Report Form
EFV	Efavirenz
EIA	Enzyme immunoassay
ETV	Etravirine
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
HCV	Hepatitis C virus
HDPE	High density polyethylene
HIV	Human Immunodeficiency Virus
HPLC/MS/MS	High-performance liquid chromatography and tandem mass spectrometry
HSP	Human Subject Protection
HVTN	HIV Vaccine Trials Network
IATA	International Air Transport Association
IB	Investigator's Brochure
IC_{90}	90% inhibitory concentration
ICH	International Council on Harmonisation
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
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
λz	Terminal slope
LA	Long-acting
LDMS	Laboratory Data Management System
LoA	Letter of Amendment
LPC	Laboratory processing chart
LSFU	Long-term Safety and Washout PK Follow-Up
MC	Monte Carlo simulations
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
NOAEL	No-observed-adverse-effect-level
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
PPN	Pre- and postnatal
Q4W	Study drug administration every 4 weeks
Q8W	Study drug administration every 8 weeks
q.d.	One a day
QTc	Corrected Q-T interval
QTcB	Corrected QT interval according to Bazett
QTcF	Corrected QT interval according to Fridericia
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	Subject Enrollment System
SID	Study Identification Number
SMC	Study Monitoring Committee
SMR	Sexual Maturity Rating
SoC	Standard of Care
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
V/F	Apparent volume of distribution
VL	Viral load
VQA	Virology Quality Assurance Program

WHO	World Health Organization

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IMPAACT 2017
Phase I/II Study of the Safety, Acceptability, Tolerability, and Pharmacokinetics of Oral and Long-Acting Injectable Cabotegravir and Long-Acting Injectable Rilpivirine in Virologically Suppressed HIV-Infected Children and Adolescents

SCHEMA

Purpose: To confirm the dose and evaluate the safety, tolerability, acceptability, and pharmacokinetics (PK) of oral cabotegravir (CAB), long-acting injectable cabotegravir (CAB LA), and long-acting injectable rilpivirine (RPV LA) in virologically suppressed children and adolescents living with HIV aged 12 to <18 years.

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

Study Population: Children and adolescents, 12 to <18 years of age living with HIV-1, who are virologically suppressed on stable cART consisting of 2 or more drugs from 2 or more classes of antiretroviral drugs, and selected parents/caregivers.

Sample Size: Up to 155 adolescents in total

Cohort 1: Up to 55 adolescents to achieve approximately 30 to 35 dose-evaluable receiving the oral followed by the LA dose of CAB (Cohort 1C) or RPV (Cohort 1R), in addition to cART, which, passing safety and PK guidelines, are recommended as dosing for Cohort 2. Cohort 1C and Cohort 1R assignment is based on the adolescent's pre-study cART regimen.

- Cohort 1C: Up to 30 adolescents to achieve approximately 15 to 20 dose-evaluable for CAB. The dose-evaluable population will include at least 4 adolescents assigned female at birth, at least 4 adolescents assigned male at birth, at least 5 adolescents weighing 35 kg to less than 50 kg at study entry, and at least 5 adolescents weighing at least 50 kg at study entry.

- Cohort 1R: Up to 25 adolescents to achieve approximately 15 dose-evaluable for RPV. The dose-evaluable population will include at least 4 adolescents assigned female at birth, at least 4 adolescents assigned male at birth, at least 5 adolescents weighing 35 kg to less than 50 kg at study entry, and at least 5 adolescents weighing at least 50 kg at study entry.

Cohort 2: Up to 155 adolescents enrolled across Cohort 2A and Cohort 2B to achieve the following:

- At least 100 participants exposed to the final recommended dose for Cohort 2 (including adolescents enrolled to Cohort 2 who previously participated in Cohort 1), which includes
- Approximately 70 evaluable participants receiving the final recommended doses for Cohort 2 who had not previously participated in Cohort 1.

Up to 60 parents or caregivers of adolescent participants, as selected by the protocol team, to complete a single qualitative phone interview (U.S. sites only).

Note: For definition of "dose-evaluable", please refer to Section 9.5.1.3 of the protocol. For definition of "evaluable", please refer to Section 9.1 (General Design Issues) of the protocol.

Study Product:

Cohort 1:

- Cohort 1C: 30 mg CAB once daily orally for at least four weeks (up to a maximum of 6 weeks) in addition to cART (Step 1 oral phase), followed by two single intramuscular injections of CAB LA four weeks apart (600 mg injections) in addition to cART (Step 2 injection phase).

- Cohort 1R: 25 mg RPV once daily orally for at least four weeks (up to a maximum of 6 weeks) in addition to cART (Step 1 oral phase), followed by two single intramuscular injections of RPV LA four weeks apart (900 mg injections) in addition to cART (Step 2 injection phase).

Dose adjustments are not anticipated but may occur as described in protocol Sections 9 and 10.

Cohort 2:

- Cohort 2A (oral lead-in followed by injections): 30 mg CAB + 25 mg RPV once daily orally for at least four weeks, and up to a maximum of 6 weeks, during Step 3 oral phase, followed by intramuscular injections of CAB LA + RPV LA: first and second injections four weeks apart (CAB LA 600 mg injection + RPV LA 900 mg injection), with subsequent injections every eight weeks through and including Week 96 (CAB LA 600 mg injections + RPV LA 900 mg injections) during Step 4 injection phase.

- Cohort 2B (start with injections): Intramuscular injections of CAB LA + RPV LA: first and second injections four weeks apart (CAB LA 600 mg injection + RPV LA 900 mg injection), with subsequent injections every eight weeks through and including Week 92 (CAB LA 600 mg injections + RPV LA 900 mg injections) during Step 5 injection phase.

Duration of Follow-Up:

Adolescents in Cohort 1 will be followed for up to 64 weeks. Adolescents will be followed for at least four weeks in Step 1 (oral phase) and at least 12 weeks in Step 2 (injection phase). All Step 2 adolescents will be followed (on cART, off study product) for up to an additional 48 weeks as part of long-term safety and washout PK follow-up (LSFU) after their last study product injection. Cohort 1 participants enroll into Cohort 2, if eligible, prior to completing long-term safety and washout PK follow-up.

Adolescents in Cohort 2 will be followed for up to 144 weeks. Cohort 2A adolescents will be followed for at least four weeks in Step 3 (oral phase) and 92 weeks in Step 4 (injection phase). Cohort 2B (start with injections) adolescents will be followed for 92 weeks in Step 5. After completing 92 weeks of follow-up in the injection phase, Cohort 2 adolescents may continue access to injectable study products through a mechanism external to the protocol and will exit the study. Cohort 2 adolescents who prematurely permanently discontinue injectable study product use or upon completion of their study product dosing regimen do not wish to receive CAB LA +

RPV LA external to the protocol, will be followed (on cART, off study product) for an additional 48 weeks as part of long-term safety and washout PK follow-up after their last study product injection.

Enrolled parents/caregivers will complete a single qualitative phone interview (U.S. sites only).

Study Duration: Approximately 7 years total. Accrual into Cohort 1 is expected to require approximately two years. Following reviews of data from Cohort 1, accrual into Cohort 2 is expected to require approximately 18 months. Adolescents in Cohort 2 will be followed for up to three years.

Primary Objectives: Cohort 1 (continuing a background cART regimen)

- To confirm the doses for oral CAB followed by injectable CAB LA in adolescents living with HIV who are virologically suppressed by evaluating:
  - Safety and multiple dose PK of oral CAB through Week 4;
  - Safety and multiple dose PK of CAB LA through Week 16.

- To confirm doses for injectable RPV LA in adolescents living with HIV who are virologically suppressed by evaluating safety and multiple dose PK of RPV LA through Week 16.

Primary Objective: Cohort 2 (discontinuing a background cART regimen)

- To assess the safety of CAB + RPV in adolescents living with HIV who are virologically suppressed through:
  - Week 24 (Cohort 2A: oral followed by injectable) ;
  - Week 20 (Cohort 2B: injectable only).

Secondary Objectives: Cohort 1

- To monitor maintenance of viral suppression through Week 16 adolescents living with HIV who are virologically suppressed.

- To evaluate the tolerability and acceptability of CAB LA through Week 16 adolescents living with HIV who are virologically suppressed.

- To evaluate the tolerability and acceptability of RPV LA through Week 16 in adolescents living with HIV who are virologically suppressed.

Secondary Objectives: Cohort 2

- To assess safety of CAB LA + RPV LA in adolescents living with HIV who are virologically suppressed through:
  - Week 48 (Cohort 2A: oral followed by injectable);
  - Week 44 (Cohort 2B: injectable only).

- To evaluate repeat-dose pharmacokinetics of CAB LA + RPV LA in adolescents living with HIV who are virologically suppressed through:
  - Week 24 and through Week 48 (Cohort 2A: oral followed by injectable);
  - Week 20 and through Week 44 (Cohort 2B: injectable only).

- To assess antiviral activity of CAB LA + RPV LA in adolescents living with HIV who are virologically suppressed through:
  - Week 24 and through Week 48 (Cohort 2A: oral followed by injectable);
  - Week 20 and through Week 44 (Cohort 2B: injectable only).

Other Objectives

- To evaluate the tolerability and acceptability of CAB LA + RPV LA in adolescents living with HIV who are virologically suppressed through:
  - Week 24, through Week 48, and through Week 96 (Cohort 2A: oral followed by injectable);
  - Week 20, through Week 44, and through Week 92 (Cohort 2B: injectable only).

- To evaluate the safety, antiviral and immunologic activity, and characterize PK of CAB LA + RPV LA in adolescents living with HIV who are virologically suppressed through:
  - Week 96 (Cohort 2A: oral followed by injectable);
  - Week 92 (Cohort 2B: injectable only).

- To evaluate adolescent participant's experience of CAB LA and/or RPV LA, and parent/caregiver's experience and perceptions of adolescent acceptability and tolerability of CAB LA and/or RPV LA (Cohort 1 and Cohort 2).

- To evaluate the tolerability and acceptability, and characterize long-term safety and washout PK through 48 weeks following permanent discontinuation of CAB LA or RPV LA (Cohort 1).

- To evaluate the tolerability and acceptability, and characterize long-term safety and washout PK through 48 weeks following permanent discontinuation of CAB LA + RPV LA (Cohort 2).

- To describe HIV-1 genotypic and phenotypic resistance patterns in participants experiencing confirmed virologic failure (Cohort 1 and Cohort 2).

Figure 1. Overview of Study Design for Cohort 1 Participants

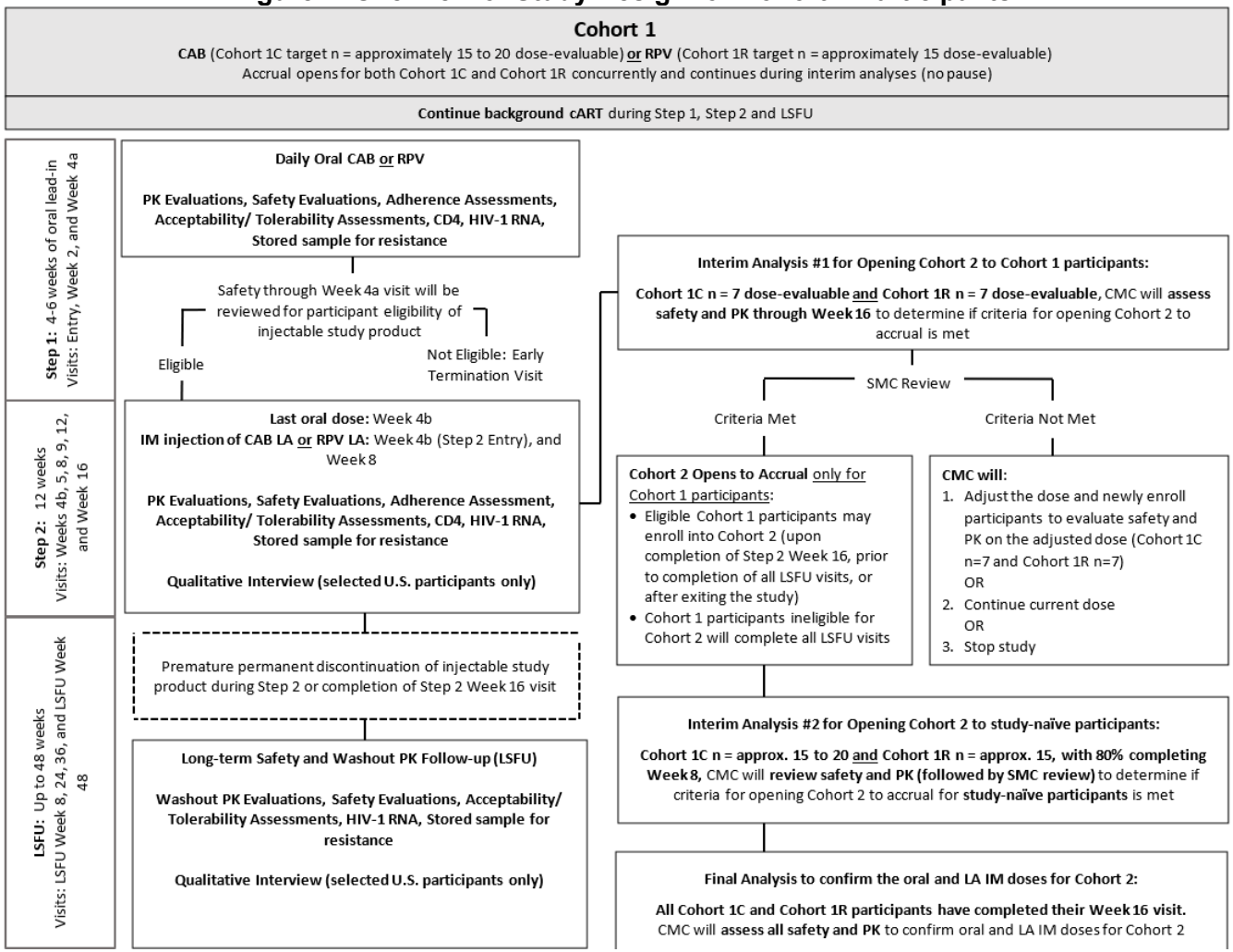
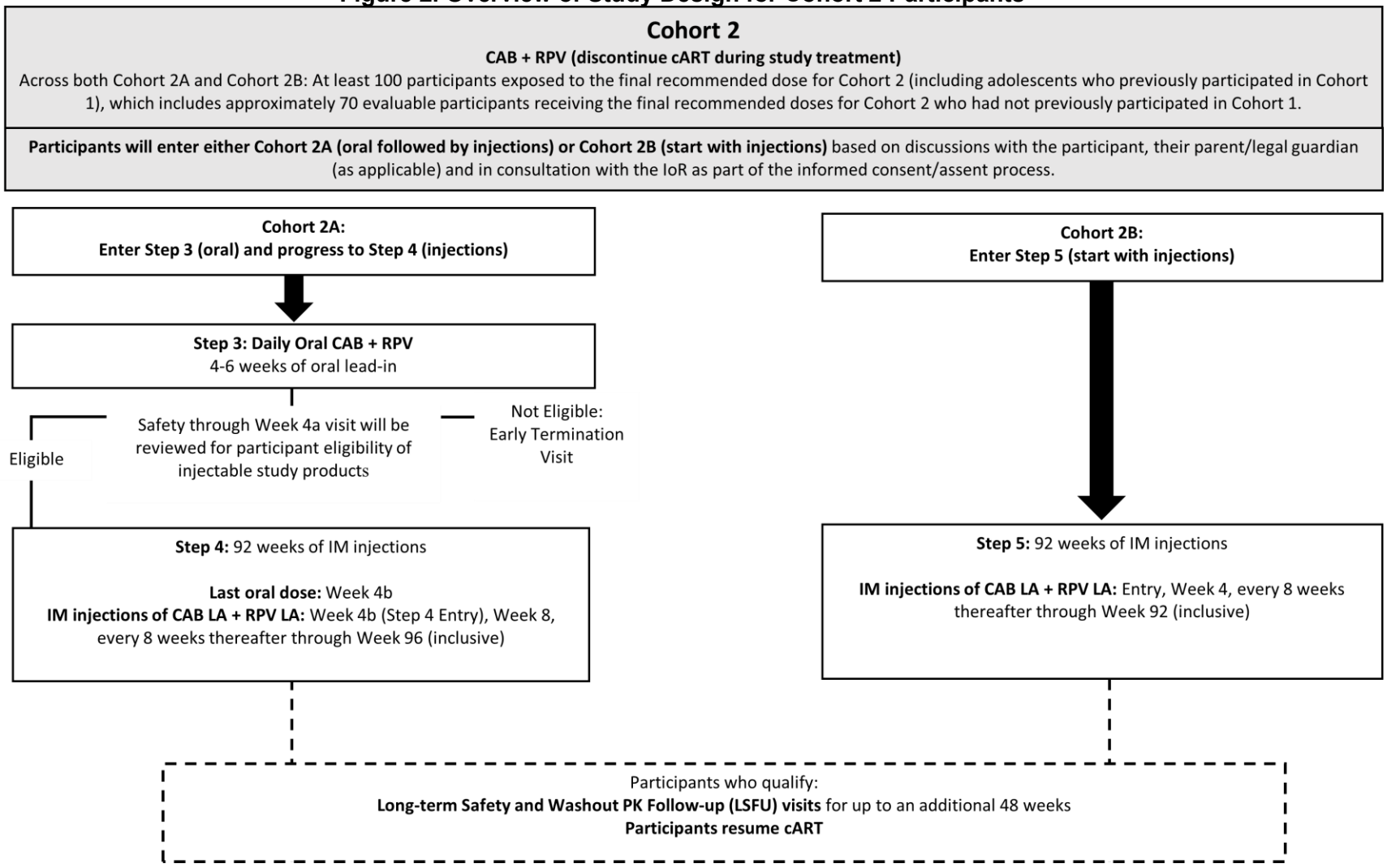


Figure 2. Overview of Study Design for Cohort 2 Participants



1 INTRODUCTION

1.1 Background

Contemporary antiretroviral therapy (ART) for management of HIV includes many potent, safe dosing options, some of which are available for adolescents and adults as one-pill, once-a-day, combination ART regimens. The long term success of HIV treatment remains dependent upon sustaining adherence to daily ART, which can be challenging (1, 2). In pediatrics, this is often further nuanced by factors specific to adolescents and their caregivers (3). Successful progression through the continuum of HIV care is poorer among adolescents than adults in the United States of America (US), with as many as 43% failing to reach and sustain HIV viral suppression (4). Unstructured treatment interruptions are a major issue for youth living with perinatally acquired HIV-1, with medication fatigue being the most common cited reason for such interruptions (5). While the current ART standard of care includes a backbone of two nucleoside reverse transcriptase inhibitors (NRTIs) plus another antiretroviral (ARV), alternative approaches are being examined that simplify treatment, reduce lifelong drug exposure and drug burden, preserve future treatment options, and minimize or avoid ART toxicities, particularly of NRTIs. Regimens being explored are "NRTI-reducing" or “NRTI-sparing”, including two-drug ART (from two independent classes) as initial treatment or a switch strategy (in virologically suppressed individuals) (6).

Long-acting (LA) injectable antiretrovirals are promising new therapies both for HIV treatment (7) and HIV prevention (8) that may change the treatment paradigm, although present unique implementation challenges. These monthly/2-monthly intramuscular (IM) injections, and other long-acting ART drug delivery platforms, could provide options to the current daily oral ART standard of care. These regimens could optimize treatment adherence and ultimately maximize the benefits of ART. This approach is similar to modern contraceptive product development, which has greatly expanded client choices and includes a diversity of drug delivery options, such as oral tablets, intramuscular injections, long-acting implants and skin patches.

Cabotegravir (CAB) is a potent integrase strand transfer inhibitor (INSTI) with attributes allowing formulation and delivery as a LA parenteral product. Rilpivirine (RPV), also formulated as a LA product, is a diarylpyrimidine derivative and a potent non-nucleoside reverse transcriptase inhibitor (NNRTI) with in vitro activity against wild type HIV-1 and select NNRTI-resistant mutants. Long-acting CAB LA and RPV LA have been shown in clinical trials in adults living with HIV to be safe, well tolerated and efficacious as a dual injectable ART in treatment-naïve settings (step down, maintenance therapy after an oral three drug ARV induction therapy (9, 10) (Phase 3 Clinical trial ongoing; FLAIR, 201584, ClinicalTrials.gov Identifier: NCT02938520). A Phase 3 clinical trial of CAB LA plus RPV LA as a dual therapy approach in treatment experienced, virologically suppressed individuals (ATLAS 201585) showed that the regimen of monthly injections of CAB LA + RPV LA was noninferior to continued 3-drug oral ART at Week 48 and is currently ongoing, [ClinicalTrials.gov Identifier: NCT02951052] (11). Another study, ATLAS-2M [ClinicalTrials.gov Identifier: NCT03299049], demonstrated the non-inferior antiviral activity and acceptable safety profile of CAB LA + RPV LA administered every 8 weeks (Q8W) compared to CAB LA + RPV LA administered every 4 weeks (Q4W) over a 48-week treatment period in virologically suppressed adults (12). These studies support both Q4W and Q8W duration regimens as treatment choices. A two-drug combination therapy with CAB LA plus RPV LA may therefore offer a comparable tolerability and resistance profile, as well as improved adherence and treatment satisfaction in virologically suppressed participants (9).

Building on the experience to date with CAB LA and RPV LA in adults living with HIV, IMPAACT 2017 Cohort 1 will assess the safety and PK of sequentially dispensed oral CAB followed by CAB LA (Cohort 1C), as well as oral RPV followed by RPV LA (Cohort 1R) in virologically suppressed adolescents living with HIV who continue their oral cART regimen. IMPAACT 2017 Cohort 2 will then establish if virologically suppressed adolescents living with HIV remain suppressed upon switching to a two-drug intramuscular (IM) regimen of CAB LA plus RPV LA. The age studied will be adolescents aged 12 to <18 years and ≥35kg.

1.2 Prior Research

1.2.1 Cabotegravir

Cabotegravir (GSK1265744) is an HIV INSTI that has attributes favorable for both HIV treatment and prevention indications. CAB is available as both oral and injectable long-acting formulations.

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 2 to 3 hours post dose in the fasted state. Co-administration of single dose CAB 5 mg and 30 mg tablets with a moderate fat meal demonstrated minimal impact (<15% increase in CAB AUC(0-∞) and no impact on C_{max}. In clinical studies to date, CAB tablets were taken without regard to the timing of or type of food consumed. CAB half-life of 35 to 42 h has been noted following oral administration. (13)

CAB LA is a 200 mg/mL nanosuspension that has been administered as an IM injection and a SC 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. Due to limited sampling, the observed apparent T_{max} is generally observed at approximately one week post IM injection in Phase 2 studies. Apparent terminal phase t½ following CAB LA reflects absorption and ranges from approximately 18 to 50 days. Steady state appears to be achieved by 20 to 40 weeks of the first IM injection of CAB LA Q4W or Q8W regimens. Variability in CAB C_{max} following CAB LA is moderate to high with CV% ranging from 30 to >100%, due to variability in absorption rate. However, AUC (0-∞), which reflects the extent of absorption rather than the rate of absorption, exhibits lower variability with CV% ranging from 12 to 53%. In addition, variability decreases upon repeat administration. (13)

Following administration in humans, CAB is primarily eliminated through metabolism, and renal elimination of unchanged CAB represents less than 1% of the total dose administered. In vitro and in vivo data indicate that CAB is primarily metabolized by UGT1A1 with some involvement from UGT1A9. CYP-mediated CAB metabolism is expected to be minimal as evidenced by the lack of effect observed when co-administered with etravirine (ETV), a known CYP3A4 inducer, in human participants. Cabotegravir 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 feces and 26.8% of the total oral dose is excreted in the urine, primarily as a glucuronide metabolite (75% of urine radioactivity, 14% of total dose). (13)

CAB LA has been administered intramuscularly to healthy adults and adults living with HIV at doses of 100mg to 800mg. In participants living with HIV, CAB LA has maintained virologic suppression on maintenance doses of 400mg IM Q4W and 600mg IM Q8W injections in conjunction with RPV LA (200056, 201584, 201585 and 207966). A population PK model including all relevant clinical PK data including IM data in 1647 adults (26% female) indicated that gender and BMI were statistically significant covariates (but clinically insignificant) affecting the absorption rate constant following IM administration, such that absorption was slower in females than males and in participants of larger BMI (up to 60kg/m2). (13) The slower absorption in females and high BMI participants resulted in lower peaks and higher troughs and was not associated with clinical outcome differences. Potential participants with high BMI have been excluded from Cohort 1 to minimize variability in characterization of PK parameters but high BMI will not be an exclusion for Cohort 2.

CAB has no reported significant effect on cardiac repolarization. (13)

Summary of cabotegravir safety data:

The integrated analysis of safety data across the Phase III clinical studies when considered in combination with Phase I and Phase II data supports an acceptable safety profile of CAB + RPV. Safety conclusions from the clinical development program demonstrate the following:

- 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 7 days. The percentage of participants reporting ISRs at each visit decreased over time. Few ISRs led to withdrawal.

- Participant acceptance scores for anxiety pre- and post-injection decreased over time during the Phase III studies in the CAB + RPV treatment regimen.

- The most common non-ISR AEs (≥10%) in the Phase III program for CAB + RPV and continued antiretroviral regimen (CAR) were nasopharyngitis, upper respiratory tract infection, and headache. The majority of events reported had an intensity of Grade 1 or Grade 2. 47 (8%) participants in the CAB + RPV group and 35 (6%) participants in the CAR group experienced AEs that were Grade 3 to Grade 5. No Grade 5 events were reported in the Phase III studies for participants receiving CAB + RPV.

- Non-ISR AEs that occurred more frequently with CAB + RPV were hemorrhoids, pyrexia, dizziness, fatigue, and headache. Except for headache, the incidence of these AEs in the CAB + RPV group was <10%.

- A higher incidence of non-ISR, drug-related AEs in the CAB + RPV group was noted. Most drug-related AEs were Grade 1, although a few Grade 3 to 4 AEs occurred. The most frequent drug-related Grade 3 to 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 participants in the comparator CAR group had been on a stable and tolerable ART regimen.

- In the pooled analysis from the Phase III Maintenance Phases, 1 participant in the CAR group died due to a serious adverse event (SAE) of methamphetamine overdose. This case was not considered to be related to study drug by the investigator and was the only Grade 5 SAE.

- The rate of SAEs was low overall and was comparable between the CAB + RPV and CAR treatment groups. The most frequently reported SAEs were hepatitis A, colitis, and anogenital warts.

- 31 (5%) participants in the CAB + RPV group and 26 (4%) participants in the CAR group had drug-related, non-ISR SAEs.

- The rate of discontinuation was low overall for the Phase III studies. Discontinuations from the study were more frequent in the CAB + RPV group. Reasons for discontinuations were primarily ISRs and acute viral hepatitis. 22 (4%) participants in the CAB + RPV group and 9 (2%) participants in the CAR group had AEs leading to withdrawal/permanent discontinuation of study drug during the Maintenance Phase. 17 (3%) participants in the CAB + RPV group and 9 (2%) participants in the CAR group had non-ISR AEs leading to discontinuation. All individual AEs leading to withdrawal had an incidence of <1%.

- Results from the Phase III studies indicate that CAB + RPV appears to have no clinically relevant effect on safety related to QT prolongation, seizures, rhabdomyolysis, pancreatitis, or impact on creatinine.

- Incidence of neuropsychiatric events was low overall for suicidal ideation/behavior, depression, and anxiety. Events occurred with similar frequency between treatment groups.

- A higher incidence for mood disorders was observed in the CAB + RPV group compared with the CAR group.

- The incidence of sleep disorders events (including drug-related events), particularly insomnia, was higher in the CAB + RPV group compared with that of the CAR group during the Phase III studies.

- Modest weight gain occurred in both CAB + RPV and CAR treatment groups, although median weight gain was greater in the CAB + RPV group. BMI increased in both CAB + RPV and CAR treatment groups, with a greater median change in the CAB + RPV group. The clinical significance of this weight gain is not clear. There were some shifts in BMI for the CAB + RPV group that trended toward unfavorable.

- Overall, the frequency and categories of drug related adverse events reported with daily oral CAB 30 mg have been similar to those reported with CAB LA and are infrequently treatment limiting.

- The majority (74.7% CAB + RPV, 80.2% CAR%) of the maximum post-baseline emergent clinical chemistry toxicities were Grade 1 or Grade 2 in intensity. 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 toxicities between the CAB + RPV and CAR groups.

- Results from the Phase III clinical program do not suggest any effect of age, sex, or race on the safety profile of CAB + RPV.

- Patients living with HIV with evidence of hepatitis B virus (HBV) coinfection were excluded from the CAB + RPV clinical program as CAB + RPV do not have activity against HBV. No conclusions can be made about the safety of CAB + RPV in Hepatitis B co-infected patients.

- In the Phase III studies, 41/591 participants on CAB + RPV and 40/591 participants on CAR were determined to be co-infected with hepatitis C virus (HCV) at Baseline, as shown by HCV serology testing alone. The participants without advanced chronic HCV were not at increased risk of developing hepatotoxicity or increased transaminases compared with participants living with HIV. None of the participants in Studies 201584 and 201585 who became acutely infected with HCV on study resumed CAB + RPV after temporarily discontinuing dosing while the acute HCV infection either spontaneously resolved or stabilized.

- No dose adjustment in CAB (oral or LA) or RPV (oral or LA) is required for patients with mild or moderate hepatic impairment. No data are available in severe hepatic impairment.

- No dose adjustment of oral CAB or CAB LA or oral RPV or RPV LA is required for patients with mild to moderate renal impairment. No dose adjustment of oral CAB or CAB LA is required for severe renal impairment. No data are available in severe renal impairment or end-stage renal disease for RPV.

- Medication errors and device malfunctions were infrequent occurrences, and no adverse events were directly attributable to these errors and no evidence for lack of efficacy has been detected as the result of an error. Overall, no discernable trends or systematic errors were identified, apart from an initial lack of familiarity by the health care provided.

- In the Phase IIIb study ATLAS-2M Q8W dosing of CAB+RPV LA was noninferior to Q4W dosing and well tolerated. CAB+RPV LA Q8W was noninferior to Q4W dosing in both the primary (proportion with plasma HIV-1 ribonucleic acid (RNA) ≥50 c/mL 1.7% vs 1.0%) and secondary analysis (proportion with HIV-1 RNA <50 c/mL 94.3% vs 93.5%) at Week 48. ISRs were mostly mild or moderate (98% overall) with a median duration of 3 days. (12)

Results from the CAB + RPV development program support the use of the regimen in virally suppressed patients living with HIV. In clinical studies, a higher incidence of AEs leading to withdrawal and Grade 3/4 AEs was reported in the CAB + RPV group. Overall, CAB + RPV appeared to be tolerated as well as comparator regimens. Although ISRs occurred frequently, few were treatment limiting.

Summary of side effects observed and/or monitored for in patients on cabotegravir include:

Long-acting properties of cabotegravir injection
Residual concentrations of CAB remain in the systemic circulation of participants who stop HIV treatment (e.g. for tolerability issues or treatment failure) for prolonged periods (up to 12 months or more) (13). Participants discontinuing an LA regimen may be at risk for developing viral resistance to CAB many weeks after discontinuing injectable therapy; therefore, adoption of an alternative, fully suppressive antiretroviral regimen is essential.

Hepatobiliary disorders
Four participants with possible or probable drug-induced liver injury (DILI) related to CAB have been identified in the Phase 2b HIV treatment studies. Three of these participants met liver stopping criteria 4-8 weeks after initiation of oral treatment with CAB (60 mg n=2, 30 mg n=1). The fourth participant met liver stopping criteria after having received approximately 44 weeks of treatment with oral CAB 30 mg. In all cases participants remained asymptomatic, did not develop hepatic dysfunction and liver aminotransferase elevations returned to normal or approached pre-treatment levels following withdrawal of all antiretroviral treatment. A role of CAB in these cases could not be ruled out. One of the four participants, with ongoing active chronic hepatitis C infection, developed a concomitant increase in total and direct bilirubin. This participant had underlying liver fibrosis. The three remaining participants had evidence of hepatosteatosis on liver imaging - which may have been pre-existing (13). In addition, a single case of suspected DILI was identified in a CAB/rifabutin drug interaction study (205712). A 55-year-old male developed Grade 3 elevations in liver aminotransferases three weeks after co-administration of oral CAB and rifabutin ended. Liver workup was unremarkable except for a fatty liver on ultrasound examination, the participant was asymptomatic throughout, and the findings were consistent with a mixed hepatocellular and cholestatic type hepatitis. The elevated liver aminotransferases fully resolved after approximately 23 weeks. One further case of possible DILI occurred in the Phase III study (207966) and involved a 20-30-year-old female who was randomized at Baseline to the Q4W group. The participant had previously received standard of care (SoC) with lopinavir + ritonavir + abacavir + lamivudine as part of Study 201585. She had an asymptomatic increase in alanine aminotransferase (ALT) and aspartate aminotransferase (AST). ALT was 206 U/L [>4x upper limit of normal (ULN)], AST was 137 U/L [>3x ULN] with no elevation in bilirubin at Week 4a, after receiving 28 days of oral CAB + RPV. Investigations were negative for viral hepatitis, syphilis, and an autoimmune screen. The oral lead-in (OLI) was extended while the participant was investigated for alternative causes. During this time ALT and AST remained elevated and the participant was eventually withdrawn from the study after receiving a total of 11 weeks of oral CAB + RPV. The participant commenced Abacavir (ABC)/Lamivudine (3TC)/Dolutegravir (DTG) and the ALT/AST returned to normal after 12 weeks.

Elevated transaminases (AST/ALT) were observed in some participants receiving CAB + RPV during the pivotal Phase 3 trials, however, the primary reason for these elevations was the occurrence of acute viral hepatitis (Hepatitis A, B, C).

No suspected cases of DILI have emerged to date in participants receiving CAB LA.

Studies to date have incorporated close monitoring of liver chemistries and have adopted liver stopping criteria. Participants with known and documented Hepatitis B or Hepatitis C infection, with clinically relevant hepatic disease, or ALT Grade 3 or higher are excluded from IMPAACT 2017, per Section 4. Additionally, studies to date involving exposure to the long-acting injection have incorporated an oral lead-in period as a precautionary measure to reduce the risk of severe hypersensitivity (see below) or liver injury developing during exposure to the LA formulation.

Injection site reactions: ISRs are very common, but generally mild or moderate, most frequently comprising pain at the injection site, with localized erythema, pruritis, warmth, swelling, nodule formation, induration or bruising occurring less commonly. Severe ISRs were reported in 4% of participants. Abscess and cellulitis at the injection site have been reported uncommonly (<1% of participants). Median duration of the reactions overall was 3 days. To date, most reactions have been self-limited. (13)

Hypersensitivity reactions
Hypersensitivity reactions have not been reported with cabotegravir but have been reported in association with other integrase inhibitors including the closely related compound, dolutegravir. These reactions were characterized by rash, constitutional findings and sometimes organ, including liver, dysfunction. However, no such reactions have been observed to date in association with CAB. An oral lead-in is being implemented within clinical studies to reduce the risk of a hypersensitivity reaction occurring following the initiation of LA therapy.(13)

Use in pregnancy:
Data in pregnancy are limited. Non-clinical 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). No-observed-adverse-effect-level (NOAEL) was established at the mid dose 5 mg/kg/day, which remains >20 fold predicted C_{max} and AUC exposures for anticipated clinical CAB LA exposures. The clinical significance of these findings is unknown. (13)

Suicidal Ideation and Behavior Monitoring:
CAB exposure has not been associated with an increased risk of suicidal ideation or psychiatric disorders. However, patients living with HIV or those in some categories with a high-incidence of HIV acquisition may occasionally experience symptoms of depression and/or suicidal ideation or behavior. In addition, there have been some reports of depression, suicidal ideation and behavior (particularly in participants with a pre-existing history of depression or psychiatric illness) in some patients being treated with INSTIs. Dolutegravir (DTG) (a closely related integrase inhibitor) has been associated with reports of suicidal ideation or behavior (particularly in patients with a pre-existing history of depression or psychiatric illness). (13)

Seizures:
Overall, there is not convincing evidence that CAB exposure may be causally associated with seizure or with reduction of seizure threshold, due to the low frequency of reports, the confounders present in the cases received to date and lack of any pre-clinical signal or identified plausible mechanism. Three cases of seizures have been documented in the CAB program cumulatively through 01 October 2016. Two of the cases occurred in HIV uninfected participants with a prior history of seizure and one case involved a participant in study 200056 with circumstantial and anecdotal evidence of illicit drug use. (13)

Dolutegravir and Pregnancy

Dolutegravir (DTG) is an INSTI in the same class of pharmaceuticals as CAB. Thus far, limited safety or efficacy data for DTG in pregnancy in humans have been published or presented. In May 2018, World Health Organization (WHO) and several other regulatory agencies released advisories regarding the safety of DTG in early pregnancy. (14)

This was based on information received from the Botswana NICHD-funded Tsepamo Birth Outcomes Surveillance Study, the largest body of data related to birth outcomes following the use of DTG in pregnancy. This study was designed to evaluate adverse birth outcomes by maternal HIV status and ART regimen, and to determine whether there is an increased risk of neural tube defects (NTDs) among infants exposed to efavirenz (EFV) from conception. Botswana's HIV program moved to universal ART with dolutegravir/tenofovir disoproxil fumarate/emtricitabine (DTG/TDF/FTC) in first line for patients starting ART (including pregnant women) in May of 2016 (women already on other regimens were not switched to DTG). The previous first-line regimen was EFV/TDF/FTC. Almost all women on DTG-based and EFV-based ART took these

drugs in combination with TDF/FTC. More than 95% of women in Botswana deliver in a hospital, and obstetric records were available for >99% of women. The Tsepamo surveillance study was originally conducted at 8 of the largest public maternity wards across Botswana (representing ~45% of the total births in the country). This was later increased to 18 sites. Research assistants abstracted exposure data from the maternity card for all consecutive in-hospital deliveries (both women living with and without HIV). Each newborn, whether stillborn or live-born, undergoes a systematic infant surface examination that is completed by trained nurse midwives. Reports and photographs (where available) of major abnormalities are reviewed by an experienced medical geneticist who is blinded to exposure information. In the birth outcome surveillance study in Botswana there were 5 cases of neural tube defects reported (as of March 2019) in 1,683 deliveries (0.3%) to mothers taking dolutegravir-containing regimens from the time of conception, compared with 15 cases in 14,792 deliveries (0.1%) to mothers taking non-dolutegravir-containing regimens from the time of conception (Prevalence Difference 0.20%; 95% CI 0.01-0.59). In the same study, one out of 3,840 deliveries (0.03%) to mothers who started dolutegravir during pregnancy had a neural tube defect, compared with three out of 5,952 deliveries (0.05%) to mothers who started non-dolutegravir-containing regimens during pregnancy. More recent data from this study suggest an even lower incidence of neural tube defects amongst women taking dolutegravir-containing regimens from the time of conception.

A causal relationship of these events to the use of dolutegravir has not been established. The incidence of neural tube defects in the general population ranges from 0.5-1 case per 1,000 live births. As neural tube defects occur within the first 4 weeks of fetal development (at which time the neural tubes are sealed) this potential risk would concern women exposed to dolutegravir at the time of conception and in early pregnancy. More than 1,000 outcomes from second and third trimester exposure in pregnant women indicate no evidence of increased risk of adverse birth outcomes.

Cabotegravir is not dolutegravir. While these medications share a common molecular backbone, and have a similar mechanism of activity, they are different chemical compounds. It is not known if the potential safety signal identified with DTG will be confirmed in other studies and/or settings where DTG is being used. There is insufficient data to confirm or refute any potential INSTI class effect.

CAB was evaluated in a complete package of reproductive toxicology studies, including embryofetal development studies, and no safety findings suggestive of teratogenesis or neural tube defects were identified as of the information included in the 17 December 2019 version of the Investigator's Brochure. Given limited clinical experience with use of CAB in pregnancy, as a precautionary measure, women of reproductive potential are required to adopt highly reliable means of contraception during participation and throughout long term follow up phases of studies following exposure to CAB LA as well as have a negative pregnancy test prior to study entry.

1.2.2 Rilpivirine

Rilpivirine (TMC278, RPV) is a NNRTI with in vitro activity against wild type and NNRTI resistant HIV-1. Rilpivirine 25-mg once daily (oral tablet) is approved for the treatment of HIV-1 in ART-naïve patients 12 years of age and older in multiple countries including the US, the European Union (EU), Canada, and Japan as EDURANT®(15). In most countries, including the US and EU, this indication is further restricted to patients with a plasma viral load (VL) ≤100,000 HIV-1 RNA copies/mL. RPV (dose 25 mg) as part of a once-daily single-tablet oral regimen is also approved for adults and adolescents in several countries as Complera®/Eviplera®

(FTC/RPV/TDF) or Odefsey® (FTC/RPV/tenofovir alafenamide [TAF]) and as part of a single-tablet dual regimen for adults, JULUCA® (DTG/RPV).

A parenteral long-acting formulation of RPV (RPV LA) for intramuscular (IM) injection is indicated, in the US and the European Union (EU), in combination with the integrase inhibitor cabotegravir long-acting (CAB LA), as a complete regimen for monthly or every 2 months dosing for the treatment of HIV-1 infection in virologically suppressed adults (single agent REKAMBYS®, component of co-pack CABENUVA®). Phase III/IIIb studies in combination with a parenteral long-acting formulation of CAB (CAB LA) are ongoing. Of note both the oral and injectable formulation of RPV needs to be protected from direct exposure to light and are dispensed accordingly.

The exposure to RPV as the tablet formulation was approximately 40 -to-50% lower when taken under fasting conditions or with only a nutritional drink as compared to intake with a standard or high fat breakfast. Therefore, oral RPV must always be taken with a meal. (16)

The exposure to RPV can be affected by modulators of CYP3A4-enzyme activity and by drugs that increase the gastric anti-logarithmic proton concentration (pH), the latter being only applicable to oral RPV. Proton pump inhibitors (e.g. omeprazole) should not be co administered with oral RPV as this will decrease the exposure to RPV due to the increase in gastric pH. H_2-receptor antagonists, however, can be used if administered either at least 12 hours before or at least 4 hours after intake of RPV, and antacids can be used if administered either at least 2 hours before or at least 4 hours after intake of RPV. Drugs that induce CYP3A4 activity (e.g. rifampin, carbamazepine) can reduce the RPV exposure (either as oral or LA formulation) and should not be co-administered. Drugs that inhibit CYP3A4 activity (e.g. ketoconazole, boosted protease inhibitors [PIs]) can increase the exposure to RPV (either as oral or LA formulation) but do not require dose adjustments. (16)

The approval of oral RPV 25 mg once daily for adolescents was based on the results of study TMC278-TiDP38-C213. The 48-week results of the adolescent cohort (N=36) in this study demonstrated that treatment with RPV 25 mg once daily, in combination with an investigator-selected background regimen, is efficacious, generally safe and well tolerated in adolescents of ≥12 to <18 years of age (17). The 25 mg once daily dose in adolescents resulted in similar RPV exposure as observed in adults. Also, no apparent relationships were observed between the RPV pharmacokinetics and efficacy or safety parameters in adolescents at Week 48. In the adult trials with the RPV doses of 25 mg once daily, no clear effect of body weight on the RPV exposure was seen. Similarly, data in adolescents between 12 and 18 years of age weighing approximately 33 to 93 kg also showed no effect of body weight on the RPV exposure. (17) 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(16).

Oral RPV 25mg has been co-administered with oral CAB in one Phase 1 study in healthy participants and two Phase 2 studies of participants living with HIV. Study LAI116181 (ClinicalTrials.gov Identifier: NCT01467531) showed that there was no relevant drug interaction between CAB and RPV. (16)

Population pharmacokinetic analysis of RPV in patients living with HIV indicate that race has no clinically relevant effect on the exposure to RPV. No clinically relevant differences in the pharmacokinetics of RPV have been observed between men and women. (16)

The pharmacokinetics of RPV have not been studied in patients with renal insufficiency. Renal elimination of RPV is negligible. Therefore, the impact of renal impairment on RPV elimination is expected to be minimal. As RPV is highly bound to plasma proteins, it is unlikely that it will be significantly removed by hemodialysis or peritoneal dialysis. No dose adjustment of RPV is required in patients with renal impairment. (16)

RPV is primarily metabolized and eliminated by the liver. In a study comparing 8 participants with mild hepatic impairment (Child Pugh score A) to 8 matched controls, and 8 participants with moderate hepatic impairment (Child Pugh score B) to 8 matched controls, the multiple dose exposure of RPV was 47% higher in participants with mild hepatic impairment and 5% higher in participants with moderate hepatic impairment. No dose adjustment is required in participants with mild or moderate hepatic impairment. RPV has not been studied in participants with severe hepatic impairment (Child Pugh score C). (16)

The effect of RPV at the recommended dose of 25 mg q.d. (marketed dose) on the QT interval corrected for heart rate according to Fridericia (QTcF) interval was evaluated in a randomized, placebo and active (moxifloxacin 400 mg q.d.) controlled crossover study thorough QT (TQT) in 60 healthy adults, with 13 measurements over 24 hours at steady state. RPV at the recommended dose of 25 mg q.d. is not associated with a clinically relevant effect on QTc. Higher doses of RPV (75 and 300 mg q.d., 3 and 12 times higher than the recommended dose, respectively) examined in a previous TQT study, were associated with mean maximum QTcF prolongations > 10 ms, which were dose and plasma concentration dependent. Plasma concentrations after administration of RPV LA are substantially lower than those obtained with 75 mg q.d. and 300 mg q.d. and comparable to or lower than the plasma concentrations achieved with RPV 25 mg q.d. given orally. Therefore, no clinically relevant increase in QTcF is expected with the plasma concentrations achieved with RPV LA. In the RPV LA studies performed in healthy participants, no increases in QTc have been seen. (16)

Data on pregnancy and lactation remain limited; the prescribing information recommends that RPV should be used during pregnancy only if the potential benefit justifies the potential risk and that the mothers should be instructed not to breastfeed if they are receiving RPV. (15) RPV in combination with a background regimen was evaluated in the RPV treatment arm of study TMC114HIV3015, in 19 pregnant women during the second and third trimesters, and postpartum. RPV was well tolerated during pregnancy and postpartum. There were no new safety findings compared with the known safety profile of RPV in adults living with HIV-1. (16)

RPV LA (formulation G001) has been administered IM to healthy adults and adults living with HIV at doses of 300 mg to 1200 mg. Up to July 2019, in total, 318 healthy volunteers participated in studies with the long acting (LA) injectable form of RPV of whom 283 received RPV LA. RPV pharmacokinetic parameters following successive monthly intramuscular administration of 1200/600/600 mg RPV LA in the gluteal muscle in healthy adult participants showed a half-life of 91 days +/- 41 days (t/1/2; mean +/- SD) (16). In a Phase IIb study in participants living with HIV (n=230), RPV LA maintained suppression of viral load following monthly (Q4W) IM injections of 600 mg or bi-monthly (Q8W) injections of 900 mg, in conjunction with CAB LA monthly or bi-monthly (study 200056 or LATTE-2 [ClinicalTrials.gov Identifier: NCT02120352]). (9) Currently, a dosing regimen of an RPV LA 900 mg IM loading dose followed by Q4W IM injections of 600 mg, in conjunction with CAB LA Q4W, is being evaluated in two Phase 3 studies in adults (ATLAS [ClinicalTrials.gov Identifier: NCT02951052] and FLAIR [ClinicalTrials.gov Identifier: NCT02938520]). and a dosing regimen of RPV LA 900 mg IM every 2 months is, in conjunction with CAB LA 600 mg, is being evaluated in Phase III

study ATLAS-2M. The results of these clinical studies in participants living with HIV are discussed in Section 1.2.3 below.

Summary of side effects observed and/or monitored for in participants on rilpivirine include:

Virologic Failure and Development of Resistance:
In the pooled analysis from the phase III trials of oral RPV with 2 NRTIs through 96 weeks, participants treated with oral RPV with a baseline viral load >100,000 HIV-1 RNA copies/mL had a greater risk of virologic failure compared to participants with a baseline viral load ≤100,000 HIV-1 RNA copies/mL. The greater risk of virologic failure for participants in the oral RPV arm was observed in the first 48 weeks of these trials while low rates of virologic failure, similar between the treatment arms, were observed from week 48 to week 96. Participants with a baseline viral load >100,000 HIV-1 RNA copies/mL who experienced virologic failure exhibited a higher rate of treatment emergent resistance to the NNRTI class. More participants who failed virologically on oral RPV than who failed virologically on EFV developed 3TC/FTC associated resistance. The use of RPV in combination with CAB is described in Section 1.2.3. No new findings were identified in adolescent participants ≥12 to <18 years of age in trial C213. (16)

Interactions with medicinal products
Caution should be given to prescribing RPV with medicinal products that may reduce the exposure of rilpivirine.

Fat Redistribution
Redistribution/accumulation of body fat, including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and 'cushingoid appearance' have been observed in patients receiving ART. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established. (16)

Injection Site Reactions
Intramuscular or SC injections are procedures which, even with physiological saline, occasionally induce transient reactions at the site of injection, called ISRs. By preferred term, local pain and erythema are the most common expected AEs of this type.

Post-injection reactions
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.

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.

Systemic reactions following RPV LA injections are rare. (16)

Further details about oral rilpivirine can be obtained from the FDA approved full prescribing information. (15)

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

Three Phase III/IIIb studies, Study 201584 (FLAIR), Study 201585 (ATLAS) and study 207966 (ATLAS-2M), and two Phase IIb studies [Study LAI116482 [LATTE] (18) and Study 200056 [LATTE-2] (9)] have been conducted with oral CAB and/or IM CAB LA and oral RPV and/or IM RPV LA.

Study 201584 (FLAIR)
The data from Study 201584 indicate that CAB + RPV is effective in maintaining the suppression of plasma HIV-1 RNA (<50 c/mL) and non-inferior to CAR at Week 48. The study employed a Q4W injection dosing regimen for CAB and RPV following a once daily oral led for 4 weeks.

Of the participants that completed the Induction Phase, a total of 566 participants were randomized (1:1) and treated with CAB+ RPV (n=283) or continue CAR (n=283). Similar proportions of participants in each treatment group withdrew from the study (CAB + RPV: 9%; CAR: 8%). The most frequent primary reason for withdrawal was adverse events (CAB + RPV: 3%; CAR: 1%).

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 CAR group met the 'virologic failure' primary efficacy endpoint of plasma HIV-1 RNA ≥50 c/mL at Week 48 (Snapshot algorithm). Based on a 6% non-inferiority margin, the efficacy analysis demonstrated that CAB + RPV is non-inferior to CAR at Week 48 because the upper bound of the 95% CI for the adjusted treatment difference [-0.4 (-2.8, 2.1)] is less than 6%. The results for the per protocol population were consistent with those from the ITT-E (primary) population. Treatment differences across stratification factors (Baseline HIV-1 RNA and sex at birth) and across additional subgroup analyses (age, race, Baseline CD4+ count, and Baseline Centers for Disease Control and Prevention [CDC] stage of disease) are consistent with the finding of non-inferiority observed in the overall population analysis of the primary endpoint (HIV-1 RNA ≥50 c/mL at Week 48).

The FLAIR 96-week results reaffirm the 48-week results, showing long-acting cabotegravir and rilpivirine 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 cabotegravir and rilpivirine, over an almost 2-year-long period, as a therapeutic option for virally suppressed adults with HIV-1. (19)

After 24 weeks of follow-up, switching to long-acting 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 to the long-acting therapy show long-acting cabotegravir plus rilpivirine remains a durable maintenance therapy with a favorable safety profile. (20)

Study 201585 (ATLAS)

The data from Study 201585 indicate that CAB + RPV is effective in maintaining the suppression of plasma HIV-1 RNA (<50 c/mL) and non-inferior to CAR at Week 48. The study employed a Q4W injection dosing regimen for CAB and RPV following a once daily oral led for 4 weeks.

A total of 616 participants were randomized (1:1) and treated with CAB+ RPV (n=308 or continue CAR (n=308). Similar proportions of participants in each treatment group withdrew from the study (CAB+ RPV: 8%; CAR: 6%). The most frequent primary reason for withdrawal was adverse events (CAB+ RPV: 4%; CAR: 2%).

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 (Snapshot algorithm). Based on a 6% non-inferiority margin, the efficacy analysis demonstrated that CAB + RPV is non-inferior to CAR at Week 48 because the upper bound of the 95% CI for the adjusted treatment difference 0.7 (-1.2, 2.5) is less than 6%. The results for the per protocol population were consistent with those from the ITT-E (primary) population. Treatment differences across stratification factors (baseline third agent treatment class and sex at birth) and across additional subgroup analyses (age, race, country, baseline viral load, baseline CD4+ count, and baseline CDC stage of disease) are consistent with the finding of non-inferiority observed in the overall population analysis of the primary endpoint (HIV-1 RNA ≥50 c/mL at Week 48).

Study 207966 (ATLAS-2M)
In ATLAS-2M, a total of 1,049 participants were randomized (1:1) and treated with CAB + RPV Q8W (n=524) or CAB + RPV Q4W (n=525). Similar proportions of subjects in each treatment group withdrew from the study (CAB + RPV Q8W: 7%); CAB + RPV Q4W: 8%. In the ITT-E population, 1.7% of subjects in the CAB + RPV Q8W group and 1.0% of subjects in the CAB + RPV Q4W group met the primary efficacy endpoint of plasma HIV-1 RNA ≥ 50 c/mL at Week 48. A multivariable logistic regression analysis demonstrated that the strongest association of Snapshot HIV-1 RNA ≥ 50 c/mL was BMI. Overall, injections for Q8W CAB LA + RPV LA were well tolerated with few withdrawals due to injection intolerability (1% in Q8W group and 2% in Q4W group). The most common AEs in both treatment groups were mild/moderate ISRs.

The frequency of subjects reporting at least 1 SAE was similar in the 2 treatment groups (Q8W: 5%; Q4W: 4%). There was 1 fatal (Grade 5) AE; 1 subject in the Q8W group died due to sepsis as a result of a complication of acute pancreatitis. Acute pancreatitis was considered related to study drug by the investigator. Overall, the data from ATLAS 2M indicate that every 2-month (Q8 Week) dosing with CAB + RPV is effective in the suppression of plasma HIV-1 RNA (<50 c/mL) and non-inferior to monthly (Q4 Week) CAB+ RPV at Week 48.

Long-acting 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 long-acting cabotegravir and rilpivirine monthly and every 2 months as maintenance therapy for people living with HIV-1. (21)

Study 200056 (LATTE-2)
In Study 200056, at Week 160, 83% of participants receiving CAB + RPV monthly IM dosing (Q4W) and 90% of participants receiving CAB + RPV bimonthly dosing (Q8W) maintained virologic suppression (HIV-1 RNA <50 c/mL by the Snapshot algorithm). 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 + RPV (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. In the Maintenance and Extension periods of this study there have been 3 protocol-defined virologic failure (PDVFs), 2 in the Q8W arm and 1 in the oral CAB arm. No PDVFs were observed in the Q4W arm throughout the study and no additional PDVFs have been observed since Week 48.

Study LAI116482 (LATTE)
In Study LAI116482, 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). After the last participant completed the Week 96 visit the study was unblinded and all participants, including those in the EFV group, were transitioned to the Sponsor selected regimen of CAB 30 mg + RPV 25 mg. The transition took place between Weeks 108 and 120. There were 9 PDVFs on the CAB arms with 3 occurring between Week 96 and Week 144.

Adverse Drug reactions
The safety assessment (and Adverse Drug Reactions [ADR] identification) was performed for the CAB + RPV regimen as these agents were administered together in the clinical studies for RPV LA. The assessment was based on the analysis of pooled 48-week data from 1,182 virologically suppressed participants living with HIV-1 in 2 international, multicenter, open-label pivotal Phase III studies, 201584 (FLAIR) and 201585 (ATLAS). Additional safety information from earlier clinical studies in the CAB and RPV programs have been considered in assessing the overall safety profile of RPV LA.

The ADR frequencies are based primarily on the pooled data of the Phase III registrational program.

The ADRs are listed by System Organ Class (SOC) and frequency. Frequencies are defined as very common (≥1/10), common (≥1/100 to <1/10) and uncommon (≥1/1,000 to <1/100).

Table 1: Adverse Drug Reactions Observed in Adult Patients Treated with RPV in Combination with CAB [16]

MedDRA System Organ Class (SOC)	Frequency Category	ARs
Psychiatric disorders	Common	depression, anxiety, abnormal dreams, insomnia
Nervous system disorders	Very common	headache
	Common	dizziness
	Uncommon	somnolence vasovagal reactions (in response to injections)
Gastrointestinal disorders	Common	nausea, vomiting, abdominal pain[2], flatulence, diarrhoea
Hepatobiliary Disorders	Uncommon	hepatotoxicity
Skin and subcutaneous tissue disorders	Common	Rash[3]
Musculoskeletal and connective tissue disorders	Common	myalgia
General disorders and administrative site conditions	Very common	injection site reactions[5] (pain and discomfort, site nodule, induration), pyrexia[4]
	Common	injection site reactions[5] (swelling, erythema, pruritis, bruising, warmth, haematoma), fatigue, asthenia, malaise
	Uncommon	injection site reactions[5] (cellulitis, abscess, anaesthesia, haemorrhage, discolouration)
Investigations	Common	weight increased
	Uncommon	transaminase increased

[1]The frequency of the identified ARs is based on all reported occurrences of the events and are not limited to those considered at least possibly related by the investigator.
[2]Abdominal pain includes the following grouped MedDRA preferred terms: abdominal pain, upper abdominal pain.
[3]Rash includes the following grouped MedDRA preferred terms: rash, rash erythematous, rash generalised, rash macular, rash maculo-papular, rash morbilliform, rash papular, rash pruritic.
[4]Pyrexia includes the following grouped MedDRA preferred terms: feeling hot, body temperature increased, pyrexia. The majority of pyrexia events were reported within one week of injections.
[5]Injection site reactions listed in the table have been reported in 2 participants or more.

ISRs were the most frequent AEs associated with the IM use of CAB + RPV. Out of 14,682 injections, 3,663 ISRs were reported. The percentage of participants reporting ISRs decreased over time (Week 4, 70% and Week 48, 16%). A total of 1% of participants discontinued treatment with CAB LA and RPV LA injections, because of ISRs. In Phase III studies 201584 (FLAIR) and 201585 (ATLAS) at the Week 48 analysis, 84% of participants had at least one local ISR at some point over the analysis period, consisting primarily of localized pain/discomfort (79% of participants), see Table 1 above for overall ISR incidence. Other manifestations of ISRs reported in more than 1% of participants over the duration of the analysis period included nodules (14%), induration (12%), swelling (8%), erythema (4%), pruritus (4%), bruising (3%), warmth (2%), and hematoma (2%). Abscess and cellulitis at the injection site were each reported in <1% of patients. The severity of reactions was generally mild (Grade 1, 75% of participants) or moderate (Grade 2, 36% of participants). 4% of participants experienced severe (Grade 3) ISRs, and no participants experienced Grade 4 ISRs. The median duration of overall ISR events was 3 days.

1.3 Study Rationale

The IMPAACT 2017 is a Phase I/II study being conducted to assess the safety, acceptability, tolerability, and pharmacokinetics of oral and long-acting injectable cabotegravir and long-acting injectable rilpivirine in virologically suppressed children and adolescents living with HIV-1. The age group studied will be adolescents aged 12 to <18 years and ≥35 kg.

1.3.1 Protocol Version History

Protocol Version 1.0 was finalized on March 2, 2018 but never implemented. Protocol Version 2.0 was finalized on August 16, 2018. The main purpose of the amendment was to implement protocol modifications recommended by the Division of AIDS (DAIDS) relating to information about the study products that became available after protocol Version 1.0 was finalized, as well as increasing the flexibility in the timing of opening of Cohort 2 to participants who have not previously enrolled to Cohort 1. The amendment also incorporated other modifications, clarifications and administrative edits to improve consistency across protocol sections. See the Summary of Changes to IMPAACT 2017 from Protocol Version 1.0 to Version 2.0 for additional details regarding the modifications and rationale, which is available upon request to the Protocol Team.

Interim analysis #1 was conducted under protocol Version 2.0 and using the evaluable participant definitions presented in protocol Version 2.0. Participants enrolled to IMPAACT 2017 protocol Version 2.0 received the Q4W dosing regimen presented in that version. The protocol was amended to Version 3.0 to incorporate a dosing regimen modification of Q8W. See the Summary of Changes to IMPAACT 2017 from Protocol Version 2.0 to Version 3.0 for additional details regarding the modifications and rationale, which is available upon request to the Protocol Team.

Protocol Version 4.0 modifies the study design of Cohort 2 to allow the oral lead-in phase to be an optional component of Cohort 2 study participation for participants enrolled under that protocol version. To accommodate this, Cohort 2 has been modified to include two groups: Cohort 2A (oral lead-in followed by injections) and Cohort 2B (injections only). Study participants enrolled to Cohort 2 under protocol Version 3 and still on-study will be re-consented to Cohort 2A. See the Summary of Changes to IMPAACT 2017 from Protocol Version 3.0 to Version 4.0 for additional details regarding the modifications and rationale, which is available upon request to the Protocol Team.

1.3.2 Preliminary Review of Study Data

Review of PK Data
Preliminary PK data were reviewed by the Study Monitoring Committee (SMC) on January 17, 2020 and were found to achieve PK targets.

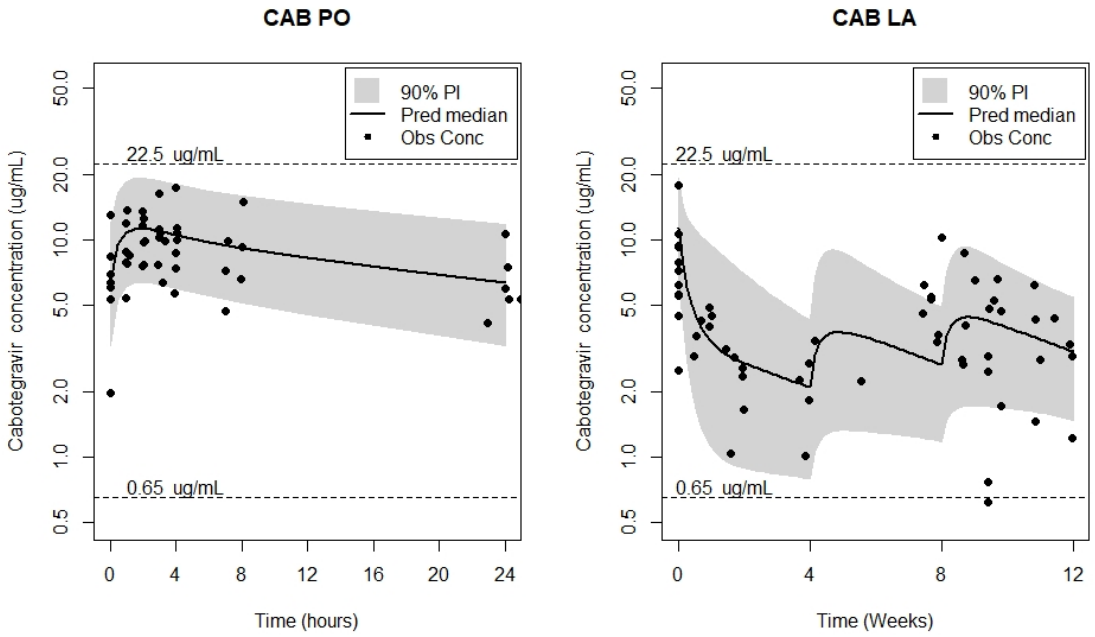
At the time of the January 2020 SMC review, a total of 16 participants had PK collected and analyzed, 7 in Cohort 1C (CAB) and 9 in Cohort 1R (RPV). The Cohort 1C median PK parameters were within the desired median PK target ranges, at Week 2 taken orally (PO) (n=7) and Week 16 IM (n=4), - PO AUC 167.4 (131.1-326.8) mcg*h/mL and IM trough 3.1 (1.2-6.2) mcg/mL. Similarly, the median Cohort 1R PK parameter was within the desired median PK target range at Week 16 IM troughs (n=6) - observed median (target range): 43.8 (40.7-126) ng/mL.

Adult CAB and RPV LA Population (POP) PK models were developed utilizing 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 taking into

account any potential age and weight related impact on PK, to recommend appropriate doses in adolescents that achieve comparable exposures to those seen in adults, initially for a Q4W dosing regimen in line with available clinical data in adults at that time. The preliminary adolescent PK data from the SMC review were compared against *a priori* model predictions and are in agreement with the predicted exposure range and within thresholds as displayed in Figure 3,

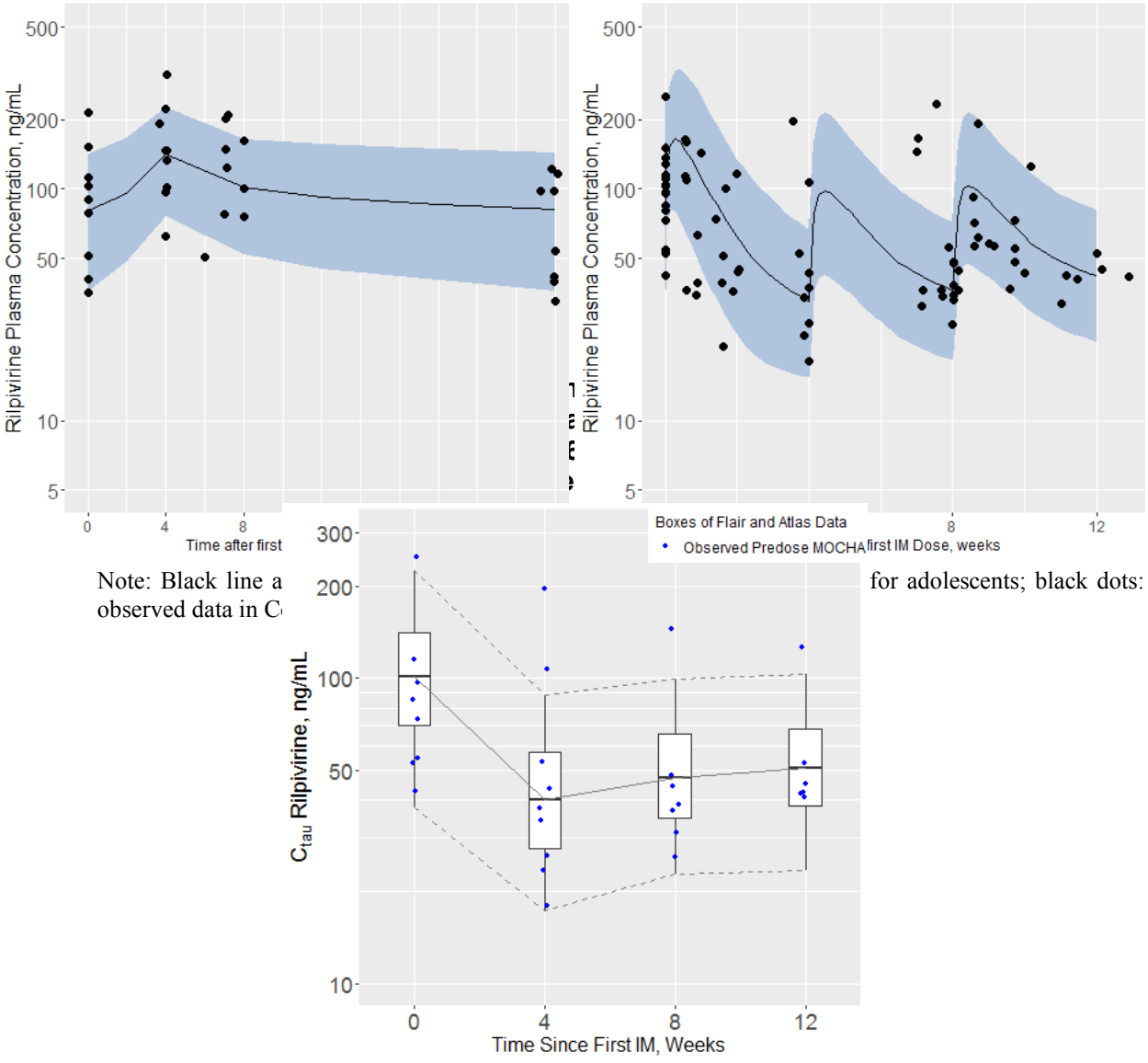
Figure 4, and Figure 5 for CAB and RPV respectively.

Figure 3. Observed preliminary IMPAACT 2017 Cohort 1C CAB concentrations in adolescents 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); the dots represent the observed individual subject data. 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 threshold concentrations at trough (0.65 mcg/mL).

Figure 4. 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 a for adolescents; black dots: observed data in C

Interim Analysis #1 took place on June 19, 2020. Based upon study data from the first seven evaluable participants in each Cohort 1C and Cohort 1R, the IMPAACT 2017 CMC concluded that dosing regimens for CAB PO and LA and for RPV LA achieved the PK targets as per protocol Version 2.0. Additionally, the LSFU PK results indicate both CAB and RPV concentrations maintain pharmacologically relevant concentrations, above the IC90, for several weeks after their final IM injection.

A preliminary analysis of safety and PK data 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 (22). 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 $AUC_{0-\tau}$: 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).

Review of Safety Data
Safety data were reviewed by the SMC in March 2020, and no safety issues or concerns were identified. All available safety data for the eight enrolled participants in Cohort 1C and the 15 enrolled participants in Cohort 1R were presented. At the time of the review, based on the available data, the following were deemed evaluable (with PK and Week 16 safety data): seven evaluable participants in Cohort 1C, and nine evaluable participants in Cohort 1R.

The safety data used in the March 2020 review showed that out of the seven evaluable participants 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. Of the first eight evaluable participants 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) which resulted in permanent discontinuation of study treatment. There were no safety concerns for the other participants in both cohorts.

Interim Analysis #1 confirmed that the doses implemented for both Cohort 1C and Cohort 1R passed the safety guidelines in Section 9.5.1.3 of protocol Version 2.0 for the first seven evaluable participants in each group. The CMC concluded that protocol criteria to open Cohort 2 to Cohort 1 graduates had been met, and the SMC agreed with this conclusion.

A preliminary safety and PK analysis was conducted based on the first 23 participants enrolled to the study: eight participants enrolled to Cohort 1C, and 15 participants enrolled to Cohort 1R (22). The analysis included all available safety data for these enrolled participants and no new or unexpected safety issues or safety concerns were identified. Based on this preliminary safety and PK analysis, as well as extrapolated data from the adult CAB and RPV studies, 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) (23).

Interim Analysis #2 was conducted in April 2022 and the doses implemented for both Cohort 1C and Cohort 1R passed the safety guidelines per Section 9.5.1.3 of protocol Version 3.0. The CMC

concluded that the analysis supported opening Cohort 2 accrual to participants who were not previously enrolled in Cohort 1, and the SMC agreed with this conclusion.

1.3.3 Rationale for use of oral lead-in prior to injectable dosing

The CAB LA and RPV LA formulations have a pharmacokinetic decay rate, resulting from gradual release from the IM injection site, that exposes the injected individual to detectable levels of cabotegravir and rilpivirine for up to 52 weeks or longer after an injection. A 4-6-week lead-in period of daily oral CAB and RPV prior to injectable administration, with serial safety assessments, will allow identification of any acute toxicity prior to administration of a non-dialyzable, non-removable depot injection. A similar oral lead-in period has been employed in previous trials in adults using these LA formulations.

The oral lead-in period is also designed to 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 injection; 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, a viral load assessment at the 2-week visit, and questionable clinical meaningfulness of a single HIV viral load blip, a repeat HIV 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 viral load sample is collected at visit 4b to time with the first injection(s).

1.3.4 Rationale for Cohort 1 and the related components of the study design

Oral RPV is approved for use as an antiretroviral medication in adolescents 12 years of age and older. In Cohort 1, CAB and RPV will first be studied separately to confirm adult-matched exposure/PK and gather initial safety information for oral and injectable CAB (Cohort 1C) as well as injectable RPV following lead-in with oral RPV (Cohort 1R). Cohort 1 eligibility criteria require study participants to have demonstrated virologic suppression on a stable cART, and this cART regimen is continued throughout the Cohort 1 study period to ensure continued virologic suppression. Enrollment into Cohort 1C versus Cohort 1R is determined by what cART regimen the participants have been receiving in order to avoid drug interactions (e.g., between RPV and boosted protease inhibitors or boosted integrase inhibitors) as well as duplication of study agent with another ARV from the same drug class. Hence, participants whose background cART contains a NNRTI or boosted PI will be enrolled in Cohort 1C and those on a non-boosted INSTI-based cART will be enrolled in Cohort 1R.

Based on the data presented above, the study target sample size for interim analysis #1 has been revised from N=8 to N=7 dose-evaluable participants for Cohort 1C and Cohort 1R. Interim analysis #1 of safety and PK data will be performed (as described in Sections 9 and 10) following the first seven evaluable Cohort 1C and the first seven evaluable Cohort 1R participants completing their Cohort 1, Step 2 Week 16 study visit.

Safety, not PK, will primarily drive Cohort 1 enrollment and flow. As long as no safety concerns are noted, Cohort 1 enrollment will continue uninterrupted while a continuous assessment of PK is made (including interim analyses for participants in Cohort 1C and Cohort 1R). See Section 10 for the details regarding the interim PK analysis.

1.3.5 Rationale for Cohort 2 (2A and 2B) and the related components of the study design

The PK and safety data from the initial group (demonstrating satisfactory agreement of observed PK with adult exposures and POP PK model predictions, and the absence of any overt safety signals) in Cohort 1 will support the opening of Cohort 2 for Cohort 1 participants, where virologically suppressed adolescents living with HIV-1 (including Cohort 1 participants meeting study eligibility criteria) will stop their oral cART and switch to CAB plus RPV. See Section 9 for the details regarding opening Cohort 2 to former Cohort 1 participants. Building on the successful experience from the trials in adult participants living with HIV-1 in LATTE-2, ATLAS, FLAIR and ATLAS-2M, based on the most recent clinical information in adults, supporting 2-monthly dosing, the Q8W injectable regimen has now also been chosen for further evaluation in adolescents, under MOCHA. (21)

Cohort 2 will begin to enroll, starting with the participants who passed Cohort 1, once the dosing of the oral/IM CAB and oral/IM RPV been established, based on data of the first 7 dose-evaluable participants from Cohorts 1C and 1R, as described above. Once approximately 15-20 participants in Cohort 1C and approximately 15 participants in Cohort 1R who could contribute to the dose-finding algorithm are enrolled with 80% of participants in each arm passing the Week 8 visit, another interim analysis of the safety and PK data will be conducted and Cohort 2 will open to accrual for study-naïve participants if approved by SMC.

The Cohort 2 component of the study design is consistent with, and responsive to, HIV pediatric regulatory guidance from the EU and US, which allow extrapolation of adult efficacy data. To incorporate an optional oral lead-in aspect to the study, as further described below, Cohort 2 will include Cohort 2A (oral lead-in followed by injections) and Cohort 2B (injections only). As Cohort 2A participants will receive the oral study product and therefore have a longer study follow-up period with an additional 4-6 weeks in the oral lead-in phase. Both Cohort 2A and Cohort 2B participants will have the same number of injections over 92 weeks in the injection phase. Therefore, the specified primary and secondary endpoints for Cohort 2B reflect the study visit weeks and shorter duration of overall study follow-up for this group of participants. The week 24 safety assessment time point will serve as the primary endpoint for Cohort 2A and week 20 will serve as the primary endpoint for Cohort 2B. For Cohort 2A, safety, acceptability, PK and antiviral efficacy will continue to be assessed through week 96 with related study endpoints at weeks 24, 48 and 96. For Cohort 2B, safety, acceptability, PK and antiviral efficacy will continue to be assessed through week 92 with related study endpoints at weeks 20, 44 and 92. These data will provide important information on the short term and long term, through 96 weeks, use of this 2-monthly, two-drug injectable ART in adolescents.

Optional Oral Lead-In

Throughout the course of the clinical development program for CAB and RPV LA including the large P3 trials of 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.

An assessment of the safety data specific to four weeks of oral lead-in for participants on

FLAIR and ATLAS (ViiV's two registrational clinical trials) was recently undertaken. After 24 weeks of follow-up, switching to long-acting treatment with or without an oral lead-in phase had similar safety, tolerability, and efficacy, supporting future evaluation of the simpler direct-to-injection approach. As a result of the accumulated safety data which has been generated, the safety of oral CAB and RPV during these four weeks of oral lead-in was not significantly different than at any other time during the FLAIR/ATLAS studies. (20)

The IMPAACT 2017 study will therefore also allow an optional oral lead in for participants entering Cohort 2 – Cohort 2A will be designated for participants choosing the oral lead-in whereas Cohort 2B will be designated for participants choosing to skip the oral lead-in and begin directly with the long-acting injections. This decision to dose with or without an oral-lead-in will be determined by the study participant following informed consent discussions with the investigator.

1.3.6 Rationale for Change in IM Dosing Regimen (from Q4W to Q8W)

CAB and RPV have demonstrated their efficacy when dosed in a Q8W (ATLAS 2M) regimen in addition to earlier Q4W data. Investigating the Q8W regimen in adolescents living with HIV facilitates its use in adolescents and the benefits that a decreased administration regime provides including ease of compliance. Adult PK data indicates that Q8W concentrations can be extrapolated from Q4W data with one descriptive POP PK model accurately predicting both regimens. The current adolescent data indicates that Q4W provided CAB and RPV concentrations similar to or higher than those observed in adults and so it is expected that Q8W will perform similarly providing efficacious concentrations and trough concentrations.

The agreement of the preliminary observed PK data with the expected criteria and model simulations indicated that the respective POP PK models for CAB and RPV are capable of accurately predicting PK in adolescents with no unexpected PK issue. Additionally, adolescent PK is generally expected to vary only slightly from adult PK for most drugs and it is commonplace to use adult dose regimes for adolescents. Of 92 products assessed by the Food and Drug Administration (FDA), 95% had equivalent dosing for adults and adolescent patients (24). When given the same CAB and RPV dosage as adults, slightly higher mean exposures are expected in adolescents due to their lower body weights. These differences are however not likely to be clinically relevant given the broad range of exposures observed in adults.

The observed concentrations following PO and IM administration are well predicted by the POP PK models with nearly all the individual participant values within the 90% prediction intervals throughout the PK sampling interval. This dosing provides exposures comparable to those previously seen in adults and it is highly unlikely that collection of additional PK data with the current dosing regimen would impact conclusions about exposure adequacy for CAB or RPV. The similarity of CAB and RPV PK between adolescents and adults is independent of dosing regimen. Subsequently, in conjunction with the clinical experience in the adult population with Q8W dosing, similar modeling and simulation has been utilized to recommend a Q8W dosing regimen for adolescents for evaluation in IMPAACT 2017.

1.3.7 Rationale for Long-Term Safety and Washout PK Follow-up (LSFU)

As earlier mentioned, the CAB LA and RPV LA formulations have a pharmacokinetic decay rate which exposes the injected individual to detectable levels of CAB and RPV for up to 52 or more weeks after an injection. Given this prolonged decay rate, clinical protocols to date using these LA agents have included a long-term follow-up to assess safety and potential viral rebound and

development of resistance in the setting of declining study product levels following the last intramuscular injection of either or both CAB LA and RPV LA. Any participant discontinuing the intramuscular injections, will then be followed per the 48-week follow-up visit schedule.

1.3.8 Rationale for Acceptability and Tolerability Assessments including Qualitative Phone Interviews: Participants and Parent/caregiver

Following enfuvirtide, an HIV fusion inhibitor, that was the first of a novel class of antiretroviral drugs proposed as twice-a-day subcutaneous injections as part of cART for the treatment of HIV-1, the intramuscular LA formulations will be the first injectable antiretroviral agents to be studied in adolescents. Acceptability and tolerability will be critical to understand from both the standpoint of the participants and their caregivers, who facilitate their access to healthcare. Soliciting feedback on the LA formulations from diverse groups of participants and their caregivers will help inform ways to further optimize the delivery of these agents and their acceptability in future clinical trials as well as their offering as part of standard of care when these agents are approved. To accomplish this important study aim, assessments will be administered by site staff to participants via questions covering topics on participant perceptions of the study product injections, reasons for switching from daily oral cART to long-acting study products, satisfaction with treatment, and quality of life at multiple time points throughout the study. In addition, a single in-depth qualitative phone interview will be conducted with selected participants, and, separately, with selected parents or caregivers, to identify acceptability concerns unique to the participant population. The written assessments are similar to ones that have been utilized for adult studies of LA agents but have been adapted to be age appropriate. These assessments will allow comparisons of adolescent feedback to that from adults. Some assessments such as the feedback from the caregivers will be unique to pediatric and adolescent populations and IMPAACT 2017 will provide the first opportunity to get this information.

1.3.9 Rationale for Proposed Doses of Study Agents

1.3.9.1 Oral CAB

Oral CAB has been administered to adults living with HIV at doses of 5 mg to 60 mg once daily. Oral CAB 10 mg, 30 mg, and 60 mg once daily were administered safely to participants living with HIV for 2 years or longer (LAI116482, LATTE). Oral CAB 30 mg was the dose used in the lead-in phases in the successful efficacy trials investigating the Q4W and Q8W regimens [the ATLAS study, FLAIR and ATLAS-2M. A geometric mean C_{max} of 22.5 μg/mL [median (range) 21.9 (16.9-39.2) μg/mL] has been observed for CAB in healthy adults at supratherapeutic doses following 150 mg q12h x 3 in the TQT study without any impact on the QT interval (LAI117009).

A CAB POP PK model was built based on CAB plasma concentrations collected from 1,647 healthy adult (28%) and (72%) adult participants living with HIV (age 18 to 74 years) in 16 studies at 7 dose levels (10 mg to 60 mg for the oral tablet; 100 mg to 800 mg for CAB LA). The CAB POP PK model was employed to recommend doses in adolescents after accounting for relevant factors related to this population e.g. body weight. The predicted exposures with the 30 mg daily dose are summarized by weight group in Table 2. For adolescents weighing 35 to <50kg, oral CAB 30mg once daily is predicted to achieve median exposures that are ~60-70% higher than that observed at 30mg in adults in LATTE and comparable to exposures observed at 60 mg in adults in LATTE, which has been administered safely in adult participants living with HIV. These slightly higher exposures predicted in adolescents are largely due to their

relatively lower body weight and are not of clinical concern based on observed efficacy and safety data from adult clinical studies. The C_{max} CAB exposures at the proposed dose regimen are expected to be below the 22.5 μg/mL – the geometric mean C_{max} exposure at 150 mg q12h x 3 f.

Table 2. Predicted Steady State CAB Exposures following Oral CAB 30mg and 60mg QD in Adolescents compared to Observed Adult Values

Plasma CAB Parameter	Observed Adult Data (LAI116482, LATTE) Median (range)		Adolescent Weight Group	
			35 to <50kg	≥50kg
	30mg QD (54-105kg)	60mg QD (69-106kg)	Predicted Median [5th, 95th %]	Predicted Median [5th, 95th %]
Cmax (μg/mL)	8.5 (4.9-10.8)	13.1 (7.3-18.5)	13.3 [8.4, 21.3]	9.7 [5.8, 15.8]
Cτ (μg/mL)	4.4 (2.5-7.7)	6.4 (2.4-11.3)	7.3 [4.0, 13.1]	5.6 [3.0, 10.0]
AUC(0-τ) (μg•h/mL)	144 (79-208)	209 (103-334)	237 [142, 393]	175 [102, 299]

1.3.9.2 Injectable Cabotegravir

CAB LA has been administered intramuscularly to healthy and adults living with HIV at doses of 100mg to 800mg. In participants living with HIV, CAB LA has maintained virologic suppression on maintenance doses of 400mg and 600 mg IM given Q4W and Q8W respectively with RPV LA (LATTE-2), demonstrating noninferiority of the Q4W regimens in the Phase 3 Studies ATLAS and FLAIR. In Phase IIIb Study 207966 (ATLAS-2M) CAB LA demonstrated noninferiority of the Q8W regimen to the Q4W regimen).

The previously developed POP PK model was updated with data from both a Q8W and Q4W CAB IM injection dosing scheme. Model performance was evaluated and deemed adequate with appropriate qualification and validation. Clinical trial simulations for adolescents were subsequently conducted with the updated CAB POP PK model to recommend a Q8W dosing regimen. The proposed dosing is the same as that in adults and listed in Section 5. 30 mg CAB once daily orally for at least four weeks in addition to cART (Step 1 oral phase), followed by a single intramuscular injection of CAB LA 600 mg as first injection and a second CAB LA 600 mg injection 4 weeks later, in addition to continuing cART (Step 2 injection phase) is recommended for the remainder of Cohort 1C. Cohort 2 will employ the following dosing for CAB – 30 mg CAB once daily orally for at least four weeks (Step 3 oral Phase), followed by a single intramuscular injection of CAB LA 600 mg as first injection, a second CAB LA 600 mg injection 4 weeks later and followed by CAB LA 600mg every 8 weeks thereafter during Step 4 injection phase.

The expected CAB concentration time profile from the Q8W injections suggest that minimal CAB accumulation is expected with the Q8W injections, as also observed in adults with the CAB Q8W regimen. The shorter first dose interval (4 weeks in between 2 first injections) will lead to predicted steady-state concentrations almost immediately after the first injection with trough concentrations expected to be well above the minimum target threshold of 0.65 ug/mL. The predicted trough exposures (Cτ) are listed in Table 3 below. Exposures in adolescents are expected to be slightly higher largely due to their relatively lower body weight. These differences are not of clinical concern based on observed efficacy and safety data from adult clinical studies.

In summary, the Q8W regimen has been demonstrated to be effective and have an acceptable safety profile in pivotal trials in adults and, as such, is suitable for investigating in adolescent participants living with HIV. Pharmacokinetics and safety data following CAB PO and LA will be reviewed for participants in Cohort 1C of the study.

Table 3. Predicted Steady State CAB Parameters following CAB LA IM Q8W regimen compared with Observed and Estimated data in Adults

		Predicted Cτ (μg/mL)[b]	
		Post First Injection	Post Second Injection[c]
Adolescent Body weight	35 to <50kg	2.49 [0.98, 4.72]	2.34 [0.84, 3.98]
	≥50kg	1.76 [0.69, 3.49]	1.76 [0.77, 3.05]
Observed adult data		1.50 [0.65, 2.90] [a]	1.61 [0.80, 2.99][d]

a. Geometric mean [5th and 95th percentile] - Week 8 pre-dose concentrations were obtained following a CAB 600 mg IM dose.
b. Median [90% prediction Interval]
c. Cτ after second injection is 8 weeks post injection
d. Geometric mean [5th and 95th percentile] - Cτ at Week 48 with Q8W dosing regimen

1.3.9.3 Oral Rilpivirine (RPV)

RPV 25-mg once daily (oral tablet) is approved for the treatment of HIV-1 in ART-naïve patients 12 years of age and older in multiple countries including the US, the EU, Canada, and Japan as EDURANT®, and as part of ODEFSEY® (emtricitabine/rilpivirine/tenofovir alafenamide). This approved dose of oral rilpivirine will be used one component of the oral lead-in in Cohort 1R and Cohort 2.

1.3.9.4 Injectable Rilpivirine

RPV LA (formulation G001) has been administered intramuscularly (IM) to healthy adults and adults living with HIV at doses of 300 mg to 1200 mg. In participants living with HIV, RPV LA maintained virologic suppression on maintenance IM doses of 600 mg monthly (Q4W), in conjunction with CAB LA monthly (ATLAS, FLAIR) or RPV 900 mg 2-monthly (Q8W) in conjunction with CAB LA bi-monthly (LATTE-2, ATLAS-2M).

A POP PK model for RPV LA after IM administration was developed based on data in healthy participants and those living with HIV. Factors including BMI, bodyweight, gender, and race were not identified as significant covariates for the POP PK model of RPV LA. Only age was identified to be a statistically significant covariate for absorption rate. This, however, was not considered clinically relevant, as it has no discernable effect on the RPV AUC and C_τ (C28D) for RPV LA, and only a limited effect on the RPV C_{max} after IM administration.

In order to assess what could occur in case bodyweight would become more important for the absorption of RPV LA in adolescents, a conservative approach using an allometric scaling term for absorption rate from the injection site was used (Table 4). The impact of making the absorption rate a function of bodyweight however had minimal effects on the RPV C_{max} or C_τ (C28D) values. Even with the added scaling factor, in adolescent participants weighing 35 to <50kg or ≥50kg, a RPV LA regimen of 600mg IM Q4W (after loading dose of 900 mg IM) or 900 mg IM Q8W (with first 2 injections separated by 4 weeks) is predicted to achieve median steady state trough concentrations that are similar to those in adults with the same RPV LA

regimen and to those with oral RPV 25mg once daily (Table 4). The first participants in Cohort 1R (Step 2) received an initial injection of RPV LA 900 mg, followed by two RPV LA 600 mg monthly doses thereafter, in line with the available adult data at that time. In the remainder of Cohort 1R, two injections of RPV LA 900mg will be given 4 weeks apart, in line with currently available data for the Q8W regimen from Study 207966 in adults.

The proposed dosing is the same as that in adults and listed in Section 5. 25 mg RPV once daily orally for at least four weeks in addition to continuing cART (Step 1 oral phase), followed by a single intramuscular injection of RPV LA 900 mg as first injection and a second RPV LA 900 mg injection 4 weeks later in addition to continuing cART (Step 2 injection phase) is recommended for Cohort 1R. Cohort 2 will employ the following dosing for RPV (in combination with CAB) – 25 mg RPV once daily orally for at least four weeks (Step 3 oral Phase) followed by a single intramuscular injections of RPV LA 900 mg as first injection and a second RPV LA 900 mg injection 4 weeks later followed by RPV LA 900mg every 8 weeks thereafter during Step 4 injection phase.

Table 4. Predicted RPV Trough Concentrations following RPV LA IM Q8W in Adolescents, compared with Observed Data in Adults

		Predicted (Adolescents)[a,c] or Observed (Adults)[b] Cτ (ng/mL)			
		Week 8 (4 Weeks After First Injection)	Week 16 (4 Weeks After Second Injection)	Week 24 (8 Weeks After Third Injection)	Week 48 (8 Weeks After Sixth Injection)
Adolescents	35 to <50kg	41.0 (19.3-81.9)	32.5 (16.3-62.1)	40.4 (20.0-75.9)	57.0 (28.7-107)
	≥50kg	41.8 (19.7-85.3)	32.7 (16.0-64.8)	40.3 (20.1-75.1)	56.9 (28.0-106)
Adults		49.1 (20.9-116)	45.2 (23.0-92.4)	50.1 (23.3-90.4)	64.7 (33.0-120)

a. Median (90% prediction Interval)
b. Median (5^{th}, 95^{th} percentile)
c. Simulations for 1000 adolescents aged 12-<18y and weighing 35-<50kg or ≥50kg, with allometric scaling.

1.4 Risk/Benefit Assessment

1.4.1 Cohort 1

Cohort 1 participants will remain on the same cART regimen on which they have a previous history of sustained HIV virologic suppression throughout Cohort 1 participation. Additionally, assignment to Cohort 1C or Cohort 1R is based on their cART composition such that there are no drug interactions with study agents and avoiding redundancy of agents from the same class of antiretrovirals. Given all of this, there is no anticipated risk of loss of HIV virologic control specifically related to participation in Cohort 1.

Oral rilpivirine is currently approved for use in patients 12 years and older living with HIV and the side effect profile has been well described and outlined in the package insert. The safety profile of oral cabotegravir, CAB LA and RPV LA is summarized earlier in this section and detailed in the related investigator's brochures. In order to help identify any safety concerns prior to administration of a non-dialyzable, non-removable depot injection of the CAB LA and RPV LA that have a slow pharmacokinetic decay, a 4-6 week lead-in period of daily oral (short acting) CAB or RPV is planned, followed by 2 injections, 4 weeks apart. By enrolling patients with a

history of sustained virologic suppression on cART and maintaining this cART backbone throughout Cohort 1 follow-up, the likelihood of virologic failure and associated development of resistance to study agents is highly unlikely.

Injection site reactions reported to date have been relatively common but not significant, becoming less frequent over time, and not life threatening nor serious. Despite occurrence of ISRs, there has been high acceptability of the long-acting study agents amongst the adult study participants.

Other than a potential for an improved understanding of, and engagement in, HIV care both from the standpoint of the patients and their caregiver through participating in a safety, PK and acceptability/tolerability study of novel antiretroviral study agents and interacting with study staff, there is no immediate benefit to participation in Cohort 1. However, there is the potential of early access of Cohort 1 participants to Cohort 2 and its related risk-benefits. Based on the results of the interim PK and safety analysis of Cohort 1, graduates of Cohort 1 are likely, as per the study design, to have earlier access to enrollment into Cohort 2 and with that an opportunity to stop oral cART and switch to an entirely IM LA regimen.

1.4.2 Cohort 2

In addition to the study agents' specific side effects, There is a growing body of evidence assessing the efficacy and safety of contemporary dual-drug antiretroviral regimens as first-line treatment or as a simplification strategy in patients living with HIV. A systematic review and meta-analysis on this topic concluded as a switch strategy, dual therapy was equally efficacious to standard cART and although the dual therapy tended to have lower rates of adverse events than standard cART be it in an initial treatment setting or a switch strategy, it was associated with a higher relative risk of selecting virus with drug resistance mutations at virological failure.(6) The overall assessment of this anticipated risk of development of resistance in Cohort 2 of IMPAACT 2017 is judged to be low for several reasons. Results from pivotal efficacy studies in naïve and treatment-experienced adults living with HIV show that the CAB LA plus RPV LA regimen is well tolerated, demonstrates durable virologic response and the rate of treatment emergent resistance is extremely low through week 96 for ATLAS and FLAIR and week 48 for ATLAS 2-M. (9, 11, 12, 25) Secondly, the dose of study agents confirmed from Cohort 1 PK in adolescents is likely to be the same as that which has currently been shown to be efficacious in adults. Lastly, only participants with durable virologic suppression are enrolled in Cohort 2 and, in addition with an injectable only regimen for majority of the study period, will get directly observed therapy making the likelihood of unobserved poor adherence to medications much less likely.

Injection site reactions reported to date in adults have been very common but not significant, becoming less frequently reported over time, and not life threatening nor serious. Despite occurrence of ISRs, there has been high acceptability of the long-acting study agents amongst the adult study participants.

The potential benefit of participating in Cohort 2 relates to the convenience of not having to take daily oral cART and avoiding any oral cART related toxicities, medication fatigue and adherence issues. Long-acting two class therapy consisting of CAB LA + RPV LA as an IM regimen has the benefit of being a NRTI-sparing regimen for long-term treatment of HIV which will avoid known NRTI-associated adverse drug reactions and associated long-term toxicities. Additionally, a two-drug combination therapy with CAB LA plus RPV LA may offer a better tolerability and resistance profile, as well as improved adherence (particularly with Q8W) and treatment

satisfaction in virologically suppressed participants improving the quality of life for participants living with HIV.

Taking into account the measures taken to minimize risk to participants in this study, the potential risks identified in association with CAB LA and RPV LA, and the study as a whole, are justified by the anticipated benefits that may be afforded to treatment-experienced adolescents living with HIV who are virologically suppressed.

1.5 Hypotheses

Cohort 1: CAB (oral and LA) and RPV LA will be safe and will achieve pharmacokinetic targets through Week 16 in adolescents living with HIV who are virologically suppressed at the chosen dose to ultimately allow for a final dose to be selected.

Cohort 2: CAB LA and RPV LA, when given as dual therapy to stable, virologically suppressed adolescents will maintain viral suppression and will be safe through Week 24 (for Cohort 2A oral followed by injectable) and through Week 20 (for Cohort 2B injectable only) in adolescents living with HIV who are virologically suppressed at the selected dose.

2 OBJECTIVES

2.1 Primary Objective: Cohort 1 (continuing a background cART regimen)

The primary objectives of this study are:

2.1.1 To confirm the doses for oral CAB followed by injectable CAB LA in adolescents living with HIV who are virologically suppressed by evaluating:

2.1.1.1 Safety and multiple dose PK of oral CAB through Week 4;

2.1.1.2 Safety and multiple dose PK of CAB LA through Week 16.

2.1.2 To confirm doses for injectable RPV LA in adolescents living with HIV who are virologically suppressed. by evaluating safety and multiple dose PK of RPV LA through Week 16.

2.2 Primary Objective: Cohort 2 (discontinuing a background cART regimen)

The primary objective of this study is:

2.2.1 To assess the safety of CAB + RPV in adolescents living with HIV who are virologically suppressed through:

2.2.1.1 Week 24 (Cohort 2A: oral followed by injectable);

2.2.1.2 Week 20 (Cohort 2B: injectable only).

2.3 Secondary Objectives: Cohort 1

The secondary objectives of this study are:

2.3.1 To monitor maintenance of viral suppression through Week 16 in adolescents living with HIV who are virologically suppressed.

2.3.2 To evaluate the tolerability and acceptability of CAB LA through Week 16 in adolescents living with HIV who are virologically suppressed.

2.3.3 To evaluate the tolerability and acceptability of RPV LA through Week 16 in adolescents living with HIV who are virologically suppressed.

2.4 Secondary Objectives: Cohort 2

The secondary objectives of this study are:

2.4.1 To assess safety of CAB LA + RPV LA in adolescents living with HIV who are virologically suppressed through:

2.4.1.1 Week 48 (Cohort 2A: oral followed by injectable);

2.4.1.2 Week 44 (Cohort 2B: injectable only).

2.4.2 To evaluate repeat-dose pharmacokinetics of CAB LA + RPV LA in adolescents living with HIV who are virologically suppressed through:

2.4.2.1 Week 24 and through Week 48 (Cohort 2A: oral followed by injectable);

2.4.2.2 Week 20 and through Week 44 (Cohort 2B: injectable only).

2.4.3 To assess antiviral activity of CAB LA + RPV LA in adolescents living with HIV who are virologically suppressed through:

2.4.3.1 Week 24 and through Week 48 (Cohort 2A: oral followed by injectable);

2.4.3.2 Week 20 and through Week 44 (Cohort 2B: injectable only).

2.5 Other Objectives

The other objectives of this study are:

2.5.1 To evaluate the tolerability and acceptability of CAB LA + RPV LA in adolescents living with HIV who are virologically suppressed through:

2.5.1.1 Week 24, through Week 48, and through Week 96 (Cohort 2A: oral followed by injectable);

2.5.1.2 Week 20, through Week 44, and through Week 92 (Cohort 2B: injectable only).

2.5.2 To evaluate the safety, antiviral and immunologic activity, and characterize PK of CAB LA + RPV LA in adolescents living with HIV who are virologically suppressed through:

2.5.2.1 Week 96 (Cohort 2A: oral followed by injectable);

2.5.2.2 Week 92 (Cohort 2B: injectable only).

2.5.3 To evaluate adolescent participant's experience of CAB LA and/or RPV LA, and parent/caregiver's experience and perceptions of adolescent acceptability and tolerability of CAB LA and/or RPV LA (Cohort 1 and Cohort 2).

2.5.4 To evaluate the tolerability and acceptability, and characterize long-term safety and washout PK through 48 weeks following permanent discontinuation of CAB LA or RPV LA (Cohort 1).

2.5.5 To evaluate the tolerability and acceptability, and characterize long-term safety and washout PK through 48 weeks following permanent discontinuation of CAB LA + RPV LA (Cohort 2).

2.5.6 To describe HIV-1 genotypic and phenotypic resistance patterns in participants experiencing confirmed virologic failure (Cohort 1 and Cohort 2).

3 STUDY DESIGN

This is a 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) among up to 155 children and adolescents aged 12 to <18 years living with HIV who are virologically suppressed.

Up to 60 parents/caregivers of adolescent participants in the U.S. will also be enrolled to take part in in-depth qualitative interviews. Unless otherwise noted, the term 'participant' will refer to the adolescent participants.

The study will open to accrual in Cohort 1, in which participants, in addition to continuing their pre-study cART regimen, will receive either oral CAB or oral RPV (Step 1) followed by either CAB LA or RPV LA (Step 2). Cohort 1 participants will be assigned either CAB (Cohort 1C) or RPV (Cohort 1R) based on their pre-study cART regimen. A first interim analysis will be performed with a sub-set of participants in Cohort 1 to first determine whether to open Cohort 2 to Cohort 1 participants who meet criteria to enter Cohort 2 and establish the doses for Cohort 2. A second interim analysis will then be performed to determine whether to open Cohort 2 to additional participants who were not previously enrolled in Cohort 1. A final Cohort 1 analysis will be performed to confirm the final doses for Cohort 2. See Section 3.1 below for further details describing these Cohort 1 data analyses.

Cohort 2 participants will discontinue their pre-study cART regimen and receive both study products — CAB and RPV — at the doses established in Cohort 1. Cohort 2 participants may enroll to either:

- Cohort 2A to receive both oral CAB + oral RPV (Step 3) followed by both CAB LA + RPV LA (Step 4), or
- Cohort 2B to receive both CAB LA + RPV LA (Step 5).

Unless otherwise specified, the term 'Cohort 2' applies to participants in both Cohort 2A and Cohort 2B.

Participants who permanently discontinue injectable study product will continue on-study for an additional 48 weeks after their last study product injection, per the long-term safety and washout PK follow-up (LSFU) schedule and as detailed in Section 3.3.

Safety and PK evaluations will be performed in each cohort, as well as during LSFU. Antiviral activity assessments will be performed in each cohort. Acceptability and tolerability will be assessed in each cohort and during LSFU, with all participants completing quantitative questionnaires and a sub-set of participants completing in-depth qualitative interviews.

Further information describing the two cohorts is provided in Sections 3.1 and 3.2. Further information describing the LSFU visit schedule, for both Cohort 1 and Cohort 2 participants, is provided in Section 3.3. Refer to Figure 1, and Figure 2 for an overview of the study design of Cohort 1 and Cohort 2 for the adolescent participants; Section 4 for the eligibility criteria relevant to each cohort and step; and Section 6 and Appendix I for the study visit and procedure schedules for each cohort. Details regarding the in-depth qualitative interviews are provided in Section 11.

Parent/caregiver eligibility criteria are provided in Section 4, with further details regarding the parent/caregiver in-depth qualitative interviews in Appendix IV.

3.1 Cohort 1

Up to 55 participants will be enrolled in Cohort 1 to achieve approximately 30-35 dose-evaluable (refer to Section 9.5.1.3 for the definition of dose-evaluable for this cohort). Within this cohort, participants will be assigned to either Cohort 1C (approximately 15-20 dose-evaluable), in which participants will receive CAB, or Cohort 1R, in which participants will receive RPV (approximately 15 dose-evaluable). Assignment to Cohort 1C or 1R will be based on each participant's pre-study cART regimen:

- Participants on a PI-based and/or NNRTI-based cART regimen will be assigned to Cohort 1C
- Participants on a non-boosted INSTI-based cART regimen will be assigned to Cohort 1R

All participants in Cohort 1 will remain on their pre-study cART regimen and will additionally receive either CAB (Cohort 1C) or RPV (Cohort 1R).

Upon enrollment, Cohort 1 participants will receive oral CAB (Cohort 1C) or oral RPV (Cohort 1R) for at least 4 weeks (and up to 6 weeks) in Step 1. An intensive PK visit will be conducted at the Week 2 visit. Data collected through the Week 4a study visit will be assessed to determine eligibility for each participant to enter Step 2 and receive injectable CAB LA or RPV LA, respectively. The Cohort 1 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 in Step 2. Clinical assessments conducted at the Week 4b visit, and prior to administering the first injection, will also be used to confirm Step 2 eligibility.

Cohort 1 participants who meet eligibility criteria for Step 2 are generally expected to receive their last oral dose of CAB or RPV on the same day as their first injection of CAB LA or RPV LA, at the Week 4b Step 2 Entry visit (see Section 6.3.4 for further details). See Section 4.3 for eligibility criteria to enter Step 2. Cohort 1 participants who do not meet eligibility criteria for Step 2 will discontinue use of oral CAB or RPV and exit the study 28 days after their last oral study product dosing.

In Step 2, participants will receive CAB LA (Cohort 1C) or RPV LA (Cohort 1R) while continuing their cART regimen. A single intramuscular (IM) injection of CAB LA or RPV LA will be administered at the following visits: once at the Week 4b (Step 2 Entry) visit and once at the Week 8 visit. Cohort 1 Step 2 participants will be followed for safety and PK assessments through their Week 16 visit.

In Step 2, Weeks 5 through 16 visits will be scheduled based on the date of first injection administration (Week 4b Step 2 Entry visit). Cohort 1 Step 2 participants will be followed for up to an additional 48 weeks, per the LSFU visit schedule, upon premature injectable study product discontinuation or upon completion of the Step 2 Week 16 visit. Cohort 1 participants who have completed all Step 2 visits may enroll to Cohort 2 (if eligible), prior to completing all LSFU visits. Further guidance on scheduling study visits is provided in the IMPAACT 2017 Manual of Procedures (MOP).

Interim Analysis #1 (conducted under protocol version 2.0; see protocol Section 1.3)
Once seven dose-evaluable Cohort 1C participants and seven dose-evaluable Cohort 1R participants have completed Step 2 injectable study product dosing and safety and PK evaluations through the Cohort 1 Step 2 Week 16 visit, an interim analysis of safety and PK data will be performed to:

- Determine whether criteria have been met to open Cohort 2 to accrual — limited to Cohort 1 participants
- Establish the dose of the oral and injectable CAB study products, and the injectable RPV study product to be provided in Cohort 2

Interim Analysis #2
Once approximately 15-20 Cohort 1C participants and approximately 15 Cohort 1R participants who could contribute to the dose-finding algorithm have enrolled, and 80% of these participants have completed the Step 2 Week 8 visit, an interim analysis of safety and PK evaluations will be performed to determine whether criteria have been sufficiently met to fully open Cohort 2 to accrual, including accrual of participants who were not previously enrolled in Cohort 1. Once Cohort 2 is opened to accrual for new participants who were not previously enrolled in Cohort 1, accrual into Cohort 1 will close.

Cohort 1 Final Analysis
Once Cohort 1 participants have all completed safety and PK evaluations through the Cohort 1 Step 2 Week 16 visit, the final analysis of all Cohort 1 safety, PK and maintenance of viral suppression data will be performed to confirm the dose of the oral and injectable CAB study products, and the injectable RPV study product provided in Cohort 2.

Refer to Section 9 for the definition of dose-evaluable, and detailed descriptions of all Cohort 1 analyses and associated decision-making.

Participant safety will be monitored throughout follow-up, and samples for antiviral activity and PK evaluations will be collected at visits as specified in Section 6, with blood volume ranges provided in . Acceptability and tolerability will be assessed with all participants completing quantitative questionnaires, and a sub-set of participants also completing in-depth qualitative interviews.

3.2 Cohort 2

Up to 155 adolescents may be enrolled across Cohort 2A and Cohort 2B to achieve the following:

- At least 100 participants exposed to the final recommended dose for Cohort 2 (including adolescents enrolled to Cohort 2 who previously participated in Cohort 1), which includes
- Approximately 70 evaluable participants receiving the final recommended doses for Cohort 2 who had not previously participated in Cohort 1.

In addition to the participants enrolling directly into Cohort 2, adolescents who participated in Cohort 1 Step 2 (up to 55 participants) may continue study participation in Cohort 2, if eligible. These participants may screen and enroll into Cohort 2 either prior to completing all scheduled LSFU study visits or resume study participation if after having already exited the study. See Section 6.2 for additional considerations regarding Cohort 1 Step 2 participants screening and enrolling into Cohort 2.

As noted above, Cohort 2 will consist of two groups: Cohort 2A and Cohort 2B. Participants enrolled to Cohort 2A will receive both oral CAB + oral RPV (Step 3) followed by both CAB LA + RPV LA (Step 4). Participants enrolled to Cohort 2B will receive both CAB LA +RPV LA (Step 5), thus skipping the oral lead-in phase. The decision of which group a Cohort 2 participant will enroll to will be determined by the potential study participant and the parent/legal guardian (as applicable) in consultation with the IoR, or designee, as part of the informed consent or assent process, and confirmed prior to study entry. Participants may not change their Cohort 2A or Cohort 2B group selection after enrollment. Upon enrollment into Cohort 2, all participants will discontinue their pre-study cART regimen.

Cohort 2A Step 3 (oral lead-in phase)
For participants enrolling to Cohort 2A Step 3 (oral lead-in), a PK visit will be conducted at the Week 2 visit. Data collected through the Week 4a study visit will be assessed to determine eligibility for each participant to enter Step 4 and receive injectable CAB LA + RPV LA. The Cohort 2A Week 4b visit serves as the Step 4 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 in Step 4. Clinical assessments conducted at the Week 4b visit, and prior to administering the first injection, will also be used to confirm Step 4 eligibility.

Cohort 2A participants who meet eligibility criteria for Step 4 are generally expected to 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 Step 4 Entry visit (see Section 6.4.4 for further details). See Section 4.4 for eligibility criteria to enter Step 4. Cohort 2A participants who do not meet eligibility criteria for Step 4 will discontinue use of oral CAB + RPV and exit the study 28 days after their last oral study product dosing. Cohort 1 Step 2 participants who continue in Cohort 2A Step 3 but are not eligible to progress to Cohort 2A Step 4 will be followed per the LSFU visit schedule.

Cohort 2A Step 4 and Cohort 2B Step 5 (injection phase)

In Cohort 2A Step 4 and in Cohort 2B Step 5, participants will receive injectable CAB LA + RPV LA. Refer to Section 5.2 for details regarding the study product administration schedule and dosing regimen. Injection study visits will be scheduled based on the date of which the first CAB LA + RPV LA injections were administered (Week 4b Step 4 Entry for Cohort 2A, and Step 5 Entry for Cohort 2B).

Upon premature discontinuation of injectable study products, participants will be followed for 48 weeks per the LSFU visit schedule. Further guidance on scheduling study visits is provided in Section 6.1 and the IMPAACT 2017 MOP. At the final study visit during the Cohort 2 injection phase (Week 96 for Cohort 2A, and Week 92 for Cohort 2B), participants who wish to receive injectable CAB LA + RPV LA external to the protocol will exit the study. Those who do not wish to receive injectable CAB LA + RPV LA external to the protocol will not exit the study and will be followed for 48 weeks per the LSFU visit schedule. See Section 14.11 for more information regarding post-trial access to study products.

Participant safety will be monitored, and samples for antiviral activity and PK evaluations will be collected, at visits as specified in Section 6; blood volume ranges are provided in Appendix I-B and Appendix I-C. Acceptability and tolerability of CAB LA and RPV LA will be assessed with all participants completing quantitative questionnaires, and a sub-set of participants also completing in-depth qualitative interviews.

3.3 Long-term Safety and Washout PK Follow-up (LSFU)

Participants will enter into the LSFU visit schedule at different timepoints for up to an additional 48 weeks to assess long-term safety and washout PK of the study products:

- Premature permanent discontinuation of injectable study product
- Completion of the Cohort 1 Step 2 Week 16 visit but not enrolling to Cohort 2
- Completion of Cohort 2A Step 4 Week 96 or Cohort 2B Step 5 Week 92 study visit but do not wish to receive injectable CAB LA + RPV LA external to the protocol
- Participants assigned female at birth who discontinue study product use (either oral or injectable study product) due to pregnancy during Steps 1-5

LSFU visits will be scheduled approximately 8, 24, 36, and 48 weeks after the last injection, after which participants will exit the study. Cohort 1 Step 2 participants who complete their Week 16 visit will skip the LSFU Week 8 visit. Cohort 1 Step 2 participants who enroll to Cohort 2 Step 3 but are then not eligible to progress to Cohort 2 Step 4 will be followed per the LSFU visit schedule, also based on the date of their last study product injection (i.e. their Cohort 1 Step 2 Week 8 visit). Cohort 2 Step 3 participants being followed per the LSFU visit schedule will resume (non-study provided) oral cART within 4 weeks of discontinuing oral study product.

As noted above, at the Week 96 or Week 92 visit, Cohort 2 participants who do not wish to receive injectable CAB LA + RPV LA external to the protocol will discontinue their study product (as they have completed the study product dosing regimen) and will be followed per the LSFU visit schedule. All Cohort 2 participants following the LSFU visit schedule will complete all LSFU study visits, including the LSFU Week 8 study visit. Cohort 2 Step 4 and Step 5 participants will resume (non-study provided) oral cART at 8 weeks (±7 days) of discontinuing injectable study products. See Section 8.8 for criteria for premature permanent discontinuation of study product.

Participants assigned female at birth who permanently discontinue study product use (either oral or injectable study product) due to pregnancy during Steps 1-5 will be followed for an additional 48 weeks based on their confirmed positive pregnancy test result, per the LSFU visit schedule. For participants who become pregnant during LSFU visits, the LSFU visits will continue as scheduled and not restart. Further details on participant management of contraception and pregnancy are located in Sections 6.13 and 8.3.

Participant safety will be monitored, and samples for antiviral activity and PK will be collected, at visits as specified in Section 6; blood volume ranges are provided in Appendix I-D. Acceptability and tolerability will be assessed with all participants completing quantitative questionnaires, and a sub-set of participants also completing in-depth qualitative interviews.

4 STUDY POPULATION

This study will be conducted among up to 155 adolescents living with HIV who are virologically suppressed, and up to 60 parents/caregivers of study participants. Inclusion and exclusion criteria for each of the study populations are provided in Sections 4.1– 4.5 below.

Adolescents will be enrolled into either Cohort 1 Step 1, Cohort 2A Step 3, or Cohort 2B Step 5. Adolescents who previously participated in Cohort 1 Step 2 and are continuing study participation by enrolling into Cohort 2, must meet the same eligibility criteria as other participants enrolling directly into Cohort 2, unless otherwise noted.

The study-specific approach to recruitment, screening, and enrollment is described in Section 4.7. Considerations related to participant retention and withdrawal/termination from the study are provided in Sections 4.8 and 8.8, respectively.

4.1 Inclusion Criteria: Cohort 1 Step 1, Cohort 2A Step 3, and Cohort 2B Step 5

All the criteria specified below must be met for inclusion of any adolescent participant in Step 1 of Cohort 1, in Step 3 of Cohort 2A, or in Step 5 of Cohort 2B. Unless otherwise noted, "at entry" is used to refer to the day of enrollment into the applicable cohort.

4.1.1 At enrollment, 12 to < 18 years of age

Note: For Cohort 1 Step 2 participants, age will not be exclusionary for enrollment into Cohort 2, if otherwise eligible.

4.1.2 *If not of legal age or otherwise not able to provide independent informed consent as determined by site SOPs and consistent with site institutional review board (IRB)/ ethics committee (EC) policies and procedures:* Parent or legal guardian is willing and able to provide written informed consent for study participation and potential participant is willing and able to provide written assent for study participation

If of legal age or otherwise able to provide independent informed consent as determined by site SOPs and consistent with site IRB/EC policies and procedures: Willing and able to provide written informed consent for study participation

4.1.3 At enrollment, body weight ≥ 35 kg (77 lbs.)

Note: For Cohort 1 Step 2 participants, body weight will not be exclusionary for enrollment into Cohort 2, if otherwise eligible.

4.1.4 For Cohort 1, at enrollment, body mass index (BMI) $\leq$ 31.5 kg/m^2

4.1.5 At enrollment, willing and able to comply with the study visit schedule and other study requirements, as determined by the site investigator or designee

4.1.6 Confirmed HIV-1 disease based on documented testing of two samples collected from two separate blood collection tubes per Sample #1 and Sample #2 requirements, at different time points. 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., CLIA, GCLP, or 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 HIV-1 status 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).

Sample #1 may be tested using any of the following:
- Two rapid antibody 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 OR immunofluorescence OR chemiluminescence
- One HIV DNA polymerase chain reaction (PCR)
- One quantitative HIV RNA PCR (above the limit of detection of the assay)
- One qualitative HIV RNA PCR
- One HIV total nucleic acid test

Sample #2 may be tested using any of the following:
- Rapid antibody test. If this option is used in combination with two rapid 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.
- One EIA OR Western Blot OR immunofluorescence OR chemiluminescence
- One HIV DNA PCR
- One quantitative HIV RNA PCR (above the limit of detection of the assay)
- One qualitative HIV RNA PCR
- One HIV total nucleic acid test

All study-specific samples tested to determine HIV 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. If both samples are

tested using antibody tests, at least one of the samples must be tested in a laboratory that operates according to Good Clinical Laboratory Practice (GCLP) guidelines and participates in an appropriate external quality assurance program. If nucleic acid testing is used, at least one test must be performed in a Clinical Laboratory Improvement Amendments CLIA-certified (US sites) laboratory or a VQA-certified laboratory (non-US sites). For tests performed in other (non-GCLP-compliant) settings, 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.

4.1.7 For at least 3 consecutive months (defined as 90 consecutive days) prior to screening, and prior to enrollment, has been on stable unchanged cART consisting of 2 or more drugs from 2 or more classes of antiretroviral drugs, ascertainment of this criterion may be based on parent or guardian report only, but available medical records should also be reviewed in relation to this criterion.

Note: Participants undergoing dose modifications to their antiretroviral regimen for growth or who are switching medication formulation(s) are considered to be on a stable cART.

4.1.8 Has at least one documented plasma HIV-1 RNA result less than the lower limit of detection of the assay from a specimen collected in the 6 to 12 months (defined as 180 to 365 days) prior to entry

OR

Has at least one documented plasma HIV-1 RNA result less than the lower limit of detection of the assay from a specimen less than 6 months (defined as within 179 days) prior to entry and at least one documented plasma HIV-1 RNA result less than the lower limit of detection of the assay from a specimen collected in the 12-18 months (defined as 365 to 545 days) prior to entry.

OR

For Cohort 1 participants enrolling to Cohort 2, has documented plasma HIV-1 RNA results less than the lower limit of detection of the assay from all indicated Cohort 1 study visits with their Cohort 1 Week 16 visit completed within 28 days prior to Cohort 2 entry.

4.1.9 At screening, has Grade 2 or lower of all the following laboratory test results:

- ALT (u/l)
- Lipase (u/l)
- Estimated creatinine clearance (CrCl; Schwartz Bedside Pediatrics formula mL/min/1.73m^2)
- Platelets (cells/mm^3)
- Hemoglobin (g/dL)
- AST (u/l)
- Absolute Neutrophil Count (cells/mm^3)

See Section 7.3.3 for guidance on severity grading. Laboratory tests may be repeated during the study screening period, with the latest result used for eligibility determination.

4.1.10 At screening, is on an atazanavir-containing (ATV) cART regimen and has total bilirubin ≤ 1.5 mg/dL or normal direct bilirubin

4.1.11 At screening, has documented plasma HIV-1 RNA < 50 copies/mL

4.1.12 At screening, mean value of QTc interval (automated machine readout or calculated using either Bazett or Fridericia) on ECG performed in triplicate, ≤ 500 msec.

4.1.13 For females, has a negative (blood or urine) hCG laboratory test result at entry

4.1.14 For females of childbearing potential, at entry, currently using at least one allowable effective method of contraception, and agrees to use at least one allowable effective method of contraception throughout study participation, for at least 30 days after discontinuation of oral study product, and for at least 48 weeks after discontinuation of CAB LA and/or RPV LA, and intending to delay any planned pregnancies until 30 days after last oral study product use or until 48 weeks after last injectable study product use.

Note: See Section 6.13 for details regarding contraceptive counseling, a list of the allowed effective contraceptive methods for this study, and the definition of a female of childbearing potential. 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.

4.1.15 For Cohort 1 participants enrolling to Cohort 2, have completed all scheduled product injections and completed Week 16 visit in Cohort 1 Step 2

Note: Cohort 1 participants unable to receive study product injections or complete the Week 16 visit due to site limitations or restrictions in response to COVID-19 or circumstances beyond the control of the participant/participant's family and not raising concerns of future adherence to protocol requirements are exempt from this inclusion criterion.

4.2 Exclusion Criteria: Cohort 1 Step 1, Cohort 2A Step 3, and Cohort 2B Step 5

Adolescents will be excluded from the study if any of the below specified criteria are identified during the screening period. The screening period begins when informed consent is obtained and ends immediately prior to enrollment to the applicable cohort. 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.

4.2.1 Within 6 months (defined as within 179 days) prior to entry, two consecutive documented HIV-1 RNA values greater than or equal to the lower limit of detection of the assay

Note: Unconfirmed virologic HIV-1 RNA value of greater than the lower limit of detection of the assay (transient detectable viremia, or "blip") prior to screening is not exclusionary.

4.2.2 For Cohort 1 participants enrolling to Cohort 2A Step 3 or to Cohort 2B Step 5, occurrence of any Grade 3 or higher adverse event assessed as related to study product or permanent discontinuation of study product due to an adverse event of any grade assessed as related to study product, during participation in Cohort 1 (including any long-term safety and washout PK follow-up visits).

4.2.3 For participants enrolling to Cohort 1 Step 1, based on available medical records, currently on either a cART regimen containing both a PI and an INSTI, or a cART regimen containing both an INSTI and a NNRTI.

4.2.4 As determined by the IoR or designee, and based on available medical records, known or suspected resistance to RPV

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

4.2.6 History of congestive heart failure, symptomatic arrhythmia, or any clinically significant cardiac disease, as determined by the IoR or designee based on available medical records

4.2.7 At entry, known active tuberculosis infection, as determined by the Investigator of Record (IoR) or designee based on available medical records

4.2.8 Known hepatitis B or hepatitis C infection, as determined by the IoR or designee based on available medical records

4.2.9 Clinically significant hepatic disease, as determined by the IoR or designee based on available medical records

4.2.10 Current or anticipated need for chronic anti-coagulation, as determined by the IoR or designee, based on available medical records

4.2.11 History of sensitivity to heparin or heparin-induced thrombocytopenia, as determined by the IoR or designee, based on available medical records

4.2.12 History of known or suspected bleeding disorder including history of prolonged bleeding, as determined by the IoR or designee, based on available medical records

4.2.13 Known or suspected allergy to study product components

Note: For Cohort 1 participants enrolling to Cohort 2, participants who experienced mild allergic reactions which resolved whilst on continued study drug or when rechallenged with study drug during Cohort 1 may be exempted from this criterion at the discretion of the IoR.

4.2.14 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, based on available medical records.

4.2.15 At entry, participant is receiving (or has received in the last 7 days) any disallowed medication listed in Section 5.7.

4.2.16 Current inflammatory skin condition that compromises the safety of intramuscular injections as determined by the IoR or designee.

4.2.17 Has a tattoo or other dermatological condition overlying the buttock region which, in the opinion of the IoR or designee, may interfere with interpretation of injection site reactions

4.2.18 Surgically-placed, or planned, buttock implants, per self-report

4.2.19 For females, lactating (per self-report and/or parent/guardian report) at entry

4.2.20 Enrolled in another clinical trial of an investigational agent, device, or vaccine

4.2.21 Any other condition or social circumstance situation that, in the opinion of the IoR or designee, would make study participation unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives

4.3 Inclusion/Exclusion Criteria, Step 2 (Cohort 1 Progression Criteria, Step 1 to Step 2)

Cohort 1 Step 1 participants 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 Cohort 1 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, order of procedures, and visit windows, respectively.

All of the following criteria must be met in order for participants to be included in Cohort 1 Step 2:

4.3.1 Currently enrolled in Cohort 1, Step 1

4.3.2 At Cohort 1 Step 1 Week 4a study visit, or from confirmatory repeat testing of Cohort 1 Step 1 Week 4a study visit laboratory tests, has Grade 2 or lower of all the following laboratory test results:

- ALT (u/l)
- Lipase (u/l)
- Estimated creatinine clearance (CrCl; Schwartz Bedside Pediatrics formula mL/min/1.73m^2)
- Platelets (cells/mm^3)
- Hemoglobin (g/dL)
- AST (u/l)
- Absolute Neutrophil Count (cells/mm^3)

Note: For a Grade 2 ALT test result from this visit, refer to Section 8.1.6 for required participant management. Abnormal laboratory test result values from the Week 4a visit may be repeated within the target visit window, and if confirmatory testing results in Grade 2 or lower, the participant may be eligible to continue onto the injection phase, should all other eligibility criteria be met.

4.3.3 For females, at Cohort 1 Step 1 Week 4b study visit, has a negative hCG laboratory test result

4.3.4 Assessed by the IoR or designee as sufficiently adherent 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

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

4.3.5 Has permanently discontinued oral study product

4.3.6 Occurrence of any grade 3 or higher adverse event assessed as related to study product during participation in Step 1

4.3.7 Any other condition or social circumstance that, in the opinion of the IoR or designee, would make study participation unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives.

4.4 Inclusion/Exclusion Criteria, Step 4 (Cohort 2A Progression Criteria, Step 3 to Step 4)

Cohort 2A Step 3 participants will be assessed for eligibility to progress from the oral lead-in phase (Step 3) to the injection phase (Step 4) primarily based on the safety assessments from the Cohort 2A Step 3 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 products. See Sections 6.4.3 and 6.4.4 for Week 4a and Week 4b visit scheduling, order of procedures, and target visit windows, respectively.

All of the following criteria must be met in order for participants to be included in Cohort 2A Step 4:

4.4.1 Currently enrolled in Cohort 2A, Step 3

4.4.2 At Cohort 2A Step 3 Week 4a study visit, or from confirmatory repeat testing of Cohort 2A Step 3 Week 4a study visit laboratory tests, has Grade 2 or lower of the following laboratory test results:

- ALT (u/l)
- Lipase (u/l)
- Estimated creatinine clearance (CrCl; Schwartz Bedside Pediatrics formula mL/min/1.73m^2)
- Platelets (cells/mm^3)
- Hemoglobin (g/dL)
- AST (u/l)
- Absolute Neutrophil Count (cells/mm^3)

Note: For a Grade 2 ALT test result from this visit, refer to Section 8.1.6 for required participant management. Abnormal laboratory test result values from the Week 4a visit may be repeated, within the target visit window, and if confirmatory testing results in Grade 2 or lower, the participant may be eligible to continue onto the injection phase, should all other eligibility criteria be met.

4.4.3 For females, at Cohort 2 Step 4 Week 4b study visit, has a negative hCG laboratory test result

4.4.4 Assessed by the IoR or designee as sufficiently adherent in Step 3 to permit an adequate evaluation of safety and tolerability as part of the oral lead-in phase prior to entry into the injection phase

Participants who meet any of the following criteria will be excluded from Cohort 2A Step 4:

4.4.5 Has permanently discontinued oral study products

4.4.6 Occurrence of any grade 3 or higher adverse event assessed as related to study product during participation in Cohort 2A Step 3

4.4.7 Any other condition or social circumstance that, in the opinion of the IoR or designee, would make study participation unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives.

4.5 Inclusion/Exclusion Criteria: Parents/Caregivers

For U.S. sites only, selected parents or caregivers of adolescents may be enrolled to complete qualitative phone interviews. See Appendix IV for more information regarding the selection process, and coordination of scheduling the interviews. All of the following criteria must be met for the parent/caregiver to be enrolled:

4.5.1 Selected by the protocol team for participation in the study

4.5.2 Willing and able to provide informed (verbal or written) consent for study participation

4.5.3 Per the adolescent participant, has knowledge of how the adolescent participant tolerated the study product, and lives with or has regular supportive contact with the adolescent participant

4.5.4 Per parent/caregiver self-report, has knowledge of how the participant tolerated the study product, and lives with or has regular supportive contact with the adolescent participant

4.5.5 Willing and able to complete interview in English by phone

Parents and/or caregivers of participants who meet the following criterion will be excluded from study participation:

4.5.6 Any condition or social circumstance that, in the opinion of the IoR or designee, would make study participation unsafe for either the parent/caregiver or the adolescent participant, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives.

4.6 Co-Enrollment Considerations

Co-enrollment in observational or other studies not involving an investigational agent, device, or vaccine may be permitted although careful consideration must be given to visit burden, blood draw volumes, and interpretation of outcome data across studies. Requests for co-enrollment must

be approved in advance by both study teams. Requests for such approval or questions related to co-enrollment should be emailed to the IMPAACT 2017 Clinical Management Committee (CMC).

4.7 Recruitment, Screening, and Enrollment Process

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

See Appendix IV for recruitment, eligibility confirmation, and enrollment processes, including the definition of enrollment, for parents/caregivers to take part in a single qualitative phone interview.

4.7.1 Recruitment and Screening of Cohort 1 (Step 1), Cohort 2A (Step 3), and Cohort 2B (Step 5) Participants

Recruitment methods for this study may vary across sites. All participants must be 12 to less than 18 years of age at the time of enrollment (with the exception of adolescents who previously participated in Cohort 1 Step 2 and continuing into Cohort 2, as noted in Section 4.1.1 above). Recruitment of participants, for both Cohort 1 and Cohort 2, is expected to rely on current patients being seen at a study clinic or from active identification and referral of children and adolescents living with HIV-1 who are ART-experienced and virologically suppressed; participants may be perinatally or behaviorally infected.

Any advertising materials must undergo approval by each participating site's IRB/EC. Sites are encouraged to solicit input and feedback on recruitment materials from their local Community Advisory Board, particularly any adolescent Community Advisory Board members.

Upon identification of a potentially eligible participant, study staff will provide information about the study to the parent or guardian and/or the potential participant (as applicable). Each parent or 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 informed consent process. The process will include detailed review of the study informed consent and assent forms (as applicable), time to address any questions or concerns the potential participant, parent, or guardian may have, and an assessment of understanding, before proceeding to informed consent and assent decisions. For potential Cohort 2 participants, the decision of Cohort 2A or Cohort 2B selection will be made during the informed consent and assent process; see Section 3.2. Study participants enrolled to Cohort 2 under protocol Version 3 and still on-study will be re-consented to Cohort 2A. Informed consent and assent processes will be fully documented, consistent with the DAIDS requirements. Refer to Section 14.3 for further information on informed consent procedures for this study.

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 informed consent and assent (as applicable) is provided. See Section 4.7.2 below for use of the Subject Enrollment System (SES) to 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 per Cohort. For adolescents who are screened and 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). Refer to Section 9.5 for more information on monitoring participant accrual in this study. Screening numbers for Cohort 2 will only be obtained for participants newly enrolling to the study. If a participant was enrolled in Cohort 1, a new screening number is not obtained for their Cohort 2 screening attempt(s).

4.7.2 Enrollment Process for Cohort 1 (Step 1), Cohort 2A (Step 3), and Cohort 2B (Step 5) Participants

Adolescents who are found to meet the study eligibility criteria will be enrolled into the applicable Cohort and Step. Screening procedures may be performed on the day of enrollment; however, all required screening laboratory test results must be available for eligibility determination prior to enrollment.

The IMPAACT Data Management Center's (DMC) SES will be used to assist with tracking the screening and enrollment process. When informed consent and assent (as applicable) are obtained for the adolescent, participant identification numbers (PIDs) will be assigned and a study-specific screening number will be obtained through the SES. For adolescents found to be eligible, enrollment into the study or into a subsequent step will occur upon successful entry of required eligibility data into the SES. Successful entry into the SES will generate a study identification number (SID) and the prescribing information for the Cohort and Step in which the participant has been enrolled.

4.8 Participant Retention

Once a participant is enrolled in this study, study staff will make every effort to retain him or her for the protocol-specified duration of follow-up, thereby maximizing statistical power and minimizing potential biases associated with loss to follow-up. Each site must establish and implement SOPs that target retention rates that are sufficient to allow the primary study outcomes to be reliably estimated (a maximum 10% loss to follow-up is assumed in sample size calculations). Additional guidance regarding special considerations for retaining adolescents and particularly Cohort 2 participants no longer on pre-study cART regimen, are provided in the IMPAACT 2017 MOP. Refer to Section 9.5 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. Refer to Figure 1 and Figure 2 for an overview of the cohorts, and study design, and to the package inserts and investigator's brochures (IBs) for further information about the study products.

5.1 Study Product Regimen and Administration

Study participants will be assigned to receive (open-label) either CAB (oral CAB followed by intramuscular CAB LA) or RPV (oral RPV followed by intramuscular RPV LA) in Cohort 1. Study arm assignments in Cohort 1 will be based on participants' pre-study cART regimen (as described in Section 5.1.1 below).

In Cohort 2A, study participants will be assigned to receive (open-label) both CAB and RPV (oral CAB + oral RPV, followed by intramuscular CAB LA + intramuscular RPV LA).

In Cohort 2B, study participants will be assigned to receive (open-label) both intramuscular CAB LA + intramuscular RPV LA.

5.1.1 Cohort 1

Participants in Cohort 1 will be assigned to Cohort 1C (oral CAB followed by intramuscular CAB LA) or Cohort 1R (oral RPV followed by intramuscular RPV LA) based on their pre-study cART regimen:

- Participants on a PI-based and/or NNRTI-based cART regimen will be assigned to Cohort 1C
- Participants on a non-boosted INSTI-based cART regimen will be assigned to Cohort 1R

All participants in Cohort 1 will continue their pre-study cART regimen and receive either CAB (Cohort 1C) or RPV (Cohort 1R) as shown in Table 5. Participants enrolled under protocol Version 2.0 received the Q4W dosing regimen presented in that version; refer to Section 1.3 for additional details regarding protocol version history.

Table 5. Cohort 1: Study Product Regimen and Administration

Cohort	Step	Study Product Regimen and Administration (with non-study provided cART regimen)
1C	1	CAB administered orally as one 30 mg tablet once daily, beginning at the Entry visit, for 4-6 weeks (up to 43 doses), with or without food.
	2	CAB LA administered as one IM injection in the gluteus medius at Week 4b (Step 2 Entry) study visit (600 mg/3 mL), and at Week 8 (600 mg/3 mL).
1R	1	RPV administered orally as one 25 mg tablet once daily, beginning at the Entry visit, for 4-6 weeks (up to 43 doses), with a meal.
	2	RPV LA administered as one IM injection in the gluteus medius at Week 4b (Step 2 Entry) study visit (900 mg/3 mL), and at Week 8 (900 mg/3 mL).

Study participants are generally expected to receive the first dose of intramuscular CAB LA (Cohort 1C) or intramuscular RPV LA (Cohort 1R) on the same day as the last dose of oral CAB dose or oral RPV, respectively (at the Week 4b Step 2 Entry visit).

5.1.2 Cohort 2

All participants in Cohort 2 will discontinue their pre-study cART regimen and receive both CAB and RPV as shown in Table 6 (Cohort 2A) and Table 7 (Cohort 2B). Cohort 2 doses may change based on experience in Cohort 1, in which case, the new doses will be specified in a letter of amendment or full amendment.

Table 6. Cohort 2A: Study Product Regimen and Administration

Cohort	Step	Study Product Regimen and Administration (without cART regimen)
2A	3	CAB administered orally as one 30 mg tablet once daily **AND** RPV administered orally as one 25 mg tablet once daily, taken together and with a meal, beginning at the Entry visit for 4-6 weeks (up to 43 doses of each).
	4	**First and second set of injections**: CAB LA administered as one 600 mg (3 mL) IM injection in the gluteus medius **AND** RPV LA administered as one 900 mg (3 mL) IM injection in the gluteus medius, at Week 4b (Step 4 Entry) and at Week 8. **Subsequent injections**: starting at the Week 16 visit, CAB LA administered as a 600 mg (3 mL) IM injection in the gluteus medius muscle **AND** RPV LA administered as a 900 mg (3 mL) IM injection in the gluteus medius, every eight weeks through Week 96.

Study participants enrolled into Cohort 2A are generally expected to receive the first doses of intramuscular CAB LA and intramuscular RPV LA on the same day as the last doses of oral CAB and oral RPV (at the Week 4b Step 4 Entry visit).

Table 7. Cohort 2B: Study Product Regimen and Administration

Cohort	Step	Study Product Regimen and Administration (without cART regimen)
2B	5	**First and second set of injections**: CAB LA administered as one 600 mg (3 mL) IM injection in the gluteus medius **AND** RPV LA administered as one 900 mg (3 mL) IM injection in the gluteus medius, at Entry (Step 5 Entry) and at Week 4. **Subsequent injections**: starting at the Week 12 visit, CAB LA administered as a 600 mg (3 mL) IM injection in the gluteus medius muscle **AND** RPV LA administered as a 900 mg (3 mL) IM injection in the gluteus medius, every eight weeks through Week 92.

5.1.3 Dispensing of Oral Study Product (Cohort 1 Step 1, or Cohort 2A Step 3)

A 30-day supply of oral study product will be provided at the Entry visit for Cohort 1 and for Cohort 2A. Cohort 1 participants will be provided a 30-day supply of only the oral study product to which they are assigned, whereas Cohort 2A participants will be provided a 30-day supply of each oral study product.

An additional 30-day supply of oral study product may be dispensed at the Week 2 or Week 4a visits (Cohort 1 and Cohort 2A) to ensure sufficient coverage for daily use through the participant's scheduled Week 4b visit and their first study product injection. See Sections 6.3.4 and 6.4.4 for more details on the Cohort 1 Step 2 Week 4b visit, and Cohort 2A Step 4 Week 4b visit, respectively.

5.1.4 Short-term Oral Bridging for Cohort 2 Participants

In exceptional circumstances and following consultation with the CMC, to address planned missed CAB LA + RPV LA injection visits, sites may provide daily oral CAB 30 mg + RPV 25 mg as a short-term bridging strategy for Cohort 2 participants who will miss a scheduled injection. Daily oral CAB 30 mg + RPV 25 mg for short-term oral bridging may be dispensed to study staff for providing to a participant off-site. Supply of oral study product for short-term oral bridging should ensure sufficient coverage for daily use until the participant can resume study product injections. The daily oral CAB 30 mg + RPV 25 mg bridging regimen is ideally to begin 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 daily oral bridging regimen should be taken on the same day and prior to resuming injectable study product.

The CMC must be consulted prior to resuming study product injections. Cohort 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 6.1 for further guidance on scheduling study visits, and Section 6.4.14 for interim injection visits.

5.1.5 Preparation and Administration of Injections

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.

All injections will be administered using standard IM injection technique in the gluteus medius. The following information must be source documented and entered into eCRFs with each injection of study product (e.g., Cohort 2 participants will have information entered for CAB LA, and information entered for RPV LA):

- Location (which side) of administration
- Needle length and needle gauge used
- Volume of injectable study product administered

Whenever possible, for Cohort 2 participants, CAB LA is to be administered in the contralateral gluteus medius muscle from the RPV LA. However, if the participant prefers, injections can both be administered on the same side with the injection sites at least 2cm apart. In these instances, site staff must source document where on the gluteus medius muscle each injection has been administered for assessing adverse reactions to the injections.

Injectable study product must be administered within the respective study visit windows or per CMC guidance (for Cohort 2 participants resuming injections following short-term oral bridging); see Section 6.1 for visit window requirements.

Refer to Section 6.4.14 for interim injection visits, Appendix V for detailed instructions on the preparation of injectable study products, and to the IMPAACT 2017 MOP for instructions on the administration of the study products.

5.2 Study Product Formulation

5.2.1 Oral CAB

CAB 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 should be stored up to 30° C (86° F), in the original container with the desiccant, and protected from moisture.

5.2.2 Oral RPV

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 should 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.

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 single-use vials, containing 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. Vials should be stored up to 30° C (86° F); do not freeze.

5.2.4 Injectable RPV LA

RPV LA is formulated as a sterile 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 should be stored refrigerated at 2° to 8° C (36° to 46° F); protect from light and do not freeze.

5.3 Study Product Supply

CAB and CAB LA (oral and injectable formulations), and RPV and RPV LA (oral and injectable formulations) will be supplied by ViiV Healthcare.

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

5.4 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.

5.5 Final Disposition of Study Product

Participants who temporarily or permanently discontinue oral study product during Step 1 or Step 3, or during oral bridging in Step 4 or Step 5, will be instructed to return all oral study products to the site clinic as soon as possible.

All unused study products remaining at US sites after the study is completed or terminated will be returned to the CRPMC (unless otherwise directed by DAIDS). At non-US 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*.

5.6 Concomitant Medications

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 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, per Section 6.10.

cART, other than CAB and RPV (oral and injectable formulations), will not be provided through the study.

5.7 Prohibited Medications

Any study participant who requires a medication considered prohibited while on study product must have the study product held or permanently discontinued. A list of prohibited medications may be found on the IMPAACT 2017 protocol-specific website (http://impaactnetwork.org/studies/IMPAACT2017.asp). Upon identification of the need for a prohibited medication, the site investigator should consult the CMC for further guidance on study product management, and per Section 8.

5.8 Precautionary Medications

A list of medications that should be used with caution while on study product may be found on the IMPAACT 2017 protocol-specific website.

6 STUDY VISITS AND PROCEDURES

All visits and procedures must be performed at the approved clinical research site or approved associated facilities unless otherwise noted (specified visits or visit procedures may be conducted off-site; see Section 6.1.3). All visits and procedures must be documented in accordance with DAIDS requirements for source documentation; refer to Section 12 for more information on data handling and record keeping. Refer to Section 7 for information on expedited adverse event (EAE) reporting, which may be required at any time during follow-up.

In addition to the protocol-specified procedures listed in this section, study staff may complete other tasks including but not limited to collecting, reviewing, and updating demographic and locator information; reviewing elements of informed consent and/or assent; scheduling telephone contacts and visits; providing instructions for contacting study staff between visits; providing visit reminders; and following up on missed visits. All such tasks should be conducted and documented consistent with site SOPs. Study staff should inform participants (or parents/guardians, if applicable) of clinically meaningful physical exam findings and laboratory test results, when available. See Section 14.9 for additional considerations of disclosing test results to the parents/guardians of adolescent participants.

Information relating to study visit windows, split and interim visits, and off-site visits is described in Section 6.1, including additional considerations for scheduling injection visits. See Section 6.4.14 for additional considerations for scheduling and conducting interim injection visits for Cohort 2 participants following short-term oral bridging. Detailed information related to specific visits, such as target visit dates, individual visit windows, required procedures per scheduled visits, and further guidance for select procedures are presented in Sections 6.2–6.16. See Section 5.1.5 for source documentation and eCRF requirements for any study product injection. Procedures required to continue oral and injectable study product administration at scheduled follow-up visits are described in Section 6.9.

PK sample collections are required at visits throughout Cohort 1, Cohort 2, and LSFU. All pre-dose PK sample collections should be performed prior to and on the same day as administration of the specified study product. The date and time of each PK sample collection must be source documented and entered into eCRFs for all PK samples. Additional source documentation, eCRF requirements, and scheduling considerations for PK sample collections during Weeks 2, and 4b (for both Cohorts 1 and 2A) are provided in the relevant visit sections below.

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 laboratory processing chart (LPC). As Cohort 2 participants will receive both CAB and RPV, the PK sample collection must be sufficient for the number of aliquots specified in the LPC for CAB and for RPV. Albumin (g/dL) will be obtained as part of blood collection for chemistries, but only at visits in which both chemistries and a PK sample are collected. See Section 6.16 for details on specimen collection considerations and processing, and Appendix I for required blood volumes.

For sites experiencing disruptions or limitations of usual operations due to COVID-19, operational guidance is provided in Appendix VI. 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.

6.1 Study Visit Windows, Split and Interim Visits, and Off-site Visits

6.1.1 Study Visit Windows and Injection Visit Spacing Requirements

For follow-up study visits, a target visit date and a target visit window are specified. Study visits should be scheduled to occur on the respective target visit date. If it is not possible to conduct a visit on the respective target visit date, the visit may be scheduled within the target visit window.

For select non-injection visits, broader allowable visit windows are provided. If the participant is unable to attend the scheduled non-injection study visit on the target visit date or within the target window, the non-injection study visit may be conducted within the allowable window.

For study product injection visits, target visit dates and target visit windows are provided and established based on the participant's first study product injection administered for the applicable Step. In addition to scheduling study product injection visits per the above, Cohort 2A Step 4 and Cohort 2B Step 5 study product injections should be scheduled to occur and administered within each respective target visit window as follows:

Cohort 2A Step 4 Injection Spacing Requirements

- For the Step 4 Week 8 injection, a minimum of 3 weeks (21 days) and a maximum of 4 weeks and 3 days (31 days) from the Step 4 Week 4b injection.
- For the Step 4 Week 16 injection, a minimum of 7 weeks (49 days) and a maximum of 8 weeks and 3 days (59 days) from the Step 4 Week 8 injection.
- For the Week 24 and all subsequent injections, a minimum of 7 weeks (49 days) and a maximum of 9 weeks (63 days) from the previous regularly scheduled injection.

Cohort 2B Step 5 Injection Spacing Requirements

- For the Step 5 Week 4 injection, a minimum of 3 weeks (21 days) and a maximum of 4 weeks and 3 days (31 days) from the Entry visit.
- For the Step 5 Week 12 injection, a minimum of 7 weeks (49 days) and a maximum of 8 weeks and 3 days (59 days) from the Step 5 Week 4 injection.
- For the Week 20 and all subsequent injections, a minimum of 7 weeks (49 days) and a maximum of 9 weeks (63 days) from the previous regularly scheduled injection.

Depending on when the previous injection was administered within the previous target visit window, the minimum and maximum spacing requirements may impact the availability of a target visit window (including the target visit date). Scheduled injection visits which do not occur within the target window are considered missed, and the CMC must be consulted regarding clinical considerations and study product management.

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 are provided in the IMPAACT 2017 MOP.

6.1.2 Split and Interim Visits

All visit procedures specified to be performed at scheduled visits should ideally be performed on the same day. Unless otherwise noted, 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 within the

target visit window or allowable visit window (if applicable). See Section 6.9 for required study visit procedures to be performed on the same day as and prior to administration of 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, and without prior approval from the CMC. Some interim visits may occur for administrative reasons or retention purposes. Interim visits at which no data are collected should be source documented but not entered into eCRFs. Other interim contacts and visits may occur in response to AEs experienced by study participants. In some instances, and per CMC guidance, a PK sample should also be collected. 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 per Section 7.2, and provide or refer the participant to appropriate medical care. See Section 8 for participant management and specified AE management.

For Cohort 2 participants initiating short-term oral bridging, an interim visit may be conducted to dispense oral study products and conduct required procedures per Section 6.9. See Section 5.1.4 for details regarding initiating short-term oral bridging and Section 6.1.3 below regarding conducting non-injection study visits at an off-site location. See Section 6.4.14 for interim injection visit scheduling and considerations for Cohort 2 participants.

6.1.3 Off-Site Visit Considerations for Non-Injection Study Visits

Sites are expected to make every effort to conduct each study visit at the clinical research site. However, if allowed per local law and regulations and/or institutional policies, participants may have non-injection follow-up study visits or non-injection interim visits conducted in their home or in other off-site locations. Off-site visits must be completed within the respective visit's target window or allowable window. Additionally, off-site visits should only be conducted if sites are able to collect and transport any PK samples required for the applicable non-injection follow-up study visit; see further guidelines below regarding off-site specimen collection.

At sites where off-site visits are permitted, study staff will discuss this option with participants (and parent or legal guardian, as applicable) in advance and agree on where and when such visits may take place, with adequate protections for participant privacy and confidentiality. Prior to each off-site visit, study staff will again confirm the date, location, and time of each visit with the participant (and parent or legal guardian, as applicable) to indicate permission for this activity and record any special instructions for the study staff.

At off-site visits when specimen collection is required, the procedures specified in Section 6.16 must be followed. Off-site visits may only be conducted by designated study staff who are qualified to perform all protocol-specified procedures and have undergone study-specific and all other applicable training relevant to the procedures they will perform off-site (e.g., Human Subject Protection [HSP], Good Clinical Practices [GCP], International Air Transport Association [IATA]). These staff should also be adequately trained and qualified to immediately manage any adverse events and/or social impacts that may occur during off-site visits (e.g., fainting during phlebotomy, family dispute in the home). If adverse events requiring further evaluation or management are identified during an off-site visit, study staff conducting the visit will arrange for the participant to return to the study site as soon as possible.

6.2 Cohort 1 Step 1, Cohort 2A Step 3, and Cohort 2B Step 5 Screening Visit

Refer to Section 4.7 for a description of the study recruitment, screening, and enrollment process.

Screening may be initiated after written informed consent/assent is obtained. All screening procedures must be performed within 28 days prior to study entry. Hematology, chemistries, HIV-1 RNA, pregnancy testing, and confirmation of HIV status (if necessary) are required, in relation to the eligibility criterion in Sections 4.1–4.2; as soon as the required laboratory screening test results are obtained, all results should be graded for severity as specified in Section 7.3.3. 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 Cohort 2 participants, the Cohort 2A or Cohort 2B determination will be made as part of the informed consent or assent process and by the potential study participant, the parent/legal guardian (as applicable), and in consultation with the IoR.

Potential Cohort 2 participants should be counseled to continue their pre-study cART regimen during the screening window, with their last pre-study cART regimen dose(s) administered on the day prior to the scheduled Cohort 2A Step 3 Entry visit or the Cohort 2B Step 5 Entry visit. Cohort 1 Step 1 participants will continue their pre-study cART regimen throughout Cohort 1 participation.

Cohort 1 Step 1, Cohort 2A Step 3, and Cohort 2B Step 5 Screening Visit Procedures		
Administrative and Regulatory		• Obtain written informed consent/assent • Assign PID to adolescent, *if indicated* • Obtain screening number from SES • Obtain available documentation of participant's HIV status • Collect demographic and locator information
Behavioral and Counseling		• Provide HIV pre-/post-test counseling, *if indicated* • Provide contraceptive counseling
Clinical		• Obtain available medical records and medical and medications history • Assess documentation of HIV status • Assess ARV history • Assess HIV-1 RNA test result history • Perform complete physical exam • Perform Sexual Maturity Rating • Perform an electrocardiogram (ECG) in triplicate • For Cohort 1 participants screening for Cohort 2, confirm completion of all study product injections and the Week 16 visit in Cohort 1 Step 2
Laboratory	**Blood**	Collect blood for: • Confirmatory HIV testing, *if needed per Section 4.1.6* • Hematology: complete blood counts, with platelets (cells/mm^3), ANC (cells/mm^3), and hemoglobin (g/dL) • Chemistries: Creatinine, Creatine kinase (CPK), Creatinine Clearance (CrCl; Schwartz formula mL/min/1.73m^2), Total bilirubin, AST (u/l), ALT (u/l), Lipase (u/l), Blood Urea Nitrogen (BUN) • HIV-1 RNA
	Blood or Urine	• For participants assigned female at birth, collect blood or urine for pregnancy test

For potential participants who do not meet the eligibility criteria, screening should be discontinued once ineligibility is determined and these individuals should be actively referred to non-study sources of care. See Section 4.7.1 for documentation requirements for adolescents who are found to be ineligible.

Participants may rescreen once per Cohort (i.e. total of two screening attempts for Cohort 1 and two screening attempts for Cohort 2 are allowed). If any participant is re-screened, all screening procedures listed above must be repeated, with the exception that:

- A new PID should not be assigned (Note: Obtain new screening number from SES for second screening attempt)
- Confirmatory HIV 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)

The Cohort 1 Entry Visit (Step 1 – oral phase) is described in Section 6.3.1. The Cohort 2 Entry Visits (for both Cohort 2A Step 3 Entry and Cohort 2B Step 5 Entry) are described in Section 6.4.1.

Additional Considerations for Cohort 1 Step 2 Participants Screening for Cohort 2

Cohort 2 will initially open to accrual limited to Cohort 1 participants. These participants must undergo screening procedures to determine Cohort 2 Step 3 or Step 5 eligibility, should they wish to participate in Cohort 2. The timing of screening and, if eligible, enrolling into Cohort 2 may occur prior to completing all scheduled LSFU study visits. In the event Cohort 1 Step 2 participants complete all scheduled LSFU study visits and exit the study (as described in Section 6.5 below), these former Cohort 1 Step 2 participants may undergo screening procedures to determine eligibility for resuming study participation in Cohort 2.

Any adolescent screening for Cohort 2 is required to meet eligibility criteria per Sections 4.1–4.2. Clinical assessments, evaluations, and laboratory values obtained during Cohort 1 Step 2 or LSFU study visits may be used to screen for Cohort 2 eligibility, if obtained within 28 days of the Cohort 2 Entry Visit. Otherwise, all screening visit procedures as described above must be completed for the applicable Cohort 2A or Cohort 2B eligibility determination. For previous Cohort 1 Step 2 participants, a new screening number will not be obtained from SES for the Cohort 2 screening attempt.

Any adolescent found to meet the applicable eligibility criteria will be enrolled into either Cohort 2A Step 3 or Cohort 2B Step 5, per Section 4.7 and Section 6.4.1. Previous Cohort 1 Step 2 participants will retain their PID as assigned during Cohort 1 procedures and a new SID will be assigned upon successful enrollment using the SES.

Additional guidance and eCRF completion processes for (former) Cohort 1 Step 2 participants enrolling into Cohort 2 may be found in the IMPAACT 2017 MOP.

6.3 Cohort 1

6.3.1 Cohort 1 Entry Visit (Step 1 – oral phase)

Refer to Section 4.7 for a description of the study recruitment, screening, and enrollment processes. The Cohort 1 Step 1 Entry visit must occur within 28 days (inclusive) from the Cohort 1 Screening Visit. Cohort 1 Step 1 Entry visit procedures that may provide information relevant to study eligibility 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 Cohort 1 Step 1 Entry visit may not be conducted over a multi-day split visit, and the following visit procedures must be conducted in the sequence specified below:

- Complete final eligibility determination and confirmation (medical and medications history including ARV history assessment, symptom-directed physical exam, and, for participants assigned female at birth, pregnancy testing); for participants assigned female at birth, pregnancy test results must be available for eligibility confirmation
- Complete a paper-based Step 1 eligibility checklist
- Enroll the participant on Cohort 1 Step 1 and obtain SID
- Prescribe assigned oral study product
- Dispense assigned oral study product
- Facilitate and observe administration of assigned oral study product

Cohort 1R participants should be provided a meal with the observed oral study product dose; see Section 5.1 regarding RPV oral dosing regimen and food intake requirements

Note that acceptability and tolerability questionnaires must be administered relative to other Entry visit procedures as specified in the IMPAACT 2017 MOP. Visit procedures not otherwise specified may be conducted at any timepoint during the Cohort 1 Step 1 Entry visit. Operational guidance on the order of Entry visit procedures may be found in the IMPAACT 2017 MOP.

Cohort 1 Step 1 Entry Visit Procedures		
Administrative and Regulatory		• 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
Behavioral and Counseling		• Provide adherence counseling • Provide contraceptive counseling • Perform acceptability/tolerability assessment questionnaires • Assess willingness for participation in qualitative phone interview (U.S. sites only), *see Section 11*
Clinical		• Update medical and medications history since last visit* • Perform symptom-directed physical exam* • Assess ARV history*
Laboratory	**Blood**	Collect blood for: • Hematology: complete blood counts, with platelets (cells/mm^3), ANC (cells/mm^3), and hemoglobin (g/dL) • Chemistries: Creatinine, Creatine kinase (CPK), Creatinine Clearance (CrCl; Schwartz formula mL/min/1.73m^2), Total bilirubin, AST (u/l), ALT (u/l), Lipase (u/l), Blood Urea Nitrogen (BUN) • CD4 count and percentage • HIV-1 RNA • Store whole blood for genotypic resistance testing
	Blood or Urine	• For participants assigned female at birth, collect blood or urine for pregnancy test*

Study Product	• Prescribe, dispense, facilitate and observe administration of the assigned oral study product, *see Section 5.1*

*Perform prior to enrollment

6.3.2 Cohort 1 Week 2 Visit (Step 1 – oral phase)

The Cohort 1 Week 2 visit is targeted to be conducted on day 14, counted from the day of entry, with a target window of +7 days from the target date. If necessary, this visit may be conducted within the allowable window of +14 days from the target date and the CMC notified.

PK samples will be collected at the Week 2 visit (intensive PK); Cohort 1C and Cohort 1R will have different PK sample collection timepoints at the Week 2 visit only. 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.

After the Entry visit and through the Week 2 visit, participants should be recommended 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. At minimum, for the three days prior to the Week 2 visit, participants should 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. In preparation for the Week 2 visit, sites may contact participants or parents and guardians, to reinforce adherence within the three days prior to the scheduled PK evaluation using retention methods as described in Section 4.8, as well as to remind the participant to hold the oral study product dose due on the day of the Week 2 visit. For example, sites may call or visit the participant and/or parent/guardian prior to the scheduled PK evaluation to reinforce adherence.

If, for the three days prior to the Week 2 visit, either 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, the Week 2 visit should be rescheduled. Additional guidelines for scheduling and conducting the Cohort 1 Week 2 visit are below.

- Participants and their parents/guardians should be reminded to hold administration of the daily oral study product due on the day of the Week 2 visit, to allow for a pre-dose PK sample collection and for the dose to be observed at the site. The Week 2 visit should be rescheduled if the oral study product dose was already taken and not observed at the site.
- Participants and their parents/guardians should also be reminded to return all oral study product at the Week 2 visit, such that the adherence assessment may be performed.
- Height and weight must be obtained on the same day as initiating the Week 2 PK evaluation.
- Cohort 1R participants should be provided a meal with the observed oral study product dose; see Section 5.1 regarding RPV oral dosing regimen and food intake requirements
- The oral study product dose dates, times, dose amounts, and food intake around the oral doses must be source documented and entered into eCRFs for the oral doses observed at the Week 2 visit in addition to the previous three doses.
- 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.
- 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.

- Depending on site capacity and participant preferences, participants and their parents or guardians may stay at the clinical research facility overnight for the intensive PK sampling.

Additional oral study product, as assigned per Cohort 1C or Cohort 1R, may be dispensed at this visit if needed to provide coverage until the Week 4a visit, per Section 5.1.3. Pregnancy test results must be obtained prior to any dispensing of additional oral study product.

Following the Week 2 visit, timing of taking the oral study product may be changed, if desired. However, participants should be encouraged to maintain the timing of taking their oral study product (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 2017 MOP.

Cohort 1 Week 2 Visit Procedures (Step 1 – oral phase)		
Behavioral and Counseling		• Provide adherence counseling • Provide contraceptive counseling • Perform acceptability/tolerability assessment questionnaires, *if indicated*
Clinical		• Update medical and medications history since last visit • Perform symptom-directed physical exam (including height and weight) • Perform adherence assessment • Identify/review/update adverse events
Laboratory	**Blood**	Collect blood for: • Hematology: complete blood counts, with platelets (cells/mm^3) , ANC (cells/mm^3), and hemoglobin (g/dL) • Chemistries: Creatinine, Creatine kinase (CPK), Creatinine Clearance (CrCl; Schwartz formula mL/min/1.73m^2), Total bilirubin, AST (u/l), ALT (u/l), Lipase (u/l), Blood Urea Nitrogen (BUN), Albumin (g/dL) • HIV-1 RNA • Store plasma for genotypic and phenotypic resistance testing
	Blood (Intensive PK evaluation)	Collect blood for: • Cohort 1C: Pre-dose, 1, 2, 3, 4, and 8 hours post-dose (6 PK collection timepoints) • Cohort 1R: Pre-dose, 4, and 8 hours post-dose (3 PK collection timepoints) ± a 15-minute window is allowed for the 1, 2, and 3-hours post-dose; ± a 30-minute window is allowed for the 4-hours post-dose; ± 1 hour window is allowed for the 8 hours post-dose
	Blood or Urine	• For participants assigned female at birth, collect blood or urine for pregnancy test; result must be obtained before observed dose of oral study product
Study Product		• Facilitate and observe administration of the assigned study product following pre-dose blood collection • Prescribe and dispense assigned oral study product, *if indicated, see Section 5.1*

6.3.3 Cohort 1 Week 4a Visit (Step 1 – oral phase)

The Cohort 1 Week 4a visit is targeted to be conducted on day 28, counted from the day of entry, with a target window of +7 days from the target date, and an allowable window of -7 days/+10 days from the target date.

Participants and their parents/guardians should be reminded to return all oral study product at the Week 4a visit, such that the adherence assessment may be performed. Additional oral study product, as assigned per Cohort 1C or Cohort 1R, may be dispensed at this visit if needed to provide coverage until the Week 4b visit, per Section 5.1.3. Pregnancy test results must be obtained prior to any dispensing of additional oral study product.

Data collected through the Week 4a study visit will be assessed to determine eligibility to enter Step 2 and receive injectable CAB LA or RPV LA, per Cohort 1C or Cohort 1R, respectively. 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 repeat 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 (see Section 6.3.4 below) for Step 2 Entry and injectable study product administration, and may be combined with the Week 4a visit. See Section 4.3 for Cohort 1 Step 2 eligibility criteria.

If Cohort 1 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 0).

Cohort 1 Week 4a Visit Procedures (Step 1 – oral phase)		
Behavioral and Counseling		• Provide adherence counseling • Provide contraceptive counseling • Perform acceptability/tolerability assessment questionnaires, *if indicated*
Clinical		• Update medical and medications history since last visit • Perform complete physical exam • Perform adherence assessment • Identify/review/update adverse events
Laboratory	**Blood**	Collect blood for: • Hematology: complete blood counts, with platelets (cells/mm^3), ANC (cells/mm^3), and hemoglobin (g/dL) • Chemistries: Creatinine, Creatine kinase (CPK), Creatinine Clearance (CrCl; Schwartz formula mL/min/1.73m^2), Total bilirubin, AST (u/l), ALT (u/l), Lipase (u/l), Blood Urea Nitrogen (BUN)
	Blood or Urine	• For participants assigned female at birth, collect blood or urine for pregnancy test; result must be obtained before dispensing oral study product, *if dispensing is indicated at this visit*
Study product		• Prescribe, dispense, and facilitate administration of the assigned oral study product, *if indicated, see Section 5.1*

6.3.4 Cohort 1 Week 4b Visit (Step 2 Entry – injection phase)

The Week 4b visit must take place after Week 4a laboratory test results are available, and with the target visit window of day 21-42, counted from the day of Step 1 entry. This visit should be scheduled to minimize the time between the Week 4a visit and initiation of the injectable study products in Step 2. Additionally, the Week 4b visit must occur within 42 days (inclusive) of Step 1 entry so as not to exceed the intended maximum of 6 weeks on oral study product (up to 43 doses).

Cohort 1 participants who meet eligibility criteria to progress to Step 2, per Section 4.3, are generally expected to receive their last oral dose of CAB or RPV on the same day as their first

injection of CAB LA or 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. Participants who report taking an oral study product dose within 12 hours (inclusive) of the scheduled Week 4b pre-dose sample collection will not take the oral study product dose during the Week 4b study visit; see below for further details regarding PK sampling and flexibility in study visit scheduling. Note that HIV-1 RNA test results collected at the Week 4b visit are not required to be obtained or reviewed prior to administering injectable study product.

After the Week 2 visit and through the Week 4b visit, participants should be recommended 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. 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. 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 or parents and guardians, to reinforce adherence and oral study product dose timing within the three days prior to the scheduled PK evaluation using retention methods as described in Section 4.8. For example, sites may call or visit the participant and/or parent/guardian prior to the scheduled PK evaluation to reinforce adherence. 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, such that the adherence assessment may be performed.

Prior to initiating the pre-dose PK sample collection, study staff should ascertain when the participant's most recent oral study product dose was administered to determine whether oral study product should be administered during Week 4b visit:

- 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 study product dose administered (and observed) at the site. Sites should provide Cohort 1R participants a meal with the observed oral study product dose; see Section 5.1 regarding RPV oral dosing regimen and food intake requirements.

- 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 Cohort 1 Week 4b visit may not be conducted over a multi-day split visit with the following procedures conducted as specified below:

- Contraceptive and adherence counseling must be provided prior to enrolling the participant into Step 2 to confirm the participant is willing to receive the injectable study product.
- Final eligibility determination and confirmation must be completed prior to completing the Step 2 eligibility checklist: medical and medications history, symptom-directed physical exam (must include height and weight), adherence assessment, and, for participants assigned

female at birth, pregnancy testing; for participants assigned female at birth, pregnancy test results must be available for eligibility confirmation.

- The pre-dose PK sample must be collected prior to the participant's first study product injection. See guidance above regarding whether the pre-dose PK sample is collected prior to an oral study product dose administered (and observed) at the site, or whether no oral study product dose is administered at this visit.
- The Step 2 paper-based eligibility checklist must be completed prior to enrolling the participant to Step 2.
- Enrollment to Step 2 must occur prior to prescribing the assigned injectable study product.
- Prescribing must occur prior to dispense assigned injectable study product.
- Administration of the assigned injectable study product must occur after enrollment into Step 2, and after prescribing and dispensing the participant's assigned injectable study product.
- The post-dose PK sample must be collected after administration of both the oral study product and the injectable study product.

Note that acceptability and tolerability questionnaires must be administered relative to other Week 4b visit procedures as specified in the IMPAACT 2017 MOP. Visit procedures not otherwise specified may be conducted at any timepoint during the Week 4b visit. Operational guidance on the order of Week 4b visit procedures may be found in the IMPAACT 2017 MOP.

Cohort 1 Week 4b Visit Procedures (Step 2 Entry - injection phase)		
Behavioral and Counseling		• Provide contraceptive counseling* • Provide adherence counseling* • Perform acceptability/tolerability assessment questionnaires • Conduct qualitative phone interview, *if indicated, see Section 11*
Administrative and Regulatory		• Complete final eligibility confirmation for Step 2 Entry, *see Section 4.3** • 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
Clinical		• Update medical and medications history since last visit* • Perform symptom-directed physical exam* • Identify/review/update adverse events* • Perform adherence assessment*
Laboratory	**Blood**	Collect blood for: • HIV-1 RNA • Store plasma for genotypic and phenotypic resistance testing • PK evaluation: Pre-dose and 2 hours post-dose (2 PK collection timepoints), ± 30 minutes window is allowed for the 2-hours post-dose
	Blood or Urine	• For participants assigned female at birth, collect blood or urine for pregnancy test*
Study product		• Facilitate and observe administration of the assigned oral study product, *if indicated, see above* • Prescribe, prepare, and administer assigned injectable study product, *see Section 5.1*

*Perform prior to completing the Step 2 eligibility checklist and prior to prescribing injectable study product.

6.3.5 Cohort 1 Week 5 Visit (Step 2 – injection phase)

The Week 5 visit is targeted to be conducted 3 days after completion of the Week 4b Step 2 Entry visit (the first administration of injectable study product), with a target window of +4 days from the target date, and an allowable window of -1 day/+5 days from the target date.

Cohort 1 Week 5 Visit Procedures (Step 2 - injection phase)		
Behavioral and Counseling		• Provide contraceptive counseling • Perform acceptability/tolerability assessment questionnaires, *if indicated* • Conduct qualitative phone interview, *if indicated, see Section 11*
Clinical		• Update medical and medications history since last visit • Perform symptom-directed physical exam • Identify/review/update adverse events
Laboratory	**Blood**	Collect blood for: • Hematology: complete blood counts, with platelets (cells/mm^3), ANC (cells/mm^3), and hemoglobin (g/dL) • Chemistries: Creatinine, Creatine kinase (CPK), Creatinine Clearance (CrCl; Schwartz formula mL/min/1.73m^2), Total bilirubin, AST (u/l), ALT (u/l), Lipase (u/l), Blood Urea Nitrogen (BUN), Albumin (g/dL) • PK evaluation: Single sample

6.3.6 Cohort 1 Week 8 Visit (Step 2 – injection phase)

The Week 8 visit is targeted to be conducted 28 days after the Week 4b Step 2 Entry visit (the first administration of injectable study product), with a target window of -7 days/+3 days from the target date.

Cohort 1 Week 8 Visit Procedures (Step 2 - injection phase)		
Behavioral and Counseling		• Provide adherence counseling • Provide contraceptive counseling • Perform acceptability/tolerability assessment questionnaires • Conduct qualitative phone interview, *if indicated, see Section 11*
Clinical		• Update medical and medications history since last visit • Perform symptom-directed physical exam • Identify/review/update adverse events
Laboratory	**Blood**	Collect blood for: • Hematology: complete blood counts, with platelets (cells/mm^3), ANC (cells/mm^3), and hemoglobin (g/dL) • Chemistries: Creatinine, Creatine kinase (CPK), Creatinine Clearance (CrCl; Schwartz formula mL/min/1.73m^2), Total bilirubin, AST (u/l), ALT (u/l), Lipase (u/l), Blood Urea Nitrogen (BUN), Albumin (g/dL) • HIV-1 RNA • Store plasma for genotypic and phenotypic resistance testing • PK evaluation: Single pre-dose sample
	Blood or Urine	• For participants assigned female at birth, collect blood or urine for pregnancy test; result must be obtained before administering injectable study product
Study product		• Prescribe, prepare, and administer assigned injectable study product, *see Section 5.1*

6.3.7 Cohort 1 Week 9 Visit (Step 2 – injection phase)

The Week 9 visit is targeted to be conducted 3 days after completion of the Week 8 visit, with a target window of +7 days from the target date, and an allowable window of -1 day/+10 days from the target date.

Cohort 1 Week 9 Visit Procedures (Step 2 - injection phase)		
Behavioral and Counseling		• Provide contraceptive counseling • Conduct qualitative phone interview, *if indicated, see Section 11*
Clinical		• Update medical and medications history since last visit • Perform symptom-directed physical exam • Identify/review/update adverse events • Perform an ECG
Laboratory	**Blood**	Collect blood for: • PK evaluation: Single sample

6.3.8 Cohort 1 Week 12 Visit (Step 2 – injection phase)

The Week 12 visit is targeted to be conducted 28 days after completion of the Week 8 visit, with a target window of +4 days from the target date, and an allowable window of -1 day/+5 days from the target date.

Cohort 1 Week 12 Visit Procedures (Step 2 - injection phase)		
Behavioral and Counseling		• Provide contraceptive counseling • Conduct qualitative phone interview, *if indicated, see Section 11*
Clinical		• Update medical and medications history since last visit • Perform symptom-directed physical exam • Identify/review/update adverse events
Laboratory	**Blood**	Collect blood for: • PK evaluation: Single sample

6.3.9 Cohort 1 Week 16 Visit (Step 2 – injection phase)

The Week 16 visit is targeted to be conducted 56 days after completion of the Week 8 visit, with a target window of ±7 days from the target date, and an allowable window of ±14 days from the target date.

Cohort 1 Week 16 Visit Procedures (Step 2 - injection phase)		
Behavioral and Counseling		• Provide contraceptive counseling • Provide adherence counseling • Perform acceptability/tolerability assessment questionnaires
Clinical		• Update medical and medications history since last visit • Perform complete physical exam • Identify/review/update adverse events • Perform Sexual Maturity Rating • Perform an ECG
Laboratory	**Blood**	Collect blood for: • Hematology: complete blood counts, with platelets (cells/mm^3), ANC (cells/mm^3), and hemoglobin (g/dL) • Chemistries: Creatinine, Creatine kinase (CPK), Creatinine Clearance (CrCl; Schwartz formula mL/min/1.73m^2), Total bilirubin, AST (u/l), ALT (u/l), Lipase (u/l), Blood Urea Nitrogen (BUN), Albumin (g/dL) • CD4 count and percentage • HIV-1 RNA • Store plasma for genotypic and phenotypic resistance testing • PK evaluation: Single sample
	Blood or Urine	• For participants assigned female at birth, collect blood or urine for pregnancy test

Participants completing the Cohort 1 Week 16 visit will be followed according to the LSFU visit schedule beginning with the LSFU Week 24 Visit (see Section 6.5 and Appendix I-D), or may screen for Cohort 2 eligibility if Cohort 2 has been opened to accrual.

6.4 Cohort 2

6.4.1 Cohort 2 Entry Visits (Cohort 2A Step 3 and Cohort 2B Step 5)

Refer to Section 4.7 for a description of the study recruitment, screening, and enrollment processes. The Cohort 2 Entry visit (for either Cohort 2A Step 3 or Cohort 2B Step 5) must occur within 28 days (inclusive) from the Cohort 2 Screening Visit. Potential Cohort 2 Step 3 or Step 5 participants should be counseled to continue their pre-study cART regimen during the screening window, with their last dose administered on the day prior to the scheduled Cohort 2 Step 3 or Step 5 Entry visit. Cohort 2 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 potential participant is found to be ineligible on the day of enrollment, enrollment should not occur.

The Cohort 2A Step 3 and Cohort 2B Step 5 Entry visits may not be conducted over multi-day split visits.

Cohort 2A Step 3 Entry Visit

The following Cohort 2A Step 3 Entry visit procedures must be conducted in the sequence specified below:

- Complete final eligibility determination and confirmation (medical and medications history, symptom-directed physical exam, and, for participants assigned female at birth, pregnancy testing); for participants assigned female at birth, pregnancy test results must be available for eligibility confirmation. Contraceptive and adherence counseling must also be provided prior to enrolling the participant to confirm the participant is willing to enter Cohort 2A Step 3 and receive the oral study products.
- Complete a paper-based Step 3 eligibility checklist.
- Enroll the participant on Cohort 2A Step 3 and obtain SID.
- Prescribe oral study product.
- Dispense oral study product.
- Facilitate and observe administration of oral study product.

Participants should be provided a meal with the observed oral study product doses; see Section 5.1 regarding RPV oral dosing regimen and food intake requirements.

Cohort 2B Step 5 Entry Visit

The following Cohort 2B Step 5 Entry visit procedures must be conducted in the sequence specified below:

- Complete final eligibility determination and confirmation (medical and medications history, symptom-directed physical exam (must include height and weight), and, for participants assigned female at birth, pregnancy testing); for participants assigned female at birth, pregnancy test results must be available for eligibility confirmation. Contraceptive and adherence counseling must be provided prior to enrolling the participant to confirm the participant is willing to enter Cohort 2B Step 5 and receive the injectable study products.
- Complete a paper-based Step 5 eligibility checklist.
- Enroll the participant on Cohort 2B Step 5 and obtain SID.
- Prescribe injectable study products.
- Dispense injectable study products.
- Administer injectable study products.
- The post-dose PK sample must be collected after administration of both injectable study products.
- The ECG must be performed after administration of both injectable study products.

Note that acceptability and tolerability questionnaires must be administered relative to other Entry visit procedures as specified in the IMPAACT 2017 MOP. Visit procedures not otherwise specified may be conducted at any timepoint during the Cohort 2 Step 3 or Step 5 Entry visit. Operational guidance on the order of Entry visit procedures may be found in the IMPAACT 2017 MOP. Upon enrolling into Cohort 2, Step 3 or Step 5, study participants will discontinue their pre-study oral cART regimen.

Cohort 2A Step 3 Entry Visit and Cohort 2B Step 5 Entry Visit Procedures		
Administrative and Regulatory		• 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
Behavioral and Counseling		• Provide adherence counseling* • Provide contraceptive counseling* • Perform acceptability/tolerability assessment questionnaires • Assess willingness for participation in qualitative phone interview (U.S. sites only), *see Section 11*
Clinical		• Update medical and medications history since last visit* • Perform symptom-directed physical exam* • Perform an ECG, 2 hours post-injection dose, ± 1 hour window is allowed (Cohort 2B only)
Laboratory	**Blood**	Collect blood for: • Hematology: complete blood counts, with platelets (cells/mm^3), ANC (cells/mm^3), and hemoglobin (g/dL) • Chemistries: Creatinine, Creatine kinase (CPK), Creatinine Clearance (CrCl; Schwartz formula mL/min/1.73m^2), Total bilirubin, AST (u/l), ALT (u/l), Lipase (u/l), Blood Urea Nitrogen (BUN) • CD4 count and percentage • HIV-1 RNA • Store whole blood for genotypic resistance testing • PK evaluation: 2-hours post-injection dose PK sample, ± 30 minutes window (Cohort 2B only)
	Blood or Urine	• For participants assigned female at birth, collect blood or urine for pregnancy test*
Study Product	**Step 3**	• For Cohort 2A Step 3 participants: Prescribe, dispense, facilitate, and observe administration of oral study products, *see Section 5.1*
	Step 5	• For Cohort 2B Step 5 participants: Prescribe, prepare, and administer injectable study products, *see Section 5.1*

*Perform prior to enrollment

Participants enrolled to Cohort 2A Step 3 will follow the applicable study visit schedule, as outlined in Appendix I-B and as described in Sections 6.4.2 – 6.4.4 below. Participants enrolled to Cohort 2B Step 5 will follow the applicable study visit schedule outlined in Appendix I-C and as described in Sections 6.4.5– 6.4.14 below.

6.4.2 Cohort 2A Week 2 Visit (Step 3 – oral phase)

The Cohort 2 Week 2 visit is targeted to be conducted on day 14, counted from the day of entry, with a target window of +7 days from the target date, and an allowable window of +14 days from the target date.

PK samples will be collected at the Week 2 visit. 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.

After the Entry visit and through the Week 2 visit, participants should be recommended 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. At minimum, for the three days prior to the Week 2 visit, participants should 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 the daily oral study product

regimen. In preparation for the Week 2 visit, sites may contact participants or parents and guardians, to reinforce adherence within the three days prior to the scheduled PK evaluation using retention methods as described in Section 4.8, as well as to remind the participant to hold the oral study product dose due on the day of the Week 2 visit. For example, sites may call or visit the participant and/or parent/guardian prior to the scheduled PK evaluation to reinforce adherence.

If, for the three days prior to the Week 2 visit, either 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, the Week 2 visit should be rescheduled. Additional guidelines for scheduling and conducting the Cohort 2 Week 2 visit are below.

- Participants and their parents/guardians should be reminded to hold administration of the daily oral study product due on the day of the Week 2 visit, to allow for a pre-dose PK sample collection and for the dose to be observed at the site. The Week 2 visit should be rescheduled if the oral study product dose was already taken and not observed at the site.
- Participants and their parents/guardians should also be reminded to return all oral study product at the Week 2 visit, such that the adherence assessment may be performed.
- Height and weight must be obtained on the same day as initiating the Week 2 PK evaluation.
- Participants should be provided a meal with the observed oral study product doses; see Section 5.1 regarding RPV oral dosing regimen and food intake requirements.
- The oral study product dose dates, times, dose amounts, and food intake around the oral doses must be source documented and entered into eCRFs for the oral doses observed at the Week 2 visit in addition to the previous three doses.
- 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 PK evaluation should be rescheduled.
- If the observed oral study product dose is not retained within 30 minutes (inclusive) of administration (e.g., the vomiting), the Week 2 visit should be rescheduled.
- 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, per Section 5.1.3. Pregnancy test results must be obtained prior to any dispensing of additional oral study product.

Following the Week 2 visit, timing of taking the oral study product may be changed, if desired. However, participants should be encouraged to maintain the timing of taking their oral study product (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 2017 MOP.

Cohort 2A Week 2 Visit Procedures (Step 3 – oral phase)		
Behavioral and Counseling		• Provide adherence counseling • Provide contraceptive counseling • Perform acceptability/tolerability assessment questionnaires, *if indicated*
Clinical		• Update medical and medications history since last visit • Perform symptom-directed physical exam (including height and weight) • Perform adherence assessment • Identify/review/update adverse events
Laboratory	**Blood**	Collect blood for: • Hematology: complete blood counts, with platelets (cells/mm^3), ANC (cells/mm^3), and hemoglobin (g/dL) • Chemistries: Creatinine, Creatine kinase (CPK), Creatinine Clearance (CrCl; Schwartz formula mL/min/1.73m^2), Total bilirubin, AST (u/l), ALT (u/l), Lipase (u/l), Blood Urea Nitrogen (BUN), Albumin (g/dL) • HIV-1 RNA • Store plasma for genotypic and phenotypic resistance testing • PK evaluation: Pre-dose and 3 hours post-dose (2 PK collection timepoints), ± 1 hour window is allowed for the 3 hours post-dose
	Blood or Urine	• For participants assigned female at birth, collect blood or urine for pregnancy test; result must be obtained before observed dose of oral study product
Study Product		• Facilitate and observe administration of oral study products following pre-dose blood collection • Prescribe and dispense oral study products, *if indicated, see Section 5.1*

6.4.3 Cohort 2A Week 4a Visit (Step 3 – oral phase)

The Cohort 2 Week 4a visit is targeted to be conducted on day 28, counted from the day of entry, with a target window of +7 days from the target date, and an allowable window of -7 days/+10 days from the target date.

Participants and their parents/guardians should also be reminded to return all oral study product at the Week 4a visit, such that the adherence assessment may be performed. Additional oral study products may be dispensed if needed to provide coverage until the Week 4b visit, per Section 5.1.3. Pregnancy test results must be obtained prior to any dispensing of additional oral study products.

Data collected through the Week 4a study visit will be assessed to determine eligibility to enter Step 4 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 4 eligibility and scheduling the Week 4b visit. See Section 4.4 for Cohort 2 Step 4 eligibility criteria. Abnormal laboratory test result values from the Week 4a visit may be repeated prior to scheduling the Week 4b visit. If repeat laboratory test results confirm Step 4 eligibility, and all other eligibility criteria are met, the Week 4b visit may be scheduled within the target visit window (see Section 6.4.4 below) for Step 4 Entry and injectable study products administration, and may be combined with the Week 4a visit.

If Cohort 2 participants (who had not previously participated in Cohort 1 Step 2) are ineligible to receive injectable study products in Step 4, 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 0). Cohort 1 Step 2 participants who continue in Cohort 2 Step 3 but are not eligible to progress to Cohort 2 Step 4 will be followed per the LSFU visit schedule (see Section 6.5).

Cohort 2A Week 4a Visit Procedures (Step 3 – oral phase)		
Behavioral and Counseling		• Provide adherence counseling • Provide contraceptive counseling • Perform acceptability/tolerability assessment questionnaires, *if indicated*
Clinical		• Update medical and medications history since last visit • Perform complete physical exam • Identify/review/update adverse events • Perform adherence assessment
Laboratory	**Blood**	Collect blood for: • Hematology: complete blood counts, with platelets (cells/mm^3), ANC (cells/mm^3), and hemoglobin (g/dL) • Chemistries: Creatinine, Creatine kinase (CPK), Creatinine Clearance (CrCl; Schwartz formula mL/min/1.73m^2), Total bilirubin, AST (u/l), ALT (u/l), Lipase (u/l), Blood Urea Nitrogen (BUN)
	Blood or Urine	• For participants assigned female at birth, collect blood or urine for pregnancy test; result must be obtained before dispensing oral study product, *if dispensing is indicated at this visit*
Study product		• Prescribe, dispense, and facilitate administration of oral study products, *if indicated, see Section 5.1*

6.4.4 Cohort 2A Week 4b Visit (Step 4 Entry – injection phase)

The Week 4b visit must take place after Week 4a laboratory test results are available, and with the target visit window of day 21-42, counted from the day of Step 3 entry. This visit should be scheduled to minimize the time between the Week 4a visit and initiation of the injectable study products in Step 4. Additionally, the Week 4b visit must occur within 42 days (inclusive) of Step 3 entry so as not to exceed the intended maximum of 6 weeks on oral study product (up to 43 doses of each oral study product).

Cohort 2 participants who meet eligibility criteria to progress to Step 4, per Section 4.4, are generally expected to 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 4 Entry visit. PK samples will be collected at the Week 4b visit. Participants who report taking oral study product doses within 12 hours (inclusive) of the scheduled Week 4b pre-dose sample collection will not take the oral study product doses during the Week 4b study visit; see below for further details regarding PK sampling and flexibility in study visit scheduling. Note that HIV-1 RNA test results collected at the Week 4b visit are not required to be obtained or reviewed prior to administering injectable study products.

After the Week 2 visit and through the Week 4b visit, participants should be recommended 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. 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 the daily oral study product regimen. 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 or parents and guardians, to reinforce adherence and oral study product dose timing within the three days prior to the

scheduled PK evaluation using retention methods as described in Section 4.8. For example, sites may call or visit the participant and/or parent/guardian prior to the scheduled PK evaluation to reinforce adherence. 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, such that the adherence assessment may be performed.

Prior to initiating the pre-dose PK sample collection, study staff should ascertain when the participant's most recent oral study product dose was administered to determine whether oral study product should be administered during Week 4b visit:

- 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 study product dose administered (and observed) at the site. Sites should provide participants a meal with the observed oral study product dose; see Section 5.1 regarding RPV oral dosing regimen and food intake requirements.

- 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 Cohort 2 Week 4b visit may not be conducted over a multi-day split visit with the following procedures conducted as specified below:

- Contraceptive and adherence counseling must be provided prior to enrolling the participant into Step 4 to confirm the participant is willing to receive the injectable study products.
- Final eligibility determination and confirmation must be completed prior to completing the Step 4 eligibility checklist: medical and medications history, symptom-directed physical exam (must include height and weight), adherence assessment, and, for participants assigned female at birth, pregnancy testing; for participants assigned female at birth, pregnancy test results must be available for eligibility confirmation.
- The pre-dose PK sample must be collected prior to the participant's first study product injection. See guidance above regarding whether the pre-dose PK sample is collected prior to an oral study product dose administered (and observed) at the site, or whether no oral study product dose is administered at this visit.
- The Step 4 paper-based eligibility checklist must be completed prior to enrolling the participant to Step 4.
- Enrollment to Step 4 must occur prior to prescribing injectable study products.
- Prescribing must occur prior to dispensing injectable study products.
- Administration of injectable study products must occur after enrollment into Step 4, and after prescribing and dispensing the injectable study products.
- The post-dose PK sample must be collected after administration of both the oral study product and the injectable study products.

Note that acceptability and tolerability questionnaires must be administered relative to other Week 4b visit procedures as specified in the IMPAACT 2017 MOP. Visit procedures not otherwise specified may be conducted at any timepoint during the Week 4b visit. Operational guidance on the order of Week 4b visit procedures may be found in the IMPAACT 2017 MOP.

Cohort 2A Week 4b Visit Procedures (Step 4 Entry - injection phase)		
Behavioral and Counseling		• Provide contraceptive counseling* • Provide adherence counseling* • Perform acceptability/tolerability assessment questionnaires
Administrative and Regulatory		• Complete final eligibility confirmation for Step 4 Entry, *see Section 4.4** • 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
Clinical		• Update medical and medications history since last visit* • Perform symptom-directed physical exam* • Identify/review/update adverse events* • Perform adherence assessment* • Perform ECG: 2 hours post-injection dose, ± 1 hour window is allowed
Laboratory	**Blood**	Collect blood for: • HIV-1 RNA • Store plasma for genotypic and phenotypic resistance testing • PK evaluation: Pre-dose and 2 hours post-injection dose (2 PK collection timepoints), ± 30 minutes window is allowed for the 2-hours post-dose
	Blood or Urine	• For participants assigned female at birth, collect blood or urine for pregnancy test*
Study product		• Facilitate and observe administration of oral study products, *if indicated, see above* • Prescribe, prepare, and administer injectable study products, *see Section 5.1*

*Perform prior to completing the Step 4 eligibility checklist and prior to prescribing injectable study products.

6.4.5 Cohort 2A Week 5 Visit (Step 4 – injection phase) and Cohort 2B Week 1 Visit (Step 5 - injection phase)

The Cohort 2A Week 5 and Cohort 2B Week 1 visits are targeted to be conducted 3 days after completion of the first administration of injectable study products – Week 4b Step 4 Entry visit (for Cohort 2A) and the Step 5 Entry visit (for Cohort 2B). The Cohort 2A Week 5 and Cohort 2B Week 1 visits have a target window of +4 days from the target date, and an allowable window of -1 day/+5 days from the target date.

Cohort 2A Week 5 (Step 4 - injection phase) and Cohort 2B Week 1 (Step 5 – injection phase) Visit Procedures		
Behavioral and Counseling		• Provide contraceptive counseling • Perform acceptability/tolerability assessment questionnaires, *if indicated*
Clinical		• Update medical and medications history since last visit • Perform symptom-directed physical exam • Identify/review/update adverse events
Laboratory	**Blood**	Collect blood for: • Hematology: complete blood counts, with platelets (cells/mm^3), ANC (cells/mm^3), and hemoglobin (g/dL) • Chemistries: Creatinine, Creatine kinase (CPK), Creatinine Clearance (CrCl; Schwartz formula mL/min/1.73m^2), Total bilirubin, AST (u/l), ALT (u/l), Lipase (u/l), Blood Urea Nitrogen (BUN), Albumin (g/dL) • PK evaluation: Single sample

6.4.6 Cohort 2A Week 8 Visit (Step 4 – injection phase) and Cohort 2B Week 4 Visit (Step 5 - injection phase)

The Cohort 2A Week 8 and Cohort 2B Week 4 visits are targeted to be conducted 28 days after completion of the first administration of injectable study products – Week 4b Step 4 Entry visit (for Cohort 2A) and the Step 5 Entry visit (for Cohort 2B). The Cohort 2A Week 8 and Cohort 2B Week 4 visits have a target window of -7 days/+3 days from the target date.

Cohort 2A Week 8 Visit Procedures (Step 4 - injection phase) and Cohort 2B Week 4 (Step 5 – injection phase) Visit Procedures		
Behavioral and Counseling		• Provide adherence counseling • Provide contraceptive counseling • Perform acceptability/tolerability assessment questionnaires
Clinical		• Update medical and medications history since last visit • Perform symptom-directed physical exam • Identify/review/update adverse events
Laboratory	**Blood**	Collect blood for: • Hematology: complete blood counts, with platelets (cells/mm^3), ANC (cells/mm^3), and hemoglobin (g/dL) • Chemistries: Creatinine, Creatine kinase (CPK), Creatinine Clearance (CrCl; Schwartz formula mL/min/1.73m^2), Total bilirubin, AST (u/l), ALT (u/l), Lipase (u/l), Blood Urea Nitrogen (BUN), Albumin (g/dL) • HIV-1 RNA • Store plasma for genotypic and phenotypic resistance testing • PK evaluation: Single pre-dose sample
	Blood or Urine	• For participants assigned female at birth, collect blood or urine for pregnancy test; result must be obtained before administering injectable study products
Study product		• Prescribe, prepare, and administer injectable study products, *see Section 5.1*

6.4.7 Cohort 2A Week 16 Visit (Step 4 – injection phase) and Cohort 2B Week 12 Visit (Step 5 - injection phase)

The Cohort 2A Week 16 visit target date is 84 days after completion of the Week 4b visit with a target window of -7 days/+3 days from the target date. Additionally, the Cohort 2A Week 16 visit and the third injection of study product should be scheduled a minimum of 7 weeks (49 days) and a maximum of 8 weeks and 3 days (59 days) from the previous injection.

The Cohort 2B Week 12 visit target date is 84 days after completion of the Step 5 Entry visit with a target window of -7 days/+3 days from the target date. Additionally, the Cohort 2B Week 12 visit and the third injection of study product should be scheduled a minimum of 7 weeks (49 days) and a maximum of 8 weeks and 3 days (59 days) from the previous injection.

Cohort 2A Week 16 Visit Procedures (Step 4 – injection phase) and Cohort 2B Week 12 (Step 5 – injection phase) Visit Procedures		
Behavioral and Counseling		• Provide contraceptive counseling • Perform acceptability/tolerability assessment questionnaires, *if indicated*
Clinical		• Update medical and medications history since last visit • Perform symptom-directed physical exam • Identify/review/update adverse events
Laboratory	**Blood**	Collect blood for: • Hematology: complete blood counts, with platelets (cells/mm^3), ANC (cells/mm^3), and hemoglobin (g/dL) • Chemistries: Creatinine, Creatine kinase (CPK), Creatinine Clearance (CrCl; Schwartz formula mL/min/1.73m^2), Total bilirubin, AST (u/l), ALT (u/l), Lipase (u/l), Blood Urea Nitrogen (BUN), Albumin (g/dL) • HIV-1 RNA • Store plasma for genotypic and phenotypic resistance testing • PK evaluation: Single pre-dose sample
	Blood or Urine	• For participants assigned female at birth, collect blood or urine for pregnancy test; result must be obtained before administering injectable study products
Study product		• Prescribe, prepare, and administer injectable study products, *see Section 5.1*

6.4.8 Cohort 2A Week 24 Visit (Step 4 – injection phase) and Cohort 2B Week 20 Visit (Step 5 - injection phase)

The Cohort 2A Week 24 visit target date is 140 days after completion of the Cohort 2A Week 4b visit, with a target window of ±7 days. Additionally, the Cohort 2A Week 24 visit should occur a minimum of 7 weeks (49 days) and a maximum of 9 weeks (63 days) from the previous injection.

The Cohort 2B Week 20 visit target date is 140 days after completion of the Step 5 Entry visit, with a target window of ±7 days. Additionally, the Cohort 2B Week 20 visit should occur a minimum of 7 weeks (49 days) and a maximum of 9 weeks (63 days) from the previous injection.

Cohort 2A Week 24 Visit Procedures (Step 4 – injection phase) and Cohort 2B Week 20 (Step 5 – injection phase) Visit Procedures		
Behavioral and Counseling		• Provide adherence counseling • Provide contraceptive counseling • Perform acceptability/tolerability assessment questionnaires • Conduct qualitative phone interview, *if indicated, see Section 11*
Clinical		• Update medical and medications history since last visit • Perform complete physical exam • Identify/review/update adverse events • Sexual Maturity Rating assessment
Laboratory	**Blood**	Collect blood for: • Hematology: complete blood counts, with platelets (cells/mm^3), ANC (cells/mm^3), and hemoglobin (g/dL) • Chemistries: Creatinine, Creatine kinase (CPK), Creatinine Clearance (CrCl; Schwartz formula mL/min/1.73m^2), Total bilirubin, AST (u/l), ALT (u/l), Lipase (u/l), Blood Urea Nitrogen (BUN), Albumin (g/dL) • CD4 count and percentage • HIV-1 RNA • Store plasma for genotypic and phenotypic resistance testing • PK evaluation: Single pre-dose sample
	Blood or Urine	• For participants assigned female at birth, collect blood or urine for pregnancy test; result must be obtained before administering injectable study products
Study product		• Prescribe, prepare, and administer injectable study products, *see Section 5.1*

6.4.9 Cohort 2A Week 25 Visit (Step 4 – injection phase) and Cohort 2B Week 21 Visit (Step 5 - injection phase)

The Cohort 2A Week 25 visit is targeted to be conducted 3 days after completion of the Cohort 2A Week 24 visit, with a target window of +4 days from the target date, and an allowable window of -1 day/+5 days from the target date.

The Cohort 2B Week 21 visit is targeted to be conducted 3 days after completion of the Cohort 2B Week 20 visit, with a target window of +4 days from the target date, and an allowable window of -1 day/+5 days from the target date.

Cohort 2A Week 25 Visit Procedures (Step 4 – injection phase) and Cohort 2B Week 21 (Step 5 – injection phase) Visit Procedures		
Behavioral and Counseling		• Provide contraceptive counseling • Perform acceptability/tolerability assessment questionnaires, *if indicated* • Conduct qualitative phone interview, *if indicated, see Section 11*
Clinical		• Update medical and medications history since last visit • Perform symptom-directed physical exam • Identify/review/update adverse events
Laboratory	**Blood**	Collect blood for: • PK evaluation: Single sample

6.4.10 Cohort 2A Weeks 32 and 40 Visits (Step 4 – injection phase) and Cohort 2B Weeks 28 and 36 Visits (Step 5 - injection phase)

The Cohort 2A Week 32 study visit is targeted to occur 196 days after the Cohort 2A Week 4b visit, with a target window of ±7 days from the target date. The Cohort 2A Week 40 study visit is

targeted to occur 252 days after the Cohort 2A Week 4b visit, with a target window of ±7 days from the target date. Additionally, the Cohort 2A Weeks 32 and 40 visits should occur a minimum of 7 weeks (49 days) and a maximum of 9 weeks (63 days) from the previous injection.

The Cohort 2B Week 28 study visit is targeted to occur 196 days after the Cohort 2B Step 5 Entry visit, with a target window of ±7 days from the target date. The Cohort 2B Week 36 study visit is targeted to occur 252 f window of ±7 days from the target date. Additionally, the Cohort 2B Weeks 28 and 36 visits should occur a minimum of 7 weeks (49 days) and a maximum of 9 weeks (63 days) from the previous injection.

Cohort 2A Weeks 32 and 40 (Step 4 – injection phase) and Cohort 2B Weeks 28 and 36 (Step 5 – injection phase) Visit Procedures		
Behavioral and Counseling		• Provide contraceptive counseling • Perform acceptability/tolerability assessment questionnaires, *if indicated* • Conduct qualitative phone interview, *if indicated, see Section 11*
Clinical		• Update medical and medications history since last visit • Perform symptom-directed physical exam • Identify/review/update adverse events
Laboratory	**Blood**	Collect blood for: • Hematology: complete blood counts, with platelets (cells/mm^3), ANC (cells/mm^3), and hemoglobin (g/dL) • Chemistries: Creatinine, Creatine kinase (CPK), Creatinine Clearance (CrCl; Schwartz formula mL/min/1.73m^2), Total bilirubin, AST (u/l), ALT (u/l), Lipase (u/l), Blood Urea Nitrogen (BUN), Albumin (g/dL) • HIV-1 RNA • Store plasma for genotypic and phenotypic resistance testing • PK evaluation: Single pre-dose sample
	Blood or Urine	• For participants assigned female at birth, collect blood or urine for pregnancy test; result must be obtained before administering injectable study products
Study product		• Prescribe, prepare, and administer injectable study products, *see Section 5.1*

6.4.11 Cohort 2A Week 48 Visit (Step 4 – injection phase) and Cohort 2B Week 44 Visit (Step 5 - injection phase)

The Cohort 2A Week 48 study visit is targeted to occur 308 days after the Cohort 2A Week 4b visit, with a target window of ±7 days from the target date. Additionally, the Cohort 2A Week 48 visit should occur a minimum of 7 weeks (49 days) and a maximum of 9 weeks (63 days) from the previous injection.

The Cohort 2B Week 44 study visit is targeted to occur 308 days after the Cohort 2B Step 5 Entry visit, with a target window of ±7 days from the target date. Additionally, the Cohort 2B Week 44 visit should occur a minimum of 7 weeks (49 days) and a maximum of 9 weeks (63 days) from the previous injection.

Cohort 2A Week 48 Visit Procedures (Step 4 – injection phase) and Cohort 2B Week 44 (Step 5 – injection phase) Visit Procedures		
Behavioral and Counseling		• Provide contraceptive counseling • Provide adherence counseling • Perform acceptability/tolerability assessment questionnaires • Conduct qualitative phone interview, *if indicated, see Section 11*
Clinical		• Update medical and medications history since last visit • Perform complete physical exam • Identify/review/update adverse events
Laboratory	**Blood**	Collect blood for: • Hematology: complete blood counts, with platelets (cells/mm^3), ANC (cells/mm^3), and hemoglobin (g/dL) • Chemistries: Creatinine, Creatine kinase (CPK), Creatinine Clearance (CrCl; Schwartz formula mL/min/1.73m^2), Total bilirubin, AST (u/l), ALT (u/l), Lipase (u/l), Blood Urea Nitrogen (BUN), Albumin (g/dL) • CD4 count and percentage • HIV-1 RNA • Store plasma for genotypic and phenotypic resistance testing • PK evaluation: Single pre-dose sample
	Blood or Urine	• For participants assigned female at birth, collect blood or urine for pregnancy test; result must be obtained before administering injectable study products
Study product		• Prescribe, prepare, and administer injectable study products, *see Section 5.1*

6.4.12 Cohort 2A Weeks 56, 64, 72, 80, 88 Visits (Step 4 – injection phase) and Cohort 2B Weeks 52, 60, 68, 76, 84 Visits (Step 5 - injection phase)

The Cohort 2A Weeks 56, 64, 72, 80, and 88 study visits have the following target dates as counted from completion of the Cohort 2A Week 4b visit:

- Cohort 2A Week 56 visit target date is 364 days after Week 4b
- Cohort 2A Week 64 visit target date is 420 days after Week 4b
- Cohort 2A Week 72 visit target date is 476 days after Week 4b
- Cohort 2A Week 80 visit target date is 532 days after Week 4b
- Cohort 2A Week 88 visit target date is 588 days after Week 4b

These Cohort 2A visits each have a target window of ±7 days from the respective target date. Additionally, each of these Cohort 2A visits should occur a minimum of 7 weeks (49 days) and a maximum of 9 weeks (63 days) from the previous injection.

The Cohort 2B Weeks 52, 60, 68, 76, and 84 study visits have the following target dates as counted from completion of the Cohort 2B Step 5 Entry visit:

- Cohort 2B Week 52 visit target date is 364 days after Step 5 Entry
- Cohort 2B Week 60 visit target date is 420 days after Step 5 Entry
- Cohort 2B Week 68 visit target date is 476 days after Step 5 Entry
- Cohort 2B Week 76 visit target date is 532 days after Step 5 Entry
- Cohort 2B Week 84 visit target date is 588 days after Step 5 Entry

These Cohort 2B visits each have a target window of ±7 days from the respective target date. Additionally, each of these Cohort 2B visits should occur a minimum of 7 weeks (49 days) and a maximum of 9 weeks (63 days) from the previous injection.

Cohort 2A Weeks 56, 64, 72, 80, 88 Visit Procedures (Step 4 – injection phase) and Cohort 2B Weeks 52, 60, 68, 76, 84 (Step 5 – injection phase) Visit Procedures		
Behavioral and Counseling		• Provide contraceptive counseling • Provide adherence counseling (Cohort 2A Week 72 only; Cohort 2B Week 68 only) • Perform acceptability/tolerability assessment questionnaires, *if indicated* • Conduct qualitative phone interview, *if indicated, see Section 11*
Clinical		• Update medical and medications history since last visit • Perform symptom-directed physical exam • Identify/review/update adverse events
Laboratory	**Blood**	Collect blood for: • Hematology: complete blood counts, with platelets (cells/mm^3), ANC (cells/mm^3), and hemoglobin (g/dL) • Chemistries: Creatinine, Creatine kinase (CPK), Creatinine Clearance (CrCl; Schwartz formula mL/min/1.73m^2), Total bilirubin, AST (u/l), ALT (u/l), Lipase (u/l), Blood Urea Nitrogen (BUN), Albumin* (g/dL) • CD4 count and percentage (Cohort 2A Week 72 only; Cohort 2B Week 68 only) • HIV-1 RNA (Cohort 2A Weeks 64 and 80 only; Cohort 2B Weeks 60 and 76 only) • Store plasma for genotypic and phenotypic resistance testing (Cohort 2A Weeks 64 and 80 only; Cohort 2B Weeks 60 and 76 only) • Cohort 2A PK evaluation: For all Cohort 2A participants, a single pre-dose sample is collected at Weeks 64, 80, and 88 visits only • Cohort 2B PK evaluation: For all Cohort 2B participants, a single pre-dose sample is collected at Weeks 60, 76, and 84 visits only
	Blood or Urine	• For participants assigned female at birth, collect blood or urine for pregnancy test; result must be obtained before administering injectable study products
Study product		• Prescribe, prepare, and administer injectable study products, *see Section 5.1*

*For Cohort 2A, Albumin (g/dL) is required at Weeks 64, 80, and 88 only; for Cohort 2B, Albumin (g/dL) is required at Weeks 60, 76, and 84 only

6.4.13 Cohort 2A Week 96 Visit (Step 4 – injection phase) and Cohort 2B Week 92 Visit (Step 5 - injection phase)

The Cohort 2A Week 96 visit target date is 644 days after completion of the Cohort 2A Week 4b visit, with a target window of ±7 days from the target date. Additionally, the Cohort 2A Week 96 visit should occur a minimum of 7 weeks (49 days) and a maximum of 9 weeks (63 days) from the previous injection.

The Cohort 2B Week 92 visit target date is 644 days after completion of the Cohort 2B Step 5 Entry visit, with a target window of ±7 days from the target date. Additionally, the Cohort 2B Week 92 visit should occur a minimum of 7 weeks (49 days) and a maximum of 9 weeks (63 days) from the previous injection.

Cohort 2 participants completing these visits who will continue to receive injectable CAB LA + RPV LA external to the protocol will exit the study. See Section 6.8 for more information on post-study contacts, and Section 14.11 for more information regarding post-trial access to study products. Participants who do not wish to continue receiving the injectable CAB LA + RPV LA beyond the Week 96 or Week 92 visit will not exit the study but will be followed per the LSFU visit schedule as described in Section 6.5 below.

Cohort 2A Week 96 Visit Procedures (Step 4 – injection phase) and Cohort 2B Week 92 (Step 5 – injection phase) Visit Procedures		
Behavioral and Counseling		• Provide contraceptive counseling • Provide adherence counseling • Provide instructions for cART administration and adherence counseling to the participant, parent or guardian, (if study exit visit only) • Perform acceptability/tolerability assessment questionnaires • Conduct qualitative phone interview, *if indicated, see Section 11*
Clinical		• Update medical and medications history since last visit • Perform complete physical exam • Identify/review/update adverse events • Sexual Maturity Rating assessment
Laboratory	**Blood**	Collect blood for: • Hematology: complete blood counts, with platelets (cells/mm^3), ANC (cells/mm^3), and hemoglobin (g/dL) • Chemistries: Creatinine, Creatine kinase (CPK), Creatinine Clearance (CrCl; Schwartz formula mL/min/1.73m^2), Total bilirubin, AST (u/l), ALT (u/l), Lipase (u/l), Blood Urea Nitrogen (BUN), Albumin (g/dL) • CD4 count and percentage • HIV-1 RNA • Store plasma for genotypic and phenotypic resistance testing • PK evaluation: Single pre-dose sample
	Blood or Urine	• For participants assigned female at birth, collect blood or urine for pregnancy test; result must be obtained before administering injectable study products
Study product		• Prescribe, prepare, and administer injectable study products, *see Section 5.1*

6.4.14 Interim Injection Visit (Step 4 or Step 5 – injection phase)

For Cohort 2A Step 4 or Cohort 2B Step 5 participants resuming injectable study products following short-term oral bridging, in consultation with and per CMC guidance, an interim injection visit may be required to administer study product injections outside of a regularly scheduled injection visit window. In consultation with the CMC, one or more interim injection visits may be necessary to appropriately reinitiate a participant on the dosing regimen or to realign to the original injection visit dosing schedule (as established based on the administration of the first injections). Regularly scheduled visits may be missed to maintain adequate spacing requirements between interim injection visits. The CMC must be consulted prior to initiating short-term oral bridging and prior resuming study product injections regarding clinical considerations, and injectable study product management and scheduling. It is generally expected that, in consultation with the CMC, the following guidelines will apply when resuming injectable study products following short-term oral bridging:

- If a participant will be on short-term oral bridging for ≤ 8 weeks (56 days) and is able to receive their study product injections with ≥ 3 weeks (21 days) before the next regularly scheduled injection visit, then an interim injection visit may be conducted; the next regularly scheduled injection visit will be conducted as originally scheduled.
- If a participant will be on short-term oral bridging for ≤ 8 weeks (56 days) but there are < 3 weeks (21 days) until the next regularly scheduled injection visit, then oral bridging should continue until the next regularly scheduled injection visit. No interim injection visit will be conducted; and the regularly scheduled injection visit should occur early within the window to facilitate the shortest course of oral bridging necessary.

- If a participant will be on short-term oral bridging for more than 8 weeks (56 days), the CMC must be consulted for guidance on resuming the injections versus premature discontinuation of study products.

An interim injection visit may also occur, in consultation with and per CMC guidance, to ensure the full injectable treatment for Cohort 2 participants and in accordance with the intended total injectable study product dosage/volumes per visit. Interim injection visit procedures are provided below, and study data will be entered into eCRFs per Section 5.1.5 and Section 7.2. Section 6.9 must also be followed prior to administering any study product injection. Further details and guidance on scheduling and conducting study injection visits, including interim injection visits, are provided in the IMPAACT 2017 MOP.

Cohort 2 Step 4 and Step 5 Interim Injection Visit Procedures (Step 4 or Step 5 - injection phase)		
Behavioral and Counseling		• Provide adherence counseling* • Provide contraceptive counseling*
Clinical		• Update medical and medications history since last visit* • Perform symptom-directed physical exam* • Identify/review/update adverse events*
Laboratory	**Blood**	Collect blood for: • Hematology: complete blood counts, with platelets (cells/mm^3), ANC (cells/mm^3), and hemoglobin (g/dL) • Chemistries: Creatinine, Creatine kinase (CPK), Creatinine Clearance (CrCl; Schwartz formula mL/min/1.73m^2), Total bilirubin, AST (u/l), ALT (u/l), Lipase (u/l), Blood Urea Nitrogen (BUN), Albumin (g/dL) • HIV-1 RNA* • Store plasma for genotypic and phenotypic resistance testing • PK evaluation: Single pre-dose sample*
	Blood or Urine	• For participants assigned female at birth, collect blood or urine for pregnancy test; result must be obtained before administering injectable study product*
Study product		• Prescribe, prepare, and administer injectable study products, *see Section 5.1*^

*Perform prior to administration of injectable study products
^Alternate dosing may be required, per CMC guidance, to ensure full injectable treatment.

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

As noted in Section 3, the below specified participants will be followed according to the long-term safety and washout PK follow-up (LSFU) visit schedule:

- For Cohort 1 Step 2 participants: upon premature permanent discontinuation of injectable study product, or completion of the Cohort 1 Step 2 Week 16 visit but not enrolling to Cohort 2

- For Cohort 1 Step 2 participants who enroll to Cohort 2A Step 3 but are ineligible for Step 4: upon premature permanent discontinuation of oral study product in Cohort 2A Step 3 (the LSFU visit schedule will be based on the date of their last study product injection, i.e., their Cohort 1 Step 2 Week 8 visit)

- For Cohort 2 participants: upon premature permanent discontinuation of injectable study products, or completion of the Cohort 2A Step 4 Week 96 or Cohort 2B Step 5 Week 92 study visit but do not wish to receive injectable CAB LA + RPV LA external to the protocol (see Section 6.4.13 above)

- Participants assigned female at birth who discontinue study product use (either oral or injectable study product) due to pregnancy during Steps 1-5

For participants permanently discontinuing injectable study product (not due to pregnancy), the LSFU visit schedule is based on the date of the participant's last study product injection. Cohort 1 Step 2 participants who complete their Week 16 visit will skip the LSFU Week 8 Visit.

Participants assigned female at birth who permanently discontinue study product (either oral or injectable study product and during Steps 1 through 5) due to pregnancy will be followed for 48 weeks, based on the date of the positive confirmatory pregnancy test result, per the LSFU visit schedule. 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 8.3 for further details on management of pregnant participants and pregnancy outcome.

Cohort 2A Step 3 participants should resume (non-study provided) cART as soon as possible and within 4 weeks from their last oral study product use. Cohort 2 participants should resume (non-study provided) cART at 8 weeks (±7 days) after their last study product injections. See the IMPAACT 2017 MOP for further guidance on scheduling LSFU study visits.

During LSFU, a single random PK sample will be collected at each visit as shown in the procedural tables below. Participants must have sufficient blood volume collection for their assigned study product(s), as specified in the LPC. See Section 6.16 for additional considerations for laboratory procedures, and Appendix I-D for blood volume ranges during LSFU visits.

6.5.1 LSFU Week 8 Visit

The LSFU Week 8 visit is targeted to be conducted 56 days after the last administration of injectable study product (or confirmatory positive pregnancy test result), with a target window of -14 days/+28 days from the target visit date. For Cohort 1 Step 2 participants completing the Week 16 visit, the LSFU Week 8 Visit will be skipped. Cohort 2 participants will resume (non-study provided) oral cART at 8 weeks (±7 days) of discontinuing study product.

LSFU Week 8 Visit Procedures (LSFU)		
Behavioral and Counseling		• Provide contraceptive counseling • Provide adherence counseling • Perform acceptability/tolerability assessment questionnaires • Conduct qualitative phone interview, *if indicated, see Section 11*
Clinical		• Update medical and medications history since last visit • Perform complete physical exam • Identify/review/update adverse events
Laboratory	**Blood**	Collect blood for: • Hematology: complete blood counts, with platelets (cells/mm^3), ANC (cells/mm^3), and hemoglobin (g/dL) • Chemistries: Creatinine, Creatine kinase (CPK), Creatinine Clearance (CrCl; Schwartz formula mL/min/1.73m^2), Total bilirubin, AST (u/l), ALT (u/l), Lipase (u/l), Blood Urea Nitrogen (BUN), Albumin (g/dL) • HIV-1 RNA • Store plasma for genotypic and phenotypic resistance testing • PK evaluation: single sample
	Blood or Urine	• For participants assigned female at birth, collect blood or urine for pregnancy test (unless currently pregnant)

Sites may conduct interim safety visits between the LSFU Week 8 and LSFU Week 24 visits to clinically assess participants as they initiate their cART regimen, per standard of care or site SOPs.

6.5.2 LSFU Week 24 Visit

The LSFU Week 24 Visit is targeted to take place 168 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.

LSFU Week 24 Visit Procedures (LSFU)		
Behavioral and Counseling		• Provide contraceptive counseling • Conduct qualitative phone interview, *if indicated, see Section 11*
Clinical		• Update medical and medications history since last visit • Perform symptom-directed physical exam • Identify/review/update adverse events
Laboratory	**Blood**	Collect blood for: • Hematology: complete blood counts, with platelets (cells/mm^3), ANC (cells/mm^3), and hemoglobin (g/dL) • Chemistries: Creatinine, Creatine kinase (CPK), Creatinine Clearance (CrCl; Schwartz formula mL/min/1.73m^2), Total bilirubin, AST (u/l), ALT (u/l), Lipase (u/l), Blood Urea Nitrogen (BUN), Albumin (g/dL) • HIV-1 RNA • Store plasma for genotypic and phenotypic resistance testing • PK evaluation: single sample
	Blood or Urine	• For participants assigned female at birth, collect blood or urine for pregnancy test (unless currently pregnant)

6.5.3 LSFU Week 36 Visit

The LSFU Week 36 Visit is targeted to take place 252 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.

LSFU Week 36 Visit Procedures (LSFU)		
Behavioral and Counseling		• Provide contraceptive counseling • Conduct qualitative phone interview, *if indicated, see Section 11*
Clinical		• Update medical and medications history since last visit • Perform symptom-directed physical exam • Identify/review/update adverse events
Laboratory	**Blood**	Collect blood for: • Hematology: complete blood counts, with platelets (cells/mm^3), ANC (cells/mm^3), and hemoglobin (g/dL) • Chemistries: Creatinine, Creatine kinase (CPK), Creatinine Clearance (CrCl; Schwartz formula mL/min/1.73m^2), Total bilirubin, AST (u/l), ALT (u/l), Lipase (u/l), Blood Urea Nitrogen (BUN), Albumin (g/dL) • HIV-1 RNA • Store plasma for genotypic and phenotypic resistance testing • PK evaluation: single sample
	Blood or Urine	• For participants assigned female at birth, collect blood or urine for pregnancy test (unless currently pregnant)

6.5.4 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 Step 1 and Cohort 2A Step 3 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. Cohort 2A Step 3 participants should resume (non-study provided) cART as soon as possible and within 4 weeks from their last oral study product use.

- For Cohort 1 Step 2, Cohort 2A Step 4, Cohort 2B Step 5, and any participant being followed per the LSFU visit schedule, an Early Termination visit is targeted to be completed within 28 days (inclusive) of the previous study visit. Cohort 2 participants should resume (non-study provided) cART at 8 weeks (±7 days) after their last study product injections.

Participants completing an Early Termination visit will be followed until resolution (return to baseline) or stabilization of any adverse events per Section 8.

Refer to Section 6.7 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 8.8 for criteria for participant withdrawal or premature termination from the study. The IMPAACT 2017 MOP provides further guidance on Early Termination visit scheduling considerations.

LSFU Week 48 /Early Termination Visit Procedures		
Behavioral and Counseling		• Provide contraceptive counseling • Provide adherence counseling • Perform acceptability/tolerability assessment questionnaires • Conduct qualitative phone interview, *if indicated, see Section 11*
Clinical		• Update medical and medications history since last visit • Perform complete physical exam • Identify/review/update adverse events • Perform additional evaluations per Section 8 and/or if clinically indicated (consult CMC if indicated) • Sexual Maturity Rating assessment
Laboratory	**Blood**	Collect blood for: • Hematology: complete blood counts, with platelets (cells/mm^3), ANC (cells/mm^3), and hemoglobin (g/dL) • Chemistries: Creatinine, Creatine kinase (CPK), Creatinine Clearance (CrCl; Schwartz formula mL/min/1.73m^2), Total bilirubin, AST (u/l), ALT (u/l), Lipase (u/l), Blood Urea Nitrogen (BUN), Albumin (only if PK is also collected at this visit, g/dL) • HIV-1 RNA • Store plasma for genotypic and phenotypic resistance testing (LSFU Week 48 visit only) • Store whole blood for genotypic resistance testing (Early Termination visit only) • PK evaluation: single sample, (except for participants completing an Early Termination visit during Cohort 1 Step 1 or Cohort 2 Step 3)
	Blood or Urine	• For participants assigned female at birth, collect blood or urine for pregnancy test (unless currently pregnant)

6.6 Confirmation of Virologic Failure Visit

Virologic failure is defined as two consecutive plasma HIV-1 RNA test results ≥200 copies/mL, from two separate specimens. Any participant with a plasma HIV-1 RNA level ≥200 copies/mL after enrollment should be recalled to the clinic for confirmatory testing 2-4 weeks after specimen collection for the initial test. Refer to Section 8.4 for more information on monitoring HIV-1 viral load, definitions of virologic failure, and managing virologic failure.

Scheduling of confirmatory testing should be in consideration of potential causes for virologic failure such as intercurrent illness, recent immunizations, inadequate adherence or interruptions to cART (for Cohort 1 or LSFU participants), interruptions of study product due to toxicity management, or other extenuating circumstances. For Cohort 1 Step 2 or Cohort 2 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. 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		• Provide contraceptive counseling • Provide adherence counseling, *if indicated* • Provide instructions for cART administration and adherence counseling to the participant, parent or guardian, *if indicated*
Clinical		• Obtain interval medical and medications history • Perform symptom-directed physical exam • Identify/review/update adverse events • Perform additional evaluations per Section 8 and/or if clinically indicated (consult CMC if indicated)
Laboratory	**Blood**	Collect blood for: • HIV-1 RNA • Plasma for genotypic and phenotypic resistance testing • PK evaluation: single sample
	Blood or Urine	• For participants assigned female at birth, collect blood or urine for pregnancy test (unless currently pregnant)

6.7 Study Exit

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

- Participants following the LSFU visit schedule will exit the study at their LSFU Week 48 study visit (see Section 6.5 above)

- Cohort 2 participants who complete the Step 4 Week 96 or Step 5 Week 92 visit and wish to receive injectable CAB LA + RPV LA external to the protocol will exit the study; see Section 14.11

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 0 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. The participant and parent or guardian should be provided information on how to remain in contact with study staff (if desired) and how to learn about the results of the study when available. The participant and the participant's parent or guardian should also be provided information, counseling, and referrals to non-study sources of care and treatment for the participant, as applicable. Cohort 2A Step 3 participants should resume (non-

study provided) cART as soon as possible and within 4 weeks from their last oral study product use. Cohort 2 participants should resume (non-study provided) cART at 8 weeks (±7 days) after their last study product injections. See Section 8.1 regarding management of adverse events at study exit, and Section 8.8 for additional considerations regarding participant withdrawal or termination.

6.8 Post-Study Contacts

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 to 8 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. However, eCRF data collection is required after the participant's study exit visit in the following scenarios:

- If a participant becomes pregnant while on study: Refer to Section 8.3; the pregnancy outcome must be ascertained and the relevant eCRFs entered after the participant exits the study to record the pregnancy outcome.

- If confirmation of virologic failure is pending after the LSFU Week 48 visit: A Confirmation of Virologic Failure Visit should be conducted (refer to Section 6.6) with all relevant eCRFs entered.

- If the participant has any Grade 3 or higher adverse event at the study exit visit: participants should be asked to be continued on study for up to 56 days or until resolution (return to baseline) or stabilization (i.e., Grade 2 or lower), whichever is sooner, with the frequency of visits determined by the site investigator.

6.9 Procedures for Continued Oral and Injectable Study Product Administration

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

- Clinical evaluations per the respective study visit (see Section 6 and Appendix I)
- Laboratory test results from the previous study visit obtained and reviewed for indication of study product hold or permanent discontinuation (see Section 8)
- For participants assigned female at birth, a negative pregnancy test result
- For participants childbearing potential, confirmation (per participant report) of effective contraception, per Section 6.13

See Section 8.1 for details regarding participant management. See Section 8.6 for details regarding 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. Refer to the IMPAACT 2017 MOP for additional guidance regarding establishing baseline history.

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 product as described in Section 8.1. Relevant dates will be recorded for all conditions and medications; see Section 5.6 for more information on concomitant medications.

Table 8 specifies the baseline and interval medical and medications history elements that must be source documented for participants, as well as associated eCRF entry requirements.

Table 8. Documentation Requirements for Medical and Medication Histories

Assess for and Source Document	Enter into eCRFs or SES
Baseline Medical and Medication History Elements	
Age, sex at birth, and other socio-demographics	Yes (all)
HIV diagnosis, mode of transmission, and ARV treatment history (including all prior ARV use)	Yes (all, including start/stop dates, dates and values of results, as applicable)
History of allergy and/or hypersensitivity (including to ARVs)	Yes (all)
Medical conditions (including malignancies) occurring during the 28 days prior to entry, ongoing at entry, as well as all prior 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.	Yes (all, including start/stop dates, and dates of diagnosis, as applicable)
Medications, (other than ARVs, see above) taken within the 28 days prior to enrollment and/or ongoing at enrollment	Yes (all, except herbal or traditional medications are not be captured on eCRFs)
Assessment of sexual activity	Yes

Assess for and Source Document	Enter into eCRFs or SES
Contraceptives ongoing at enrollment, including start date and most recent date of administration of current contraceptive method. Note: 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	Yes
Any other information needed to determine eligibility for the study	—
Interval Medical and Medication History Elements	
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	Any newly identified adverse events that meet criteria in Section 7.2
Current status of medications (including contraceptives) 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 (see Section 5.6 for more information on concomitant medications) **Note:** For participants in Cohort 1 and LSFU, ARVs would be considered concomitant medications.	• Any concomitant ARVs taken • Any new use of concomitant medications, including contraceptives • All medications taken at onset of or in response to adverse events that are specified to be entered into eCRFs per Section 7.2 **Note**: herbal or traditional medications taken during follow-up should not be captured on eCRFs.
Oral Study Product since the last visit (for Cohort 1 Step 1, Cohort 2A Step 3 participants, and any Cohort 1 or Cohort 2 participants on oral bridging) **Note:** Injectable study product information is not considered as part of medical and medications history since last visit, and will be collected as per Section 5. See Section 6 above for details regarding study product dosing documentation requirements for PK evaluations.	• Oral study product doses taken from time of enrollment through completion of follow-up
Assessment of sexual activity since the last visit	—

6.11 Physical Examinations

A physical examination is required at each scheduled visit, either as a complete physical exam or as a symptom-directed physical exam, per the specified procedures for each visit. Table 9 below outlines the visits when a complete physical exam is required; symptom-directed exams are required at all other scheduled visits.

Table 9. Visits Requiring Complete Physical Examination

Cohort 1	Screening, Week 4a, and Week 16 Visits
Cohort 2A	Screening, Week 4a, Week 24, Week 48, and Week 96
Cohort 2B	Screening, Week 20, Week 44, and Week 92
LSFU	LSFU Week 4, and LSFU Week 48/Early Termination Visit

Complete exams should include the following:

- Height and weight
- Vital signs, including heart rate, temperature and blood pressure
- 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) (at Screening for both Cohort 1 and Cohort 2, Cohort 1 Week 16, Cohort 2A Week 24 and 96, Cohort 2B Week 20 and 92, and LSFU Week 48/Early Termination visits)
- Examination of other body systems driven by other identified signs or symptoms

Symptom-directed 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

At all visits, additional assessments may be performed at the discretion of the examining site investigator. All exam findings should be source documented, with vital signs and any abnormal findings entered into eCRFs, as specified in Section 7.2. Additionally, height and weight must be obtained on the same day as any PK sample collection, and source documented and entered into eCRFs, even if a physical exam was already conducted as part of that visit.

6.12 Performing an Electrocardiogram (ECG/EKG)

Electrocardiogram (ECG) readings are required as specified in Sections 6.2 through 6.5 above. 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.

At the Cohort 1 Screening and Cohort 2 Screening visits, 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. Once the QT correction formula of either Bazett or Fridericia has been chosen for a participant's eligibility, the same formula must continue to be used for that participant for ECG monitoring and all QTc data being collected for data analysis. This formula may not be changed or substituted once the participant has been enrolled. For example, if a participant is eligible for the protocol based on QTcB (calculated using Bazett's formula), then QTcB must be used for this individual participant during study follow-up. During follow-up, single automated readings will be compared to the baseline value, with the following requiring two repeat readings (for a total of three readings separated by at least 2 minutes):

- For QTcB (using Bazett's formula), a result of > 500 msec or ≥ 60 msec increase from baseline.
- For QTcF (using Fridericia formula), a result of ≥ 500 msec or > 60 msec increase from baseline.

All ECG readings should be source documented and entered into eCRFs. See Section 8.2 for Management of QTc Prolongation.

6.13 Pregnancy Testing and Contraceptive Counseling

Pregnancy testing is required for all participants assigned female at birth, at specified study visits and prior to administration of study product, regardless of self-reported sexual activity or childbearing potential. See Section 8.3 for details on participant and study product management relating to Management of Contraception and Pregnancy.

As stated in Section 4.1.14, participants of childbearing potential are required to use at least one allowable effective method of contraception to enroll to the study. For participants who become of childbearing potential during the study, an allowable effective contraceptive method must be initiated prior to administration of study product (oral or injectable study product). A participant assigned female at birth is considered of childbearing potential following the initiation of puberty (Tanner stage 2 based on genitalia and/or breast assessment) or onset of menarche, whichever is noted first, until becoming post-menopausal, unless permanently sterile or with medically documented ovarian failure. Participants assigned female at birth are considered to be in a postmenopausal state when they are > 54 years of age with cessation of previously occurring menses for > 12 months without an alternative cause. Permanent sterilization includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a participant of any age assigned female at birth.

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

- Complete abstinence from intercourse of reproductive potential. Abstinence is an acceptable method of contraception only when it is in line with the participant's preferred and usual lifestyle

  OR

- Consistent and correct use of 1 of the following methods of birth control listed below.
  - Intrauterine device (IUD) with a failure rate of < 1% per year
  - Intrauterine hormone-releasing system (IUS) with a failure rate of < 1% per year
  - Tubal sterilization
  - Essure micro-insert system (provided confirmation of success 3 months after procedure)
  - Vasectomy in the male partner (provided that the partner is the sole sexual partner and had confirmation of surgical success 3 months after procedure)

  OR

- Consistent and correct use of one hormonal method AND one barrier method
  - Barrier methods
    - Diaphragm with spermicide
    - Cervical cap with spermicide
    - Male condom (with or without spermicide)
  - Hormonal methods
    - Oral contraceptives (either combined or progesterone only)
    - Injectable progesterone
    - Implants of levonorgestrel
    - Transdermal contraceptive patch
    - Contraceptive vaginal ring

For 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 staff will provide contraception counseling to all participants (regardless of gender, self-reported sexual activity, or childbearing potential) at all study visits. 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. Participants assigned female at birth should also be encouraged to delay pregnancy for at least 30 days following oral study product use, or 48 weeks following any single injection of study product.

At any point during study participation, additional counseling on correct use of chosen contraceptive methods should also be offered according to site SOPs; this will include information on correct use of barrier methods. For Cohort 1 and all 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. Contraceptive counseling may 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. 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. Study staff should confirm (per participant report) effective contraception with one of the study-required contraceptive methods for all participants of childbearing potential at each visit in which study product is administered.

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 informed consent and assent forms.

6.14 Study Product Adherence Assessment and Adherence Counseling (Study Product, cART Regimen, Study Visits)

Prior to progressing to the injection phase, Cohort 1 and Cohort 2A 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. Pill counts will be conducted at the Week 2, Week 4a and Week 4b visits (for both Cohort 1 and Cohort 2A) but will not be used as a basis for counseling participants on oral study product adherence. Information obtained through the pill counts, 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 or Step 4 eligibility with regards to Sections 4.3.4 and 4.4.4.

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, Step and whether participants are also taking a (non-study provided) cART regimen:

- For Cohort 1 participants, adhering to the (non-study provided) cART regimen and instructions on cART administration will be provided. These topics will also be discussed prior to participants transitioning to the LSFU visit schedule (if permanently discontinuing injectable study product), during specified LSFU visits, and at Early Termination visits.
- For Cohort 1 Step 1 and Cohort 2A Step 3 participants, counseling on adhering to the oral study product will be provided in relation to the purpose of the oral lead-in phase and allowing for sufficient evaluations of safety and tolerability.
- For Cohort 1 Step 2, Cohort 2A Step 4, and Cohort 2B Step 5 participants, counseling will include discussion with participants regarding the importance of adhering to the intended injectable study product dosing regimen and adhering to the study visit schedule.
- For all Cohort 2 participants, counseling will include confirmation of the decision to enroll to the selected Cohort 2 group (Cohort 2A versus Cohort 2B), and discussion on the importance of adhering to the study visit schedule as these participants are no longer receiving a (non-study provided) cART regimen.
- For participants exiting the study at the Cohort 2A Week 96 or Cohort 2B Week 92 visit (to continue injectable CAB LA + RPV LA external to the protocol), counseling will include the importance of adhering to the intended injectable dosing regimen and schedule.

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

Acceptability and tolerability of the study products will be assessed at specified study visits, and at visits during which permanent study product discontinuation is initiated. These assessments will be administered to participants by site staff via questionnaires covering topics on participant 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. A shortened assessment battery will be utilized for individuals who are unable to complete the questionnaires in English or Spanish. Prior to the participant leaving the clinic, questionnaires should be reviewed, and any potential adverse events reported in the participant's responses should be clinically 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 study-specific MOP.

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 LPC, which will be posted on the study-specific webpage: http://impaactnetwork.org/studies/IMPAACT2017.asp. Site staff collecting specimens for PK evaluations must prepare the workspace and supplies with regards to protecting all specimens from light, as specified in the LPC.

In accordance with US National Institutes of Health (NIH) recommendations, pediatric (less than 18 years) blood collection will not exceed 5 mL/kg in a single day or 9.5 mL/kg over any eight-week period. Adult (18 years and older) blood collection will not exceed 10.5 mL/kg or 550 mL, whichever is smaller, over any eight-week period.

In the event blood collection must be limited, available specimens will be prioritized for use in the following order: (1) safety (chemistries, hematology, pregnancy testing), (2) PK, (3) HIV-1 viral load, and (4) genotypic and phenotypic resistance storage sample.

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 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.

The following will be performed in real time at local laboratories that are CLIA-certified or equivalent (for US sites) or at any network-approved non-US laboratory that operates in accordance with Good Clinical Laboratory Practices (GCLP) and participates in appropriate external quality assurance programs:

- Pregnancy tests
- Hematology laboratory testing: complete blood counts, with platelets (cells/mm3), ANC (cells/mm3), and hemoglobin (g/dL)
- Chemistry laboratory testing: Creatinine, Creatine kinase (CPK), Creatinine Clearance (CrCl; Schwartz formula mL/min/1.73m2), Total bilirubin, AST (u/l), ALT (u/l), Lipase (u/l), Blood Urea Nitrogen (BUN), Albumin (g/dL)
- CD4 count and percentage tests
- Plasma HIV-1 RNA assays

HIV genotypic and phenotypic resistance samples for storage (collected at study visits other than the Confirmation of Virologic Failure visit) must be processed and stored per the LPC.

HIV genotypic and phenotypic resistance samples collected at the Confirmation of Virologic Failure visit must be processed with plasma retained at the site laboratory, as specified in the LPC, pending HIV-1 RNA test results to confirm virologic failure. For participants with confirmed virologic failure, aliquots of plasma stored for resistance testing collected during the Confirmation of Virologic Failure visit, the visit in which the participant had an initial elevated viral load test result, the whole blood sample stored at the Entry visit, and any other study visits as requested by the CMC, will be shipped with testing performed in real time at a designated CLIA-certified or equivalent testing laboratory, as specified in the LPC. If failure is not confirmed, resistance samples collected during the Confirmation of Virologic Failure visit will remain stored at the site laboratory.

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

- For Cohort 1: PK samples from Week 2 through Week 8 visits should be shipped upon completion of the Week 8 visit. Cohort 1 PK samples from Week 9 through Week 16 visits should be shipped upon completion of the Week 16 visit. Samples from all LSFU visits should be batched and shipped quarterly.
- For Cohort 2A: PK samples from Week 2 through Week 16 should be shipped upon completion of the Week 16 visit. PK samples from the Week 24 visit should be shipped in real time and upon completion of the Week 24 visit. Samples from Week 25 through Week 48 visits should be shipped upon completion of the Week 48 visit. Samples from Week 56 through Week 96 visits and all LSFU visits should be batched and shipped quarterly.
- For Cohort 2B: PK samples from Entry through Week 20 should be shipped in real time and upon completion of the Week 20 visit. Samples from Week 21 through Week 44 visits should be shipped upon completion of the Week 44 visit. Samples from Week 52 through Week 92 visits and all LSFU visits should be batched and shipped quarterly.
- All Confirmation of Virologic Failure visits (from both Cohorts 1 and 2) should be batched and shipped quarterly.

After all protocol-specified laboratory testing has been performed, residual specimens may be of interest for future research use. Participants and participants' parents or guardians (if applicable) will be asked to provide written informed consent/assent for future research use of these

specimens, if permitted by IRBs/ECs and other applicable review bodies. Parents or guardians (or participants) may choose to provide or to decline informed consent for future research use of residual specimens with no impact on other aspects of participation in the study. If informed consent for future research use of residual specimens is initially provided but if participants or their parent/guardian subsequently change their mind and withdraw that consent, all remaining residual samples will be destroyed.

6.16.3 Biohazard Containment

As the transmission of HIV 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 Sections 9.5.1 and 9.5.2.

Unless otherwise noted, the specifications of this section only apply to adolescent participants in Cohort 1, Cohort 2, and LSFU.

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 CMC 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.

Importantly, site investigators must inform the CMC of any of the following:

- New onset seizure
- Grade 3 or higher absolute neutrophil count (ANC), alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatine kinase (CPK), total bilirubin (unless isolated atazanavir related hyperbilirubinemia with normal direct bilirubin), or lipase
- Grade 3 or higher adverse events assessed as related to study product
- Missed scheduled study product injection visit
- Suspected maladministration and/or post-injection reaction

For new onset of seizure and suspected maladministration and/or post-injection reactions, the CMC should be informed within 24 hours of awareness of the event. For all other events specified above, the CMC should be informed as soon as possible and within 48 hours of awareness of the event.

For participants who miss a scheduled study product injection, or who have a temporary hold which will cause the participant to miss a scheduled study product injection, the CMC should be consulted as soon as possible and within 48 hours of site awareness.

7.1.2 Clinical Management Committee (CMC)

The following Protocol Team members comprise the CMC: Co-Chairs, Medical Officers, Statisticians, Data Managers, Clinical Research Managers, Laboratory Center Representatives, protocol Pharmacologists, at least one protocol Investigator, at least one Statistician representative from ViiV, at least one medical (or designee) representative from each ViiV and Janssen, and at least one Pharmacologist representative from each ViiV and Janssen. 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, management of adverse events, study product administration, cART regimens, and other 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 9.5.1.

Detailed toxicity management algorithms including criteria for discontinuation of study product can be found in Section 8 below.

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 9.5.2 for more information on the composition and role of the SMC in monitoring of this study.

7.2 Safety-Related Data Collection

This section describes eCRF data collection for pre-existing conditions and adverse events. Criteria for expedited reporting of specified adverse events are further detailed in Sections 7.3.2 and 7.3.3 below.

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 only to the adolescent participants, beginning at the time of enrollment (as defined in Section 4.7), regardless of subsequent administration of or exposure to study product. Any untoward medical conditions (including abnormal laboratory test results, signs, symptoms, or diseases) identified prior to enrollment will be considered pre-existing conditions.

Pre-Existing Conditions

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

- All conditions identified during the 28 days prior to study entry
- All conditions ongoing at the time of enrollment
- All prior 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

Adverse Events

The following adverse events will be entered into the adverse events eCRFs:

- Grade 1 and higher clinical adverse events (including all signs, symptoms, and associated laboratory test results of the clinical adverse event)
- Grade 3 or higher laboratory-only adverse events
- All adverse events that result in temporary study product hold or permanent discontinuation of study product
- All adverse events that meet criteria for expedited reporting per protocol Section 7.3.2
- For Cohort 1 participants enrolling to Cohort 2, all Grade 1 or higher clinical adverse events ongoing at the time of Cohort 2 Entry as well as any event that occurred within the 28 days prior to Cohort 2 Entry (i.e., Cohort 2A Step 3 Entry or Cohort 2B Step 5 Entry, as applicable)

Laboratory Test Results

All protocol-required laboratory test results will be entered into laboratory 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 Manual for Expedited Reporting of Adverse Events to DAIDS (DAIDS EAE Manual), which is available on the DAIDS RSC website 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 on the DAIDS RSC website 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 severity or relationship to study product:

- ALT ≥3x ULN with total bilirubin ≥2x ULN
- ALT ≥8x ULN
- ALT ≥3x baseline ALT with signs/symptoms of acute hepatitis
- ALT ≥5x ULN that persists >2 weeks
- Any seizure event

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

Information on Aes 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. This table is available at:

https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables

The DAIDS AE Grading Table provides grading for creatinine and creatinine clearance (or eGFR) values based on both absolute value and change from baseline. For this study, for creatinine, only the comparison to upper limit of normal (ULN) will be used and not change from baseline. For creatinine clearance (or eGFR), only the absolute value will be used, and not percent change from baseline, using the Bedside Schwartz formula.

The DAIDS AE Grading Table provides grading for prolonged QTc interval assessed per Bazett's formula (QTcB); protocol-specific grading for prolonged QTc interval assessed per Fridericia's formula (QTcF) is as follows:

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

7.3.4 EAE Reporting Period

The EAE reporting period for this study is the protocol-specific period of follow-up, beginning at the time of study entry and ending on the date of the final follow-up visit. For all participants who continue per the LSFU visit schedule, EAE reporting requirements continue throughout LSFU follow-up. For Cohort 1 participants who may enter Cohort 2 after having exited the study, EAE reporting requirements resume upon re-entry into the study.

After this reporting period, unless otherwise noted, only Suspected, Unexpected Serious Adverse Reactions (SUSARs) as defined in Version 2.0 of the 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 12. 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 product, 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. Unless otherwise specified below, AEs (clinical as well as abnormal laboratory values) should be managed per general management guidelines in Section 8.1.1.

Individual dose adjustments or reductions of study products for management of toxicity-related AEs are not allowed. For Cohort 2 participants, 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 Cohort 2 participants and resuming (non-study provided) cART, see Section 8.6 regarding temporary product holds, and Section 8.7 regarding permanent discontinuation of study product.

Unless otherwise noted in the protocol, laboratory values obtained and clinical assessments performed at the Entry visit for the applicable cohort will be used as baseline. Laboratory values obtained and clinical assessments performed as part of screening procedures for the

applicable cohort may be used as baseline if not available from the Entry visit or per CMC guidance. Refer to the IMPAACT 2017 MOP for additional guidance. All adverse events must be followed to resolution (return to baseline) or stabilization, 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. In some instances, and per CMC guidance, a PK sample should also be collected. Clinical management of all adverse events should be provided consistent with the best medical judgment of the site investigator and local clinical practice standards.

Adverse events that are ongoing at the time of the final study visit, particularly those of Grade 3 or higher severity, should generally be followed to resolution or stabilization 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 8.1.2–8.1.10 provide detailed participant and study product management on specified adverse events and 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 s/he feels that continued product use would be harmful to the participant or interfere with treatment deemed clinically necessary. See Sections 8.6 and 8.7 below.

- **Grade 1 or Grade 2, regardless of relationship to study product:** 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 AE 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 AE 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 product:** 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 out of proportion of what would be expected when a person gets an intramuscular injection, tenderness, erythema, redness, induration or swelling, or pruritis, regardless of when it occurs after administration of an injection. 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 product:

- **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

Procedural pain and/or discomfort from the needle or from the volume of the suspension entering the tissue at the time of injection that is normal and expected with an intramuscular (IM) injection, in the opinion of the investigator, is not considered an adverse event or an ISR. See the IMPAACT 2017 MOP for more details related to procedural pain and Injection Site Reactions (ISRs).

8.1.3 Suspected Maladministration of Injectable Study Product 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, a PK sample (4 mL) should be drawn approximately 2 hours post-dosing for evaluation of CAB and RPV plasma concentrations. The CMC should be consulted for additional guidance on participant safety management within 24 hours after a suspected maladministration and/or suspected post-injection reaction 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 CPK results from baseline should be assessed for a history of use of drugs known to cause increase of CPK (such as statins), and/or physical activity or exercise preceding the CPK 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 CPK 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), 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 product:

- **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

This section provides guidance on study product and participant management due to elevations in ALT (or AST), including considerations of accompanying bilirubin test results. Participants with an abnormal total bilirubin test result should have serum bilirubin fractionation (i.e. direct bilirubin) testing requested (ideally from the same sample - i.e. automatic fractionation - if raised bilirubin results), regardless of whether they are on an atazanavir-containing regimen. Confirmatory repeat testing should be performed, at the timepoints indicated below (if ALT or AST is also elevated) or per CMC consultation (if ALT or AST is normal).

In all cases of elevated ALT (or 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.

As noted in Section 7.1.1, the CMC must be informed of any Grade 3 or higher total bilirubin, unless isolated atazanavir related hyperbilirubinemia with normal direct bilirubin. Note that to assess total hyperbilirubinemia as atazanavir-related, demonstration of a normal direct bilirubin is

needed. Asymptomatic Cohort 1 participants on an atazanavir-containing cART regimen, who present with hyperbilirubinemia (any grade) with a normal direct bilirubin, normal ALT (or normal AST), and no other alternate etiology for the unconjugated hyperbilirubinemia, may continue study product use in consultation with the CMC.

ALT or AST SEVERITY GRADE WITH ACCOMPANYING BILIRUBIN SEVERITY GRADE (TOTAL OR DIRECT)	PARTICIPANT AND STUDY PRODUCT MANAGEMENT
Grade 1 ALT (or AST), and/or Grade 1 bilirubin	Continue study product use, and repeat testing at the next scheduled study visit, or more frequently at the discretion of site investigator.

ALT or AST SEVERITY GRADE WITH ACCOMPANYING BILIRUBIN SEVERITY GRADE (TOTAL OR DIRECT)	PARTICIPANT AND STUDY PRODUCT MANAGEMENT
Grade 2 ALT (or AST)	• With ≤ Grade 1 bilirubin (at the Week 4a visit): Continue study product use, and repeat testing within 72 hours. If repeat test results return to baseline, continue per study visit schedule (see Sections 6.3.3, and 6.4.3). If repeat test results in Grade 2, consult the CMC immediately and manage per CMC guidance. • With ≤ Grade 1 bilirubin (all visits except the Week 4a visit): Continue study product use, and repeat testing weekly. If still Grade 2 ALT (or AST) after 4 weeks, consult the CMC. • With Grade 2 or higher bilirubin: Hold study product, and repeat testing weekly. If repeat test results of both ALT (or AST) and bilirubin return to baseline, resume study product use, inform the CMC, and continue to monitor per applicable Schedule of Evaluations. If after 4 weeks repeat test results of ALT (or AST) is still ≥ Grade 2, and/or bilirubin is still ≥ Grade 1, continue to hold study product and consult the CMC. • If baseline ALT (or AST) was ≤ ULN and participant is symptomatic (i.e. has nausea, abdominal discomfort or anorexia), regardless of accompanying bilirubin test results: Hold study product, and repeat testing weekly. If repeat test results of ALT (or AST) return to baseline, resume study product use, inform the CMC, and continue to monitor per applicable Schedule of Evaluations. If after 4 weeks repeat test results are still Grade 2 ALT (or AST), continue to hold study product and consult the CMC.

ALT or AST SEVERITY GRADE WITH ACCOMPANYING BILIRUBIN SEVERITY GRADE (TOTAL OR DIRECT)	PARTICIPANT AND STUDY PRODUCT MANAGEMENT
Grade 3 ALT (or AST), regardless of accompanying bilirubin test result	Hold study product, inform the CMC within 24 hours, and repeat testing within 72 hours. Reinforce participant awareness and knowledge 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. Participants should be advised to seek immediate medical attention and contact the site as soon as possible. • If repeat test results in ≤ Grade 2 without addressing possible alternative etiology, manage as per Grade 2 above. • If upon addressing possible alternative etiology repeat test results in ≤ Grade 2, consult CMC. If CMC agrees, resume study product. If event recurs at ≥ Grade 3, permanently discontinue study product and inform CMC. • If repeat test results in ≥ Grade 3, continue to hold study product and consult the CMC. If no possible alternative cause identified, permanently discontinue study product.

ALT or AST SEVERITY GRADE WITH ACCOMPANYING BILIRUBIN SEVERITY GRADE (TOTAL OR DIRECT)	PARTICIPANT AND STUDY PRODUCT MANAGEMENT
Grade 4 ALT (or AST), regardless of accompanying bilirubin test result	Hold study product, inform the CMC within 24 hours, and repeat testing within 72 hours. Reinforce participant awareness and knowledge 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. Participants should be advised to seek immediate medical attention and contact the site as soon as possible. • If repeat test results in ≤ Grade 2, manage as per Grade 2 above. • If repeat test results in Grade 3, manage as per Grade 3 above. • If repeat test result is still Grade 4, inform CMC and permanently discontinue study product.

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 product, 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 the 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 product:

- **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. Cohort 1 participants should also discontinue their cART regimen, at the discretion of the site investigator and in consultation of the CMC. Participants may be referred to a dermatologist, at the discretion of the site investigator.

Additionally, for any rash determined to be related to study product and presenting prior to the Week 4b visit (for both Cohort 1 and Cohort 2A participants), 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 with HIV 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 product, 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 2017 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

8.2 Management of QTc Prolongation

Management of QTc Prolongation

See Section 6.12 for QTc intervals requiring repeat readings.

- If any one of the repeated readings confirm a QTc interval (for QTcB: > 500 msec or a ≥ 60 msec increase from baseline; for QTcF: ≥ 500 msec or > 60 msec increase from baseline), temporarily hold study product and assess participant for concomitant medications known to cause prolonged QT or Torsades de pointes.
- If the prolonged QTc is assessed as not related, study product may be resumed in consultation with the CMC.
- 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.

8.3 Management of Contraception and Pregnancy

Participants of childbearing potential must agree to maintain use of an allowable effective contraceptive method throughout study participation, in addition to:

- at least 30 days after discontinuation of oral study products (if terminating early from the study during Cohort 1 Step 1 or Cohort 2A Step 3), and
- at least 48 weeks after discontinuation of injectable study products.

Counseling should begin during the screening visit and continue for each participant throughout their participation in the study. See Section 6.13 for more details on pregnancy testing, contraceptive counseling, and a list of the allowable effective contraception methods.

For all participants assigned female at birth, a negative pregnancy test result must be obtained on the same day and prior to administration of study product. For participants of childbearing potential, confirmation of contraceptive use (per participant report) must also be obtained on the same day and prior to administration of study product. If effective contraception cannot be confirmed, and in the opinion of the investigator early pregnancy cannot be excluded, then study product should be temporarily held, and the CMC consulted for further guidance on study product use and participant management.

Participants with a positive pregnancy test result will temporarily discontinue study product, with confirmatory testing conducted within 48 hours. Upon a confirmatory positive pregnancy test result, study product will be permanently discontinued; Cohort 2 participants will resume an oral cART regimen. 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. Additionally, the CMC should be notified within 2 weeks of obtaining the initial positive pregnancy test result.

Pregnant participants will be followed per the LSFU visit schedule based on the date of the positive confirmatory test result. Pregnant participants already being followed per the LSFU visit schedule will continue their scheduled visits, however any pregnancy outcome occurring after study exit will be entered into eCRFs, as further described below.

Pregnancy test results and pregnancy outcomes will be ascertained and entered into eCRFs. Pregnancy outcomes should be ascertained based on medical records; when medical records are unavailable, maternal report may be used. For participants who are pregnant at the time of study exit, or early study termination, additional post-study contacts should be completed to ascertain their pregnancy outcomes (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 product, the CMC should be notified within 2 weeks of 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).

8.4 Monitoring and Management of HIV 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. As noted in Section 6.6, 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.

Any participant with a plasma HIV-1 RNA level ≥200 copies/mL after enrollment should be recalled to the clinic for confirmatory testing 2-4 weeks after specimen collection for the initial test. Specimen collection for antiretroviral resistance testing and other procedures will also be performed at the time of specimen collection for confirmatory HIV-1 RNA testing. Refer to Section 6.6 for more details regarding the visit procedure and scheduling of the Confirmation of Virologic Failure visit.

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 8.7 for participant management regarding permanent discontinuation of study product, and Section 6.5 for those participants who will be followed per the LSFU visit schedule upon permanent discontinuation of study product.

HIV genotypic and phenotypic resistance samples will be processed, stored, and shipped per Section 6.16.2 and the LPC. Upon confirmation of virologic failure, testing of resistance samples will be performed in real time, per Section 6.16.2 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. Cohort 1 participants may be recommended to change their ongoing cART regimen, based on these results. Cohort 2 participants should resume the recommended non-study provided oral cART as soon as possible and within 4 weeks.

8.5 Substitution or Dose Modification of cART for Cohort 1 Participants

Cohort 1 participants will continue their pre-study cART regimen while receiving study products in both Step 1 and Step 2. Dose changes for growth are permitted. In the event that a change or substitution is required for an acute safety event that requires regimen changes (e.g., renal compromise on TDF for which alternative NRTI is sought), sites should consult CMC for guidance for drugs that can be co-administered. Cohort 1 participants will be permanently discontinued from study product use if a cART regimen change is required that would affect Cohort 1C vs Cohort 1R assignment.

8.6 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 based on review of medical and medications history, physical examination findings, and prior laboratory test results (see Section 6.9). Study product administration must be deferred consistent with the guidance provided in Section 8.

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 product 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 Cohort 2 participants who have a temporary hold, both study products should be held, and the CMC should be consulted as soon as possible and within 48 hours of site awareness; 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 2017 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 8.5.
- Report of use of prohibited concomitant medications (as listed in 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.

Participants who temporarily or permanently discontinue oral study product during the oral phase (Step 1 or Step 3), or during oral bridging (in Step 4 or Step 5) will be instructed to return all oral study products to the site clinic as soon as possible.

8.7 Criteria for Premature Permanent Discontinuation of Study Product

See Section 8.8 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 phase (Cohort 1 Step 1, or Cohort 2A Step 3), sustained non-adherence to oral regimen (study product, or non-study provided cART for Cohort 1 participants) 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 8.6).
- The participant requires treatment with prohibited medications (see Section 5.7).
- Pregnancy (see Section 8.3)
- The participant experiences an adverse event that requires discontinuation as defined in Sections 8.1 through 8.5.
- Virologic failure as described in Section 8.4.
- 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.

In the event of premature permanent discontinuation of study product, participants will either be followed per the LSFU visit schedule or complete an Early Termination visit, as described below. For Cohort 2 participants, in the event of a permanent discontinuation of study product, both study products will always be discontinued, and participants should immediately resume (non-study provided) oral cART.

See Section 6.5 for the specified participants who will be followed per the LSFU visit schedule upon permanent discontinuation of study product.

Cohort 1 Step 1 and Cohort 2A Step 3 participants (without prior Cohort 1 Step 2 participation) not eligible to progress to their respective injection phase will complete an Early Termination visit upon permanent discontinuation of study product.

8.8 Participant Withdrawal or Termination from the Study

Regardless of the participant retention procedures referenced in Section 4, participants may voluntarily withdraw from the study. Participants may also be terminated from the study by the site investigator or designee under the following circumstances:

- Participant re-locates away from the study site, is otherwise determined to be lost-to-follow-up, or withdraws consent/assent
- 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 at the discretion of the FDA, IMPAACT, the site IRB or EC, US Office for Human Research Protection (OHRP), NIAID, NICHD, or other country-specific governmental agencies

A participant may voluntarily discontinue study participation at any time, and the site investigator may also, at their discretion, discontinue the participant from the study at any time. Participants who are withdrawn from the study will not be replaced.

Should the consenting parent or 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, cART resumed for Cohort 2 participants, and no further study-specific evaluations should be performed until informed consent 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 consent to continued study participation, the participant must be terminated from the study. Refer to Section 8.6 for additional guidance on communication with the CMC for temporary study product holds, and Section 14.3 for guardian consent 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 complete final evaluations as described in Section 0. 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

For all PK-related matters, including PK endpoints, outcome measures and analyses, refer to Section 10.

9.1 General Design Issues

This is a Phase I/II, multi-center, open-label, non-comparative dose-finding study with the primary objective of evaluating the safety, acceptability, tolerability, and pharmacokinetics of oral CAB and CAB LA as well as RPV LA in children and adolescents 12 to <18 years of age living with HIV who are virologically suppressed.

This statistical section describes the methodology and analyses planned for the primary endpoints and outcome measures with respect to safety and the secondary endpoints and outcome measures other than PK. Please refer to Section 10 for all matters which deal with pharmacokinetics (PK), including the outcome measures and primary analyses, in more detail.

It is expected that up to 55 participants will be enrolled into Cohort 1 to achieve approximately 15-20 dose-evaluable for CAB and approximately 15 dose-evaluable for RPV, with CAB and RPV to be evaluated separately in this stage of the study. Most (or all) of these participants are expected to proceed to Cohort 2, where they will take the full regimen (CAB + RPV), consisting of both products. There is not a restriction (minimum or maximum) on the number of eligible Cohort 1 participants allowed to proceed to Cohort 2, to provide the most flexibility in study design. It is expected that 100 additional participants will need to be enrolled directly into Cohort 2 to achieve an approximate additional 70 evaluable participants receiving the final recommended dose of CAB and RPV. This sample of participants (approximately 100 for 70 evaluable) will be treated as the primary subgroup of Cohort 2 participants, since their results will generalize to the population of patients who would be treated by simultaneous exposure to the two study products without a prior period of exposure to one or the other as in Cohort 1.

For analysis purposes, evaluable participants will be defined as having been treated exclusively on the final recommended dose for a given cohort and (1) having either completed all treatment regimen through the said week periods (Week 4, Week 16 for Cohort 1, Week 24 for Cohort 2A, Week 20 for Cohort 2B), or (2) having experienced any of the following:

- death that is attributable to the study product/s, OR
- study product-related Grade 3+ events (excluding injection-site Aes) OR
- permanently discontinued from treatment due to study product-related toxicities (regardless of grade) during these weeks of treatment.

Dose-evaluable participants for dose-finding purposes are defined in Section 9.5.1.3.

Although oral bridging in Cohort 2 will not be counted as a substitute for an injection, the participant will be considered evaluable following the definition given above as long as the recommended injectable total dosing has been given through Week 24 (for Cohort 2A) and through Week 20 (for Cohort 2B), even if they were out of window. For participants requiring more than one injection visit to receive full injectable treatment dosing, the participant will also be considered evaluable following the definition given above, if the recommended injectable total dosing has been given through Week 24 (for Cohort 2A) and through Week 20 (for Cohort 2B) within the injection visit window.

In making dosing decisions, the protocol team will review Cohort 1 safety data, as well as the results of PK data (modeling data as needed). Please refer to Section 9.5.1.3 (*Dose Finding/Confirmation*) for the dose-finding algorithm and the safety guidelines for making dosing decisions.

To assess the acceptability and tolerability of the study products based on the perceptions of parents and caregivers, up to 60 parents or caregivers of the adolescent participants, as selected by the protocol team, will be accrued to complete a single qualitative phone interview.

9.2 Outcome Measures

For all PK-related matters, including PK outcome measures and analyses, refer to Section 10.

For safety monitoring and reporting purposes, a study product related AE is defined as an adverse event that is judged (based on attribution by the site with concurrence from the CMC) to be related to the study products (CAB/RPV). To document the attribution concurrence or lack thereof, the CMC assessment will be collected.

Primary and secondary outcome measures listed below will be addressed in the study's primary Statistical Analysis Plan, which will define the content of the Primary Analysis Report. This report will form the basis for the primary study manuscript, results reporting to ClinicalTrials.gov, and supporting the drug development in adolescence population. Outcomes of interest intended for subsequent publications are listed under "Other Outcome Measures".

9.2.1 Primary Endpoints and Outcome Measures	
9.2.1.1	Safety through Week 4 for oral CAB, through Week 16 (CAB LA or RPV LA) for Cohort 1 • Safety Outcome: All adverse events, regardless of grade • Number of participants who: o Had Grade 3 or higher adverse events o Had Grade 3 or higher adverse events assessed as related to study product/s o Had serious adverse events meeting ICH criteria assessed as related to study product/s o Permanently discontinued study product due to adverse events assessed as related to study product/s o Died due to adverse events assessed as related to study product/s
9.2.1.2	Safety through Week 24 for Cohort 2A (oral followed by injectable); through Week 20 for Cohort 2B (injectable only) • Safety Outcome: All adverse events, regardless of grade • Number of participants who: o Had Grade 3 or higher adverse events o Had Grade 3 or higher adverse events assessed as related to study product/s o Had serious adverse events meeting ICH criteria assessed as related to study product/s o Permanently discontinued study product due to adverse events assessed as related to study product/s o Died due to adverse events assessed as related to study product/s
9.2.2 Secondary Endpoints and Outcome Measures	
9.2.2.1	HIV-1 RNA through Week 16 for Cohort 1 • Number of participants with HIV-1 RNA < 50 copies/mL
9.2.2.2	Tolerability of CAB LA or RPV LA through Week 16 for Cohort 1 • Tolerability measures will include measures of side effects, pain during and after injections, injection site reactions, and perceptions of injections from comprehensive surveys of adolescents Acceptability of CAB LA or RPV LA through Week 16 for Cohort 1 • Acceptability measures will include assessments of motivation for changing regimens, satisfaction with treatment, preferences for injectable versus oral regimen, quality of life, changes in attitudes towards the study products from comprehensive surveys of adolescents

9.2.2.3	Safety through Week 48 for Cohort 2A (oral followed by injectable); through Week 44 for Cohort 2B (injectable only) • Safety Outcome: All adverse events, regardless of grade • Number of participants who: o Had Grade 3 or higher adverse events o Had Grade 3 or higher adverse events assessed as related to study product/s o Had serious adverse events meeting ICH criteria assessed as related to study product/s o Permanently discontinued study product due to adverse events assessed as related to study product/s o Died due to adverse events assessed as related to study product/s
9.2.2.4	Virologic activity of CAB LA+RPV LA through Weeks 24 and 48 for Cohort 2A (oral followed by injectable); through Week 20 and 44 for Cohort 2B (injectable only) • Outcome: Plasma HIV-1 RNA • Number of participants with HIV-1 RNA ≥50 copies/mL, HIV-1 RNA ≥200 copies/mL, per snapshot algorithm
9.2.3 Other Endpoints and Outcome Measures	
9.2.3.1	Tolerability of CAB LA+RPV LA through Week 24, Week 48, and Week 96 for Cohort 2A (oral followed by injectable); through Week 20, Week 44, and Week 92 for Cohort 2B (injectable only) • Tolerability measures will include measures of side effects, pain during and after injections, injection site reactions, and perceptions of injections from comprehensive surveys of adolescents Acceptability of CAB LA+ RPV LA through Week 24, Week 48, and Week 96 for Cohort 2A (oral followed by injectable); through Week 20, Week 44, and Week 92 for Cohort 2B (injectable only) • Acceptability measures will include assessments of motivation for changing regimens, satisfaction with treatment, preferences for injectable versus oral regimen, quality of life, changes in attitudes towards the study products from comprehensive surveys of adolescents
9.2.3.2	Safety through Week 96 weeks for CAB LA+ RPV LA for Cohort 2A (oral followed by injectable); through Week 92 for Cohort 2B (injectable only) • Safety Outcome: All adverse events, regardless of grade • Number of participants who: o Had Grade 3 or higher adverse events o Had Grade 3 or higher adverse events assessed as related to study product/s o Had serious adverse events meeting ICH criteria assessed as related to study product/s o Permanently discontinued study product due to adverse events assessed as related to study product/s o Died due to adverse events assessed as related to study product/s

9.2.3.3	Virologic activity of CAB LA+RPV LA through Week 96 for Cohort 2A (oral followed by injectable); through Week 92 for Cohort 2B (injectable only) • Outcome: Plasma HIV-1 RNA • Number of participants with HIV-1 RNA ≥200 copies/mL, missing HIV-1 RNA, study treatment discontinuations Immunologic activity of CAB LA+RPV LA through Week 96 for Cohort 2A (oral followed by injectable); through Week 92 for Cohort 2B (injectable only) • Outcome: CD4 count and percentage
9.2.3.4	Participants' and parents/caregivers' overall perceptions of their/their child's experience with CAB LA and/or RPV LA for Cohorts 1 and 2 as elicited through in-depth interviews centered around an ecological model of health behavior
9.2.3.5	Tolerability through 48 weeks following permanent discontinuation of CAB LA or RPV LA for Cohort 1 and CAB LA+RPV LA for Cohort 2 • Tolerability measures will include measures of side effects, pain during and after injections, injection site reactions, and perceptions of injections from comprehensive surveys of adolescents Acceptability through 48 weeks following permanent discontinuation of CAB LA or RPV LA for Cohort 1 and CAB LA+RPV LA for Cohort 2 • Acceptability measures will include assessments of motivation for changing regimens, satisfaction with treatment, preferences for injectable versus oral regimen, quality of life, changes in attitudes towards the study products from comprehensive surveys of adolescents
9.2.3.6	Long-term safety through 48 weeks following permanent discontinuation of CAB LA or RPV LA for Cohort 1 and CAB LA+RPV LA for Cohort 2 • Safety Outcome: All adverse events, regardless of grade • Number of participants who: o Had Grade 3 or higher adverse events o Had Grade 3 or higher adverse events assessed as related to study product/s o Had serious adverse events meeting ICH criteria assessed as related to study product/s o Died due to adverse events assessed as related to study product/s
9.2.3.7	HIV-1 genotype and phenotype resistance to CAB and/or RPV in participants experiencing confirmed virologic failure (defined in Section 9.6.3) in both Cohort 1 and Cohort 2

9.3 Randomization and Stratification

There will be no randomization for Cohorts 1 and 2. Participants for Cohort 1 will be placed into CAB or RPV arms based on suppressive oral cART at entry: participants on PI-based or NNRTI-based cART will be assigned to Cohort 1C, while participants on INSTI-based cART will be assigned to Cohort 1R. In Cohort 2, participants will either receive oral CAB+RPV for 4 weeks followed by CAB LA +RPV LA Q8W (Cohort 2A) or directly receive CAB LA+ RPV LA Q8W (Cohort 2B) per participant's preference.

9.4 Sample Size and Accrual

The sample size is the minimum number of participants, driven primarily by safety considerations, which is likely to be needed to determine the dosage across the possible weight, age and sex at birth distributions. Monte Carlo simulations based on existing PK models in adults with extrapolation to the study population characteristics were performed to estimate the variability for selected primary and secondary parameters and confidence intervals.

(i) To ensure a Cohort 1 sample size able to provide precise estimates of apparent clearance (CL/F) consistent with the FDA guidelines for pediatric trials. Monte Carlo (MC) simulations incorporated adult CAB and RPV population PK model and the expected adolescent IMPAACT 2017 participant characteristics. One hundred virtual PK trials were generated with 20 CAB and 15 RPV simulated participants for each study. Each simulated trial was analyzed independently for median PK parameter estimates (including CL/F) specific for that trial, resulting in 100 median values for each PK parameter. Confidence intervals of the individual median PK parameters (from each study) were generated from these 100 values. The 90% CI of the medians from the 100 simulated trial CAB CL/F estimates ranged from 0.84 -1.17 of the overall adolescent median CL/F value and no study estimated deviated from the overall median by $\geq$ 25%. The corresponding 90% CI for CAB median V/F estimates were 0.92-1.09 of the overall median V/F. For RPV the 90% CI for RPV CL/F was 0.86-1.15 of the overall adolescent median value.

(ii) To ensure a sample size able to provide precise estimates of oral CAB AUC (Cohort 1C); CAB LA and RPV LA concentration at 28 days (C28D) (Cohort 1C and 1R). Simulated PK trials were also used to construct confidence intervals for these exposure parameters. For CAB, the AUC 90% CI ranged from 0.86-1.19 of the overall value and the C28D 90% CI ranged from 0.80-1.29 of the overall value. For RPV LA the C28D 90% CI ranged from 0.80-1.29. While a few individual simulated participants had concentrations outside of target, all 100 of the virtual trials had median exposure parameters within the target range.

Table 10 presents exact 95% confidence intervals around various potential rates of Grade 3+ AEs which might be observed in a total sample of 100 participants who might contribute data to the safety analysis, a minimum sample of 15 participants from Cohort 1C, a minimum of 15 participants from Cohort 1R, a potential sample of 30 or 35 participants which represents the combined arms of Cohort 1, and a potential sample of 70 participants who enrolled directly into Cohort 2A or 2B and who will be regarded as the primary sample for the Cohort 2 safety assessment. This table indicates that confidence intervals will be quite wide around the sample size of 15 participants but would be considerably more precise around the target samples of 70 primary or 100 overall Cohort 2 participants.

Table 10. Percent of Participants Experiencing ≥ Grade 3 Adverse Events (or ≥ Grade 3 Adverse Events Attributed to the Study Medications) with Exact 95% Confidence Intervals

N*	n (%) With ≥ Grade 3 Adverse Events	95% C.I.
15	0 (0%)	0.00, 0.22
20	0 (0%)	0.00, 0.17
30	0 (0%)	0.00, 0.12
35	0 (0%)	0.00, 0.10
70	0 (0%)	0.00, 0.05
100	0 (0%)	0.00, 0.04
15	3 (20%)	0.04, 0.48
20	4 (20%)	0.06, 0.44
30	6 (20%)	0.08, 0.39
35	7 (20%)	0.08, 0.37
70	14 (20%)	0.11, 0.31
100	20 (20%)	0.13, 0.29

** Note: N refers to total sample size of possible sub-group analysis but note that dosing decisions will make use of all available data.*

9.5 Monitoring

Implementation of this study will be monitored at multiple levels, consistent with standard procedures described in the IMPAACT Network Manual of Procedures. A study monitoring plan that details monitoring roles and responsibilities and data to be reviewed at each level will be prepared before the study opens to accrual. Sections 12 and 13 provide more information concerning 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 Monitoring by the Protocol Team

9.5.1.1 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 the quality of study conduct.

The team will closely monitor participant accrual and retention based on reports that will be generated at least monthly by the SDMC. The team has developed a study accrual plan that includes site-specific and total enrollment projections over the course of the accrual period, and actual accrual will be monitored relative to these projections. The team will monitor the timing of site-specific study activation, which will determine when each site will begin accruing participants, and accrual performance following activation. For any site that is delayed in completing the study activation process, or that falls short of its accrual projections, the team will communicate with the site to identify the barriers it has encountered and the operational strategies and action plans to address these.

The Protocol Team will monitor participant retention in a manner similar to participant accrual. On behalf of the Protocol Team, the CMC will monitor other key indicators of the quality of

study conduct (e.g., adherence to study product regimen, data quality, and data and specimen completeness), based on reports generated by the SDMC, and will take action with study sites as needed to ensure high quality study conduct throughout the period of study implementation.

9.5.1.2 Participant Safety

On behalf of the Protocol Team, the CMC will closely monitor participant safety through routine review of safety reports generated by the SDMC. These reports will provide tabulations of adverse events specified for entry into eCRFs, as described in Section 7.2. The CMC will review these reports via conference call or other means at least monthly. At the time of each review, the DAIDS Medical Officer will also review any EAEs (defined in Section 7.3) 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 events and will identify any individual issues or trends of concern.

The CMC will assess the relationship of adverse events listed in toxicity summary reports and these assessments will be recorded by the SDMC. Except in the two specific scenarios listed in this section and in Section 9.5.2, the CMC's assessments will not be used for study-related decision-making.

The CMC will also monitor whether any of the safety-related triggers specified in Section 9.5.2 are met. If so, the CMC will rapidly review the triggering events and notify the SMC that an ad hoc review is required. The CMC will likewise request SMC review of any other safety concerns that may be identified throughout the course of the study.

9.5.1.3 Dose Finding/Confirmation

During the dose finding/confirmation stages of this study (Cohort 1), the CMC will also review the pharmacokinetic data, with the aim of determining the appropriate dose of each product for Cohort 2, while protecting participant safety. The CMC will review PK and safety data reports at least monthly and take action as needed according to the guidelines in Section 10.3 (PK) and Section 9.5.1.2, Participant Safety, above. In addition, the CMC and relevant members of the protocol team in conjunction with the SMC will discuss any dose adjustment changes based on the PK (of cohort level data) and safety reviews.

In the case of any pause to address safety concerns, participant accrual may be resumed if recommended by the CMC and SMC.

For the purpose of dose-finding, dose-evaluable participants will be defined as participants having been treated exclusively on the dose being evaluated for a given cohort, and having either (1) completed all treatment regimen and completed Week 16 visit or (2) having experienced any of the following:

- death that is attributable to the study product/s, OR
- study product-related Grade 3+ events (excluding injection-site AEs) OR
- permanently discontinued from treatment due to study product-related toxicities (regardless of grade) during the dose-finding period.

Dose Finding/Confirmation Algorithm

Cohort 1

The study will implement a dose-finding/confirmation algorithm separately for oral CAB/CAB LA and RPV LA based on PK and safety data through Week 16. The PK elements from this algorithm are based on CAB and RPV exposures seen in adult studies that maintain concentrations above the protein adjusted (PA) 90% inhibitory concentration (IC_{90}). Cohorts 1C and 1R will each enroll an initial group of 7 dose-evaluable participants and their PK and safety data will be evaluated as follows:

- If these 7 dose-evaluable participants meet the PK guidelines (see Section 10) and there are no safety concerns (see *Safety Guidelines for the First 7 Participants Started at a Given Dose Level in Each Group in Cohort 1* below), then the oral/LA IM doses for CAB and LA IM doses for RPV in Cohort 2 will be established and Cohort 2 will be open to accrue for Cohort 1 participants, following an interim analysis (see Section 9.5.2, *Monitoring by the SMC*).
- If either group fails the safety or PK criteria and an alternative dose is determined by the study team to be needed to safely achieve necessary study product concentrations, another N=7 dose-evaluable participants will be enrolled into that group and administered a modified dose which will be evaluated as described above.
- If there is more variability than expected in the PK results in each or both groups of Cohort 1, such that a confident determination regarding achievement of the PK targets cannot be made, an additional interim evaluation of the PK results will be done after additional 4 participants have been enrolled into the appropriate group/s of Cohort 1 to clarify the PK results as needed. In this scenario, Cohort 2 accrual for Cohort 1 participants will be delayed until an interim analysis which includes these extra participants has been performed and Cohort 2 dosing established by the study team.
- Cohort 1 study enrollment and study procedures will not be interrupted for the preliminary PK and safety assessments to be performed on the first 7 dose-evaluable participants enrolled into each group. (Note: interim analysis #1 was conducted under protocol Version 2.0; see Section 1.3)
- Once approximately 15-20 Cohort 1C participants and approximately 15 Cohort 1R participants who could contribute to the dose-finding algorithm have enrolled, and 80% of these participants have completed the Step 2 Week 8 visit, an interim analysis of all available safety and PK data will be conducted to determine if Cohort 2 accrual can be opened to study-naïve participants. Once all Cohort 1C and 1R participants complete Week 16 visit, the final analysis of all safety and PK data for Cohort 1 will be conducted to confirm the oral and LA IM doses for Cohort 2.

Cohort 2

Cohort 2 will begin to enroll, starting with the participants who passed Cohort 1, once the dosing of the oral/IM CAB and oral/IM RPV been established, based on data of the first 7 dose-evaluable participants from Cohorts 1C and 1R, as described above. Once approximately 15-20 participants in Cohort 1C and approximately 15 participants in Cohort 1R who could contribute to the dose-finding algorithm are enrolled with 80% of participants in each arm passing the Week 8 visit, another interim analysis of the safety and PK data will be conducted and Cohort 2 will open to accrual for study-naïve participants if approved by SMC.

Sparse PK sampling will be collected from Cohort 2 participants to further describe the oral/IM CAB and RPV exposure.

Safety Guidelines for the Evaluation of Cohort 1 Starting Doses

The study site's attribution of any serious adverse event to study product will be used for the purposes of employing the start, stop, and pause rules. However, when assessments will affect conduct of the study or dose-finding decisions, the CMC will review the AE and the site's attribution. In an event of disagreement in assessments, the protocol team will try to reach a consensus with the site with respect to attribution. If this should prove impossible, the SMC will be consulted and will make the final judgment concerning the relationship between study product/s and the adverse event. Attribution of AE to study product will use the following terminology: 'Not related' and "Related".

Table 11 and Table 12 use a multinomial response model to assess the probability of failing the safety criteria under each of the hypothetical situations in those tables. The calculations are performed as follows: Each of the total number of participants represents a trial, which may have 1 of 3 mutually exclusive outcomes: (1) a fatal or life threatening adverse event assessed as related to study treatment; (2) a Grade 3+ adverse event (excluding injection site AEs), not satisfying the criteria set forth in #1, immediately above, but judged to be related to study treatment, or an adverse event assessed as related to study treatment resulting in termination of study treatment; and (3) a relatively benign outcome, satisfying neither the criteria in #1 nor #2, immediately above.

Each table has its sets of results under which the set of trials would pass the safety criteria. The probability of passing the safety criteria represents the sum of the probabilities of these sets of results, and "1 minus the probability of passing the safety criteria" represents the probability of failing them. The "True Toxicity Rates" presented in the tables, along with the true rate of having neither of the types of toxicity represented by the true toxicity rates (which is 1 - the sum of the true toxicity rates), provide the probabilities for the outcomes which are used in the multinomial calculations for each of the hypothetical situations.

Safety Guidelines for the First 7 Dose-evaluable Participants Started at a Given Dose Level in Each Group in Cohort 1

For each group in Cohort 1, the frequency of adverse reactions to the starting dose of the study medication will be evaluated on the first 7 dose-evaluable participants, and will include all their safety data through the Week 16 visit. Safety data will be monitored on frequent conference calls to assess safety across both oral dosing and injections. Moreover, a CMC review of safety will be triggered during which accrual into Cohort 1C or 1R will be paused, if the following safety issues are encountered:

If any of the first 7 dose-evaluable participants should experience death or a life-threatening event that is attributable to the study product/s, or 3 or more participants have experienced study product-related Grade 3+ events (excluding injection-site AEs) or have been permanently discontinued from treatment due to study product-related toxicities (regardless of grade), accrual will be stopped into this dose group. In addition, if patterns of concern are noted, a safety review by the CMC will be conducted.

If these safety issues have been encountered, all of the relevant safety and pharmacokinetic data will be reviewed. If the CMC determines that it is safe to proceed, it will recommend any changes in the dosing and/or monitoring procedures which have been judged to be necessary. The SMC will then review all of the relevant safety and pharmacokinetic data, along with the

recommendations of the CMC, and will determine whether and under what conditions further dose finding activities for this group may proceed. Note that there may be a point, prior to accruing and evaluating the 7 participants, where it becomes inevitable that the dose under consideration will fail the safety criteria. In this event, the reviews described above will be performed immediately and no further accrual will occur until the CMC and SMC determine the conditions under which further treatment may proceed.

The protocol will only proceed if this review has led to a CMC recommendation that it is safe to do so, and the SMC agrees. The safety review may lead to a recommendation that the dose be de-escalated. Before implementing such a recommendation, the CMC will review the PK data to determine whether a lower dose is likely to achieve adequate study product exposure.

If none of the first 7 dose-evaluable participants has experienced death or life-threatening event that is attributable to the study products, and fewer than 3 of these 7 dose-evaluable participants have experienced study product-related Grade 3+ event (excluding injection-site AEs) or have been permanently discontinued for study product-related toxicities (regardless of grade) then this group has passed the initial safety guidelines. The safety and PK results of the overall group of approximately 15-20 (Cohort 1C) or approximately 15 (Cohort 1R) participants will be evaluated when all participants in these groups have reached Week 16.

Given the small sample sizes within each cohort, the information available for preliminary safety decisions will be imperfect. Two types of sampling errors are possible:

1) In a group where the true rate of toxicity is too high to warrant increased exposure to the current starting dose of the medication, the sample data may pass the safety guidelines;
2) In a group where the true rate of toxicity is low enough that further exposure to the current starting dose is warranted, the sample data may fail the 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 medication were used extensively among the participant population at the dose level under question. The hypothetical situations presented in Table 11 range from conditions under which a given dose level would cause a high incidence of study product-related severe and life-threatening AEs to conditions under which severe adverse events would be relatively rare and would not be life threatening. For each of these hypothetical situations it is assumed that a sample of 7 participants is drawn from the participant population and that the safety guidelines, summarized above, are followed.

As an example of how to read Table 11, the second row shows that there is a 87% chance of failing the safety guidelines at doses in which the true rate of study product-related life-threatening AEs is 5% and the true rate of study product-related non-life-threatening adverse events is 50%.

Table 11. Probability of Failing Dose Guidelines Under Potential Rates of True Toxicity

True Toxicity Rates		Probability of Failing Safety Guidelines
Non-life-threatening study product-related Grade 3+ AEs, or AEs assessed as product related resulting to permanent treatment discontinuation	Study product related life-threatening AEs or death	
0.50	0.00	0.77
0.50	0.05	0.87
0.50	0.25	0.99
0.25	0.00	0.24
0.25	0.05	0.49
0.25	0.25	0.92
0.05	0.00	0.004
0.05	0.05	0.30
0.05	0.25	0.87
0.00	0.05	0.30
0.00	0.25	0.87

Under the conditions specified in row 2 of the table, assuming that it would be undesirable to treat additional participants at a dose that had these true rates of adverse events, the 13% chance of NOT failing the safety guidelines would represent the probability of error. As a further example, the table also shows that there is 0.4% chance of failing, when the true rate of study product-related non-life-threatening AE is only 5% and the true rate of study product-related life-threatening AE is zero. Assuming that the potential benefits associated with exposing additional participants to this dose of the study product would outweigh the risks associated with this relatively low rate of toxicity, failing the safety guidelines under these conditions would be an error.

If the safety criteria discussed above are met by the initial 7 dose-evaluable participants treated with each of the study products, and the PK estimates are judged to be sufficiently precise and

indicate adequate exposure to each of these medications, then participants who have participated in Cohort 1 will be allowed to progress to Cohort 2 upon completion of their Week 16 visit.

Safety Guidelines for the Total Group of Approximately 15-20 (Cohort 1-C) or Approximately 15 (Cohort 1-R) Potentially Dose-evaluable/ Dose-evaluable Participants Started at a Given Dose Level in Cohort 1

The second safety evaluation of a given starting dose of the study medication administered to each Cohort 1 group will happen once approximately 15-20 participants in Cohort 1C and approximately 15 participants in Cohort 1R who could contribute to the dose-finding algorithm are enrolled with 80% of participants in each arm passing the Week 8 visit. The safety evaluation will make use of available safety data from all enrolled participants except those who have been determined to be not dose-evaluable at that time. The final safety evaluation of a given starting dose of the study medication administered to each Cohort 1 group will make use of data from all dose-evaluable participants in that group who started at that dose. In both evaluations, if any of these participants has experienced death or a life-threatening event that is attributable to the study product/s, or more than 25% of the participants have experienced study product-related Grade 3+ events (excluding injection-site AEs) or have been permanently discontinued from treatment due to study product-related toxicities (regardless of grade), this starting dose will fail the safety guidelines for the group under investigation. If none of these participants has experienced a study product-related death or life-threatening AE, and no more than 25% have experienced study product-related Grade 3+events or have been permanently discontinued for study product-related toxicities (regardless of grade), then this starting dose will pass the safety guidelines for the group under investigation. Some participants may have Cohort 1 data well beyond Week 16, and the CMC will examine events occurring during this extended time period to determine whether there are serious or life-threatening events which may be study product related and may require SMC review before determining whether and under what conditions further treatment with this dose of the medication may proceed.

As in Table 11, the hypothetical rates of "true toxicity" which could occur if the study medication were used extensively among the participant population at the dose level are again presented in Table 12, this time assuming that a sample of 15 or 20 participants is drawn from the participant population and the safety guidelines allow no drug-related death or life-threatening events or no more than a 25% rate of drug-related Grade 3+ events.

Table 12. Probability of Failing Dose Guidelines Under Potential Rates of True Toxicity

True Toxicity Rates		Probability of Failing Safety Guidelines N=20/ N=15
Non-life-threatening study product related Grade 3+ AEs, or AEs assessed as product related resulting to permanent treatment discontinuation	Study product-related life-threatening AEs or death	
0.50	0.00	0.98 / 0.98
0.50	0.05	1.00 / 0.99
0.50	0.25	1.00 / 1.00
0.25	0.00	0.38 / 0.54
0.25	0.05	0.80 / 0.81
0.25	0.25	1.00 / 1.00
0.05	0.00	0.00 / 0.01
0.05	0.05	0.64 / 0.54
0.05	0.25	1.00 / 0.99
0.00	0.05	0.64 / 0.54
0.00	0.25	1.00 / 0.99

9.5.2 Monitoring by the SMC

An independent IMPAACT SMC will review this study regularly, following policies described in the IMPAACT Network Manual of Procedures.

SMC reviews will occur at least annually and may also occur on a more frequent or *ad hoc* basis if any issues or concerns arise, or if requested by the CMC. Reviews will focus on participant accrual, retention, study conduct, safety, and PK. In addition, analyses of the safety and PK data will take place: 1) interim analysis #1 prior to opening Cohort 2 for Cohort 1 participants, 2) interim analysis #2 prior to opening Cohort 2 for accrual of study-naïve participants, and 3) the final Cohort 1 analysis after all Cohort 1 participants have completed Week 16 visit. Additional SMC reviews focused on safety may also 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 identified during their reviews.

Study Progress and Quality of Study Conduct

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

Participant Safety

The SMC will monitor participant safety through review of the same types of safety data reports as the CMC, which will be described in a separate Study Monitoring Plan. For ad hoc or triggered safety reviews, more limited data may be provided, focusing on the events that triggered the reviews.

Triggered SMC reviews will occur in the following scenarios:

(1) In the event of **any adverse event that is life-threatening or results in death**, the CMC will review the event as soon as possible (ideally within three business days of site awareness) and assess its relationship to study product:
   - If either the site investigator or the CMC assesses the event as related to study product/s, participant accrual will immediately be paused. An ad hoc SMC review will be convened as soon as possible to discuss how the study should proceed.
   - If the site investigator and the CMC assess the event as not related to study product, participant accrual will continue. The SMC will be informed of any of these events along with the CMC's assessment and decision-making.

(2) In the event of any unresolvable disagreement within the CMC on an issue that would impact decision making, or in the event of an unresolvable disagreement between the CMC and a site regarding the site's attribution of any adverse event to study product(s) that will affect conduct of the study or dose-finding decisions, or if the CMC requests SMC review of any other event or trend of concern, an SMC review of the relevant data will be convened. The CMC may choose to pause participant accrual and/or administration of study product(s), pending the outcome of the SMC review.

(3) If, for each cohort (1R, 1C, 2), more than 25% of the planned total sample for that cohort experiences study product-related Grade 3+ events (excluding injection-site AEs) or have been permanently discontinued from treatment due to study product-related toxicities (regardless of grade), an ad hoc SMC review will be convened as soon as possible. The SMC will review all the relevant safety and pharmacokinetic data, along with the recommendations of the CMC, and will determine whether and under what conditions further accrual and/or opening of Cohort 2 may proceed.

9.6 Analyses

9.6.1 Analyses of the Dose-Finding Data

The analysis of dose finding data will consist of descriptive statistics summarizing the safety and PK data from the dose finding phase in Cohort 1 of the study. The safety data of dose-evaluable participants in Cohort 1 will be used and will be broken down by group (Cohort 1R and Cohort 1C) and will present the results of the safety evaluations applied to each starting dose tested

within each group, including information indicating which starting doses have passed or failed the safety guidelines. For each starting dose within each group, every adverse event of Grade 3 or higher will be listed, along with participant demographics, the dose prescribed to the participant at the time of the event and the site's assessment of the probability that this event was due to the study treatment.

9.6.2 Primary Safety Analyses

The primary safety analyses will focus on the Week 4 (CAB), Week 16 (CAB LA or RPV LA) periods for Cohort 1, Week 24 (Cohort 2A-oral CAB and oral RPV followed by CAB LA+RPV LA), and Week 20 (Cohort 2B – directly receive CAB LA+RPV LA), where the primary safety analysis will include only evaluable participants. An additional requirement for inclusion in the primary analyses for Cohort 2 is that the participants be directly accrued to this cohort and be exclusively treated with the combination of the two study products without a prior period of exposure to one or the other; this will be approximately 70 participants.

Two primary safety analyses will be performed: (1) after the last participant in Cohort 1 has completed the Week 16 visit, and (2) after the last participant in Cohort 2A has completed 24 weeks on therapy or the last participant in Cohort 2B has completed 20 weeks on therapy (whichever is later).

Each participant's safety data will be summarized as:

(1) the worst grade of AEs, and
(2) the worst grade of AEs judged to be related to study treatment.

Proportions will present participants experiencing:

(1) ≥ Grade 3 AEs,
(2) ≥ Grade 3 events which have been judged to be related to study product/s,
(3) serious adverse events assessed as related to study products,
(4) permanent discontinuation of study product due to adverse events assessed as related to study product/s, and
(5) deaths due to product-related adverse events.

Overall proportions of participants meeting any of these criteria will be presented, in addition to specific proportions meeting each individual criterion.

Listings of all ≥ Grade 3 events regardless of treatment attribution, ≥ Grade 3 events and serious adverse events assessed as related to study product/s, as well as AEs which resulted in permanent discontinuation of study product/s or deaths will be provided, broken down by System Organ Class and Preferred Term.

The proportions of participants meeting each of the endpoints which would trigger an SMC review will be presented descriptively.

All proportions will be presented together with their exact 95% confidence intervals (Clopper-Pearson).

The safety data will also be presented separately for Cohort 2A, Cohort 2B, and for Cohort 2A and 2B combined.

Details concerning the analyses will be included in a separate statistical analysis plan.

For regulatory submission purposes, all the above analyses will be performed for all Cohort 1 and Cohort 2 evaluable participants and all-treated participants, where all-treated is defined as participant who received at least one dose of the study drug. For Cohort 2, frequency distributions of the safety outcomes will be presented in aggregate and will be broken down by prior participation in Cohort 1 vs. exclusive participation in Cohort 2. In addition, the safety data will be presented separately for those who were in Q4W and Q8W LA IM dosing.

9.6.3 Secondary Analyses

9.6.3.1 Maintenance of Viral Suppression

Virologic outcomes, based on HIV-1 RNA (copies/mL), will be assessed through Week 16 for Cohort 1 participants. The proportion of participants maintaining suppression (<50 copies/mL) will be presented, along with the exact 95% confidence intervals (Clopper-Pearson).

9.6.3.2 Acceptability and Tolerability

Acceptability and tolerability measures on CAB LA or RPV LA reported by the Cohort 1 participants through Week 16 will be summarized.

9.6.3.3 Safety

Week 24 (Cohort 2A)/Week 20 (Cohort 2B) analyses described above for the primary analysis will be repeated as secondary analyses through Week 48 (Cohort 2A)/Week 44 (Cohort 2B) for the same participants mentioned under the primary analysis.

In addition to the primary analyses restricting the sample to appropriate participants as described above, further analyses which include safety data from all treated participants through all mentioned periods will be performed. These secondary safety analyses will cover all safety data collected from first participant exposure to the end of the study. The Cohort 2 secondary analyses will include approximately 30-35 participants whose treatment started in Cohort 1 at the final recommended dose and who progressed to Cohort 2 after completing participation in Cohort 1 (see Section 9.1 for a discussion of about the potential for selection bias in this group, and this section on how this bias will be addressed). All Cohort 2 secondary analyses will be presented separately for Cohort 2A, 2B, and in aggregate.

Descriptive and exposure-related analyses will present safety data from participants who were treated on doses other than the final recommended dose for their cohorts. This will include data representing the final dose for each cohort, as well as data gathered during the dose finding stage, which may represent exposure to doses which have failed. For each starting dose, every AE of ≥ Grade 3 will be listed, along with participant demographics, the dose prescribed to the participant at the time of the event and the protocol team's assessment of the probability that this event was due to the study products.

9.6.3.4 Virologic activity

Virologic outcomes, based on HIV-1 RNA (copies/mL), will be assessed at Weeks 24 (Cohort 2A)/Week 20 (Cohort 2B), Weeks 48 (Cohort 2A)/Week 44 (Cohort 2B) for Cohort 2 evaluable participants. At both of these time points the virologic outcome will be calculated according to

the FDA's snapshot algorithm with three main categories (i.e., HIV-1 RNA <50 c/mL, HIV-1 RNA ≥50 c/mL, and no virologic data). The detailed algorithm for defining virologic response will be described in the statistical analysis plan. The snapshot outcome will be presented at the above Weeks. The exact 95% confidence intervals (Clopper-Pearson) for the proportion of participants with HIV-1 RNA <50 c/mL will be calculated. The similar summary and analysis will also be performed using the cutoff of HIV-1 RNA 200 c/mL. In addition to the snapshot analysis, the proportions of participants meeting the criteria for confirmed virologic failure through the above Weeks will also be presented.

In addition, the above analyses results will also be presented for all treated Cohort 2 participants.

The efficacy analysis will be presented for Cohort 2A and 2B respectively, and for Cohort 2A+2B combined.

Table 13 presents exact 95% confidence intervals (Clopper-Pearson) around various potential rates of virologic success which might be observed in a total sample of 100 participants or in subsamples of various sizes (N=15, 20, 35, 70).

Table 13. Percent of Participants with HIV-1 RNA<50 c/mL per Snapshot algorithm with Exact 95% Confidence Intervals

N	% Undetectable RNA	95% C.I.
15	40%	0.16, 0.68
20	40%	0.15, 0.59
35	40%	0.24, 0.58
70	40%	0.28, 0.52
100	40%	0.30, 0.50
15	80%	0.52, 0.96
20	80%	0.56, 0.94
35	80%	0.63, 0.92
70	80%	0.69, 0.89
100	80%	0.71, 0.87
15	90%	0.68, 1.00
20	90%	0.68, 0.99
35	90%	0.77, 0.98
70	90%	0.80, 0.96
100	90%	0.82, 0.95

9.6.4 Other Analyses

9.6.4.1 Acceptability and Tolerability

The acceptability and tolerability measures on CAB LA + RPV LA through Week 24 (Cohort 2A/Week 20 (Cohort 2B), through Week 48 (Cohort 2A)/Week 44 (Cohort 2B), and through Week 96 (Cohort 2A)/Week 92 (Cohort 2B) will be summarized. Additionally, these participants' acceptability and tolerability measures through 48 weeks following permanent discontinuation of CAB LA or RPV LA (Cohort 1), through 48 weeks following permanent discontinuation of CAB LA + RPV LA (Cohort 2) will be summarized.

See Section 11.6 for the planned analyses regarding the adolescent and parent/caregiver interviews and relating to the outcomes listed in Section 9.2.

9.6.4.2 Safety

The Week 24 (Cohort 2A)/Week 20 (Cohort 2B) analyses described above for the primary analysis will be repeated as secondary analyses through Week 96 (Cohort 2A)/Week 92 (Cohort 2B), and through 48 weeks following permanent discontinuation of and CAB LA + RPV LA for the same participants mentioned under the primary analysis. Refer to Section 3.3.

In addition to the primary analyses restricting the sample to appropriate participants as described above, further analyses which include safety data from all treated participants through all mentioned periods will be performed. These safety analyses will cover all safety data collected from first participant exposure to the end of the study. Descriptive and exposure-related analyses will present safety data from participants whose doses have undergone cohort-based adjustment or who were treated on doses other than the final recommended dose for their cohorts. This will include data representing the final dose for each cohort, as well as data gathered during the dose finding stage, which may represent exposure to doses which have failed.

All these Cohort 2 analyses will be done separately for Cohorts 2A, 2B, and in aggregate.

For each starting dose, every AE of ≥ Grade 3 will be listed, along with participant demographics, the dose prescribed to the participant at the time of the event and the site's assessment of the probability that this event was due to the study products.

9.6.4.3 Virologic Activity

The Week 24(Cohort 2A)/Week 20 (Cohort 2B) and Week 48 (Cohort 2A)/Week 44 (Cohort 2B) analyses described in Section 9.6.3.3 Safetyfor the secondary analysis on virologic activity will be repeated as other analysis through Week 96 (Cohort 2A)/Week 92 (Cohort 2B) for the same participants mentioned under said secondary analysis.

9.6.4.4 Immunologic Activity

Absolute values and change from baseline in CD4+ lymphocyte count and percentage will be summarized over time for Cohort 2 participants.

Median and the associated interquartile range for changes in CD4+ count and percentage from baseline to Weeks 24/20, 48/44, 72/68 and 96/92 will be presented for Cohorts 2A/2B and in aggregate. Missing CD4+ values for participants who discontinued study drug prior to the time point of interest due to safety or virologic failure will be replaced with their baseline CD4+ values.

9.6.4.5 Genotype and Phenotype Resistance

The incidence of HIV drug resistance for Cohorts 1 and 2 participants will be presented descriptively at the point of failure for those who meet the criteria for confirmed virologic failure (CVF). Participants will be evaluated for HIV genotypic and phenotypic drug resistance for CAB and/or RPV at the time of CVF. Plasma collected at the Confirmation of Virologic Failure visit, the visit in which the participant had an initial elevated viral load test result, whole blood collected at the Entry (baseline) visit, and any other study visits as requested by the CMC for

genotypic and phenotypic resistance testing, will be shipped per Section 6.16 and the LPC for testing. See Section 6.16 and the LPC for more details.

9.6.4.6 Additional considerations

Additionally, special statistical and data analysis considerations may be warranted in the event that the COVID-19 or related epidemics or natural disasters may affect the study and data integrity. To the extent possible, these will be described in the main study analysis plan; alternatively, a separate analysis plan focusing on modified data handling rules (e.g., changes to analysis populations, visit windows, and endpoints) and analyses (e.g., sensitivity analyses to assess impact of and account for missing data) may be prepared, taking in to account applicable regulatory guidance and industry best practices for handling such situations. (26-28)

Further data cuts and analyses may be conducted as necessary to support regulatory submissions and publications. The details for such analyses will be described in the statistical analysis plan, which will be finalized prior to database lock.

10 CLINICAL PHARMACOLOGY PLAN

10.1 Clinical Pharmacology Objectives

10.1.1 Cohort 1

Under protocol Version 2.0 (see Section 1.3), injectable CAB and RPV were evaluated with a Q4W injection dosing regimen i.e. oral CAB 30mg once daily followed by CAB LA 600mg then 400mg every 4 weeks (Cohort 1C) or oral RPV 25mg once daily followed by RPV LA 900mg then 600mg every 4 weeks (Cohort 1R) in adolescents weighing at least 35kg living with HIV who are virologically suppressed. Recent results from clinical studies (FLAIR, ATLAS, ATLAS-2M) in adults now justify use of CAB LA and RPV LA with every 8-week administration: IM CAB LA 600 mg at Week 4b and Week 8 and every 8 weeks thereafter and IM RPV LA 900 mg at Week 4b and Week 8 and every 8 weeks thereafter.

Since daily oral RPV 25mg is already approved in this population, the approved oral dose will be used for both Cohort 1R and Cohort 2A, and only limited intensive RPV PK will be collected in Step 1 (oral lead-in phase) of Cohort 1R. In Cohort 1C and 1R, study product will be added onto the participants' existing ARV therapy and participants will be assigned into Cohort 1C versus 1R based on the agents used in their suppressive ARV regimen (avoiding study product interactions between the ARVs). Multiple PK samples will be collected throughout the oral and LA dose intervals to allow determination of PK parameters for CAB or RPV, as applicable, using appropriate analyses.

The PK results from all evaluable Cohorts 1C and 1R participants will be used to confirm the use of adult doses for the oral (CAB only) and LA (CAB and RPV) products in adolescents, to be used in combination in Cohort 2: oral CAB + oral RPV in Cohort 2A, Step 3, and CAB LA+RPV LA in Cohort 2, Step 4 and Step 5. The exposures observed with the proposed CAB and RPV doses evaluated in adolescent participants living with HIV in the study will be characterized and compared to exposures observed in adult pivotal efficacy trials to aid dosing recommendation in this population.

Primary Pharmacology Objectives within Cohort 1

- To confirm the doses for oral CAB followed by injectable CAB LA in adolescents living with HIV who are virologically suppressed by evaluating:
  - Safety and multiple dose PK of oral CAB through Week 4
  - Safety and multiple dose PK of CAB LA through Week 16

- To confirm doses for injectable RPV LA in adolescents living with HIV who are virologically suppressed by evaluating safety and multiple dose PK of RPV LA through Week 16

Other Pharmacology Objectives within Cohort 1

- To characterize washout PK through 48 weeks following the final Cohort 1 dose of CAB LA or RPV LA (except when participants rollover into Cohort 2)

10.1.2 Cohort 2

Cohort 2 will use CAB and RPV in combination. Cohort 2A will first use oral and then as an IM injectable with the LA formulations, as a complete ARV regimen, in adolescents living with HIV who are virologically suppressed and weighing at least 35kg. Cohort 2B will only use CAB and RPV as an IM injectable with the LA formulations, as a complete ARV regimen, in adolescents living with HIV who are virologically suppressed and weighing at least 35kg.The Cohort 2 dosage regimen will be the confirmed dosages based on data observed in Cohorts 1C and 1R, with the exception of oral RPV for which the dose of daily 25 mg has already been previously approved.

The overall PK goal for Cohort 2 is to characterize the plasma concentrations following more prolonged LA dosing in Cohort 2 confirming their ability to achieve concentrations comparable to those observed in adults. Only sparse PK samples will be collected during Cohort 2 which may limit the PK analysis to descriptive summaries of study product concentrations and future population pharmacokinetic analyses.

Secondary Pharmacology Objectives within Cohort 2

- To evaluate repeat-dose pharmacokinetics of CAB LA + RPV LA in adolescents living with HIV who are virologically suppressed through:
  - Week 24 and through Week 48 (Cohort 2A: oral followed by injectable);
  - Week 20 and through Week 44 (Cohort 2B: injectable only).

Other Pharmacology Objectives within Cohort 2

- To evaluate the safety, antiviral and immunologic activity, and characterize PK of CAB LA + RPV LA in adolescents living with HIV who are virologically suppressed through:
  - Week 96 (Cohort 2A: oral followed by injectable);
  - Week 92 (Cohort 2B: injectable only).

- To characterize long-term safety and PK through 48 weeks following permanent discontinuation of CAB LA + RPV LA

10.2 Primary and Secondary Data: Cohorts 1 and 2

Demographic data used in the PK analysis will include age, sex at birth, race, ethnicity, height, weight, weight Z score, weight group (35-<50kg vs ≥50kg), BMI, and BSA. Available laboratory data will include serum creatinine, albumin, AST, ALT, bilirubin, and hemoglobin. Complete dosing information will also be utilized including dose dates, times, dose amounts, food intake (Step 1 and 3 only), dose administration, location of injections, and sample collection dates and times.

Plasma concentrations will be measured:

- Cohort 1C (CAB)
  - Step 1 (oral dosing): Wk. 2: Pre-dose, 1, 2, 3, 4, and 8h post dose (6 samples)
  - Step 2 (LA dosing): Wk. 4b: Pre-dose and 2h post dose, Wk. 5: Day 3-7 post-dose, Wk. 8: pre-dose, Wk. 9: Day 3-7 post-dose, Wk. 12: Day 28 post dose, Wk. 16: Day 56 post-dose.
- Cohort 1R (RPV)
  - Step 1 (oral dosing): Wk. 2: Pre-dose, 4, and 8h post dose (3 samples)
  - Step 2 (LA dosing): Wk. 4b: Pre-dose and 2h post dose, Wk. 5: Day 3-7 post-dose, Wk. 8: pre-dose, Wk. 9: Day 3-7 post-dose, Wk. 12: Day 28 post dose, Wk. 16: Day 56 post-dose.
- Cohort 2 (CAB and RPV)
  - Step 3 (Cohort 2A oral dosing): Wk. 2: Pre-dose and 3h post dose (2 samples)
  - Step 4 (Cohort 2A LA dosing): Wk. 4b: Pre-dose and 2h post dose, Wk. 5 and Wk. 25: Day 3-7 post-dose, pre-dose prior to every injection at Wk. 8, Wk. 16, Wk. 24, Wk. 32, Wk. 40, Wk. 48, Wk. 64, Wk. 80, Wk. 88, Wk. 96.
  - Step 5 (Cohort 2B LA dosing): Entry: 2h post dose, Wk. 1 and Wk. 21: Day 3-7 post-dose, pre-dose prior to every injection at Wk. 4, Wk. 12, Wk. 20, Wk. 28, Wk. 36, Wk. 44, Wk. 60, Wk. 76, Wk. 84, Wk. 92.
- LSFU
  - Samples collected 8, 24, 36 and 48 weeks after the final injection (random PK samples).

Assay Site: Plasma pharmacokinetic samples collected will be sent to the IMPAACT Pharmacology Laboratory listed in the LPC for both CAB and RPV containing specimens. Sample collection, processing, storage and shipping details are provided in the LPC. Of note RPV samples need to be protected from light as detailed in the 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: Cohort 1 samples will undergo ongoing analysis and reporting with scheduled interim PK analyses to assess if the initial dosing is achieving the PK targets. Assaying of Cohort 2A PK samples through the Wk. 24 visit, and then through the Wk. 48 visit, may be performed in batches and reported. Assaying of Cohort 2B PK samples through the Wk. 20 visit, and then through the Wk. 44 visit, may be performed in batches and reported. Remaining Cohort 2 PK samples may be assayed in batches and reported at completion of the study, along with PK samples collected during LSFU for the final PK analyses. PK samples collected from Cohort 2 after Wk. 48 and collected from any Confirmation of Virologic Failure visit, will be assayed as

requested by the team. Additional sample PK analysis may be performed prior to the completion of the study based on the study team's review of the initial interim analyses or at the request of the CMC or SMC.

10.3 Endpoints and Outcome Measures

10.3.1 Primary Endpoints and Outcome Measures	
10.3.1.1	Pharmacokinetic output measures as data permit • Cohort 1C – Step 1 PO dosing: Wk. 2 AUC, CL/F, C_{max}, T_{max}, and pre-dose concentrations (C_0). • Cohort 1C – Step 2 LA dosing: Wk. 16 concentrations (C_{16WK}), C_{max}, T_{max} (Dose 1) and C_0 prior to IM doses. • Cohort 1R – Step 2 LA dosing: Wk. 16 concentrations (C_{16WK}), C_{max}, T_{max} (Dose 1) and C_0 prior to IM doses.
10.3.2 Secondary Endpoints and Outcome Measures	
10.3.2.1	Pharmacokinetic outcome measures as data permit • Cohort 2A (oral followed by injectable): CAB and RPV pre-dose concentrations following PO administration at Step 3 Wk. 2. • Cohort 2A (oral followed by injectable): CAB and RPV concentrations following IM administration at Step 4 from Wk. 8 (after the first LA injections) to Wk. 24 and accumulation ratio (Wk. 24 Pre-dose Conc: Wk. 8 Pre-dose concentration). • Cohort 2B (injectable only): CAB and RPV concentrations following IM administration at Step 5 from Wk. 4 (after the first LA injections) to Wk. 20 and accumulation ratio (Wk. 20 Pre-dose Conc: Wk. 4 Pre-dose concentration). • Cohort 2A (oral followed by injectable): CAB and RPV concentrations following IM administration at Step 4 from Wk. 8 (after the first LA injections) to Wk. 48 and accumulation ratio (Wk. 48 Pre-dose Conc: Wk. 8 Pre-dose concentration). • Cohort 2B (injectable only): CAB and RPV concentrations following IM administration at Step 5 from Wk. 4 (after the first LA injections) to Wk. 44 and accumulation ratio (Wk. 44 Pre-dose Conc: Wk. 4 Pre-dose concentration). • Cohort 2A (oral followed by injectable): CAB and RPV concentrations following IM administration at Step 4 from Wk. 16 (after the first LA injections) to Wk. 24 and accumulation ratio (Wk. 24 Pre-dose Conc: Wk. 16 Pre-dose concentration). • Cohort 2B (injectable only): CAB and RPV concentrations following IM administration at Step 5 from Wk. 12 (after the first LA injections) to Wk. 20 and accumulation ratio (Wk. 20 Pre-dose Conc: Wk. 12 Pre-dose concentration). • Cohort 2A (oral followed by injectable): CAB and RPV concentrations following IM administration at Step 4 from Wk. 16 (after the first LA injections) to Wk. 48 and accumulation ratio (Wk. 48 Pre-dose Conc: Wk. 16 Pre-dose concentration). • Cohort 2B (injectable only): CAB and RPV concentrations following IM administration at Step 5 from Wk. 12 (after the first LA injections) to Wk. 44 and accumulation ratio (Wk. 44 Pre-dose Conc: Wk. 12 Pre-dose concentration).

10.3.3 Other Endpoints and Outcome Measures	
10.3.3.1	CAB and RPV Pharmacokinetic outcome measures as data permit • Cohort 2A (oral followed by injectable): CAB and RPV concentrations following IM administration at Step 4 from Wk. 48 to Wk. 96 and accumulation ratio (Wk. 96 Pre-dose Concentration: Wk. 48 Pre-dose Concentrations). • Cohort 2B (injectable only): CAB and RPV concentrations following IM administration at Step 5 from Wk. 44 to Wk. 92 and accumulation ratio (Wk. 92 Pre-dose Concentration: Wk. 44 Pre-dose Concentrations). • Cohort 1: CAB or RPV concentrations 8 to 48 weeks following final IM dose. • Cohort 2A&B: CAB and RPV concentrations 8 to 48 weeks following final IM dose.

10.4 Study Design, Data Analysis, and Modeling

Pharmacokinetic blood samples will be collected as noted in Section 6.16 and Appendix I. The samples will be 2 mL whole blood for Cohort 1 (and for Cohort 1 participants during the LSFU visit schedule) and 4 mL whole blood for Cohort 2 (and for Cohort 2 participants during the LSFU visit schedule). Cohort 2 plasma samples, which should be protected from light, will be split into individual aliquots for CAB and RPV each containing 0.4-1.2 mL plasma; same will be done for Cohort 2 participants during the LSFU visit schedule. RPV samples should be protected from light at all times from collection through storage and during sample analysis. Plasma concentrations will be summarized by Cohort, analyte, and nominal time. PK analysis will be performed by appropriate methodology e.g., noncompartmental methods and/or population methods.

CAB: The observed concentrations and parameter estimates will be compared to those seen in adults (Sections 1.3.9.1 and 1.3.9.2).

Specifically, following oral CAB 30mg once daily in adolescents ≥ 35kg C_{max} and C_{τ} are expected to be at steady state. Owing to the lower body weight of adolescents, their exposures are predicted to be 60-70% higher than the exposures seen with the 30mg daily oral dose in adults but comparable to the 60 mg dose in adults. These differences are considered to be not clinically relevant and higher CAB exposures have been observed without any safety findings in adults at supratherapeutic doses (150 mg administered orally every 12h x 3 doses).

Little accumulation between LA doses is expected following the CAB LA Q8W regimen (Section 5.1). In the adult clinical study (207966) with the same regimen, the geometric mean (5th and 95th percentiles) of the trough concentration following the initiation injection was 1.50 mcg/mL (0.65 mcg/mL – 2.90 mcg/mL), similar to that following the 6th LA IM injection (44 weeks after the initiation injection) of 1.61 mcg/mL (0.80 mcg/mL – 2.99 mcg/mL). Based on the POP PK model and simulations of the Q8W dosing in adolescents, the CAB concentrations are expected to be slightly higher but comparable to the levels observed in adults given the lower body weight in adolescents as compared to adults. These CAB levels are several folds higher than the PA-IC_{90} (CAB PA-IC_{90}=0.166 mcg/mL).

RPV: The observed concentrations and parameter estimates following IM administration will be compared to those seen in adults (Section 1.3.9.4). With the every 2 months dosing regimen in the adult clinical study 207966 (ATLAS-2M, RPV oral 25mg for 4 weeks followed by IM RPV 900 mg at Week 4 and Week 8 and every 8 weeks thereafter), the median (5th and 95th percentiles) trough concentration was 49.1 ng/mL (20.9 ng/mL – 116 ng/mL) at Week 8 (4 weeks following the first initiation injection), and was 64.7 ng/mL (33.0 ng/mL – 120ng/mL) following the 6th LA IM injection (44 weeks after the initiation injection). Greater than 80% of the RPV steady-state concentrations are reached within 48 weeks, with limited further accumulation thereafter.

10.4.1 Interim Pharmacokinetic Analyses

A non-compartmental pharmacokinetic analysis (NCA) will be performed on the plasma CAB or RPV concentration-time data generated for each individual in Cohort 1C and 1R. 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}),
- trough concentration (C_{τ}),
- apparent clearance (CL/F),
- terminal rate constant (λ_z), and
- the terminal half-life ($T_{1/2}$).

The accumulation for C_{28D} from Dose 1 to the last dose following LA administration will also be determined. C_{max} and T_{max} will be taken directly from the observed concentration-time data. Data permitting, the terminal slope, λ_z, will be determined from log- linear portion of the curve and the terminal half-life ($T_{1/2}$) calculated as $0.693/\lambda_z$. $AUC_{0-\tau}$ will be determined using the linear trapezoidal method and C_0 will be used as an estimate of C_{24h} (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.

Pharmacokinetic analyses will be performed as data from each Cohort become available. Individual participant's PK data results will be included if they are available for analysis.

10.4.2 Population Pharmacokinetic Analysis

POP PK analyses may be performed using the IMPAACT 2017 PK data alone or in combination with existing adult PK data using appropriate methodology. There are no population PK analysis outputs required for the dose selection in Cohort 1 nor do any Cohort 1 or 2 PK objectives require POP PK analysis for generation. Thus, POP PK analysis will be considered outside of the scope of this protocol and will be reported separately. However, other PK analyses of collected data, including POP PK evaluations, may be performed to assist the study team with assessment of safety or dosing.

10.5 Expected Outcome

Based on simulations presented in Section 1.3.9, oral and LA regimens in this adolescent participant population are expected to achieve concentrations within an acceptable range of those observed clinically in adults. If results deviate from expected predictions, dose modifications will be considered.

PK Acceptance Criteria
Oral CAB (Cohort 1C, Step 1)

The CAB PK acceptable criteria following oral administration in Cohort 1C Step 1 is:

- A median Wk. 2 $AUC_{0-\tau}$ between 46 and 277 mcg*h/mL (approximately 33-200% of the geometric mean in adults which is 134 mcg*h/mL).
- Median Trough (C_τ) concentrations $\geq$0.45 mcg /mL
- Median $C_{max} \leq$ 22.5 mcg/mL that was observed in the TQT study in adults without any impact on QT interval.

The study team will review all of the PK parameters following oral CAB, safety and tolerability data to determine if a dose modification is warranted. In general, slightly higher exposures may be expected in adolescents when administered the same dose as adults due to lower body weight.

Dose Modification (Cohort 1C, Step 1)

No individual dose modification for the use of short-term oral lead-in will be explored in Cohort 1C. In the event of failure with respect to safety concerns and/or PK criteria that are deemed potentially avoidable by a lower exposure to CAB, as judged by the protocol team, dose adjustment will be considered for a future Cohort 1C, subject to availability of a suitable formulation if deemed appropriate. Any participant that fails Cohort 1C due to safety concerns will not receive CAB LA in Cohort 1C Step 2.

CAB LA (Cohort 1C, Step 2)

For the participants that received CAB LA with Q4W dosing under protocol version 2.0, the Week 16 C_t data were within the median target range applicable for that dosing regimen (see Section 1.3.2) at the time of safety review (January 2020). The study exposure will also be assessed against the 5th percentile CAB concentration (0.45 mcg/mL) observed in the pivotal successful efficacy trials in adults, ATLAS and FLAIR, and similar to ATLAS-2M and oral CAB.

The CAB PK acceptable criteria following LA administration in Cohort 1C Step 2 is:

- A median Wk. 16 C_t between 0.71-6.7 mcg/mL
- A calculated 5th percentile Wk. 16 $C_t \geq$0.45 mcg/mL

If the PK results fail to meet the above Wk. 16 C_t acceptability criteria, the IMPAACT 2017 study team will review all available PK data to determine if any changes are deemed necessary in the proposed dosing regimen.

RPV LA (Cohort 1R, Step 2)

For the participants that received RPV LA with Q4W dosing under protocol version 2.0, the Week 16 C_t data were within the median target range applicable for that dosing regimen (see Section 1.3.2) at the time of safety review (January 2020). The study exposure will also be assessed against the 5th percentile RPV concentration (17.3 ng/mL) observed in the pivotal successful efficacy trials in adults, ATLAS and FLAIR, and similar to ATLAS-2M and oral RPV.

The RPV PK acceptable criteria following LA administration in Cohort 1R Step 2 is:

- A median Wk. 16 C_t between 25-100 ng/mL
- A calculated 5th percentile Wk. 16 $C_t \geq$17.3 ng/mL

If the PK results fail to meet the above Wk. 16 C_t acceptability criteria, the IMPAACT 2017 study team will review all available PK data to determine if any changes are deemed necessary in the proposed dosing regimen.

11 QUALITATIVE PHONE INTERVIEWS (U.S. Sites Only)

A single in-depth qualitative phone interview will be conducted with a sub-set of adolescent participants enrolled at U.S. study sites and as selected by the protocol team, to identify acceptability and tolerability concerns unique to the participant population, and to evaluate adolescent participants' experience of CAB LA and/or RPV LA. This section provides details on the qualitative phone interviews, including selection of participants, coordinating the phone interviews, conducting the interviews, and data analysis.

See Appendix IV for details regarding qualitative phone interviews with the parents/caregivers of adolescent participants.

11.1 Sample Size and Selection Process

Adolescent participants will be selected to take part in a single in-depth qualitative interview to achieve up to 30 completed phone interviews in each Cohort (for a maximum of 60 completed phone interviews in Cohort 1 and Cohort 2 combined). The sample size is based on the likely number of interviews needed to achieve thematic saturation. For each Cohort, selection for the interviews will continue until there is either saturation of themes, or the maximum sample size is reached, whichever occurs first. See Section 11.6 regarding thematic saturation and qualitative interview data analyses.

Self-reported demographics from Screening and Entry visits will be used to inform selection with the goal of balancing participant sex at birth and age (both older and younger adolescents) in the completed interviews. This will ensure that perspectives from participants assigned both male and female at birth, as well as older and younger participants, are reflected in the final analysis. Additionally, participants who permanently discontinue injectable study product will be purposefully selected to ensure reasons for discontinuing the injections are also reflected in the final analysis. Participants will be selected across multiple U.S. sites but restricted to those willing and able to conduct the interview by phone in English.

Participants will be selected on an on-going basis as they approach the respective interview procedure window for their Cohort, and some participants may be selected after they have entered the interview procedure window. The selection process will continue until thematic saturation or the sample size is reached for each Cohort; see Section 11.2 below for the interview procedure windows for each Cohort. The interviews must be completed within the specified interview

window to allow for comparison between participants. Participants enrolling to the study early will thus be selected for interviews first, as they will be the first to enter the specified interview windows.

11.2 Qualitative Phone Interview Procedural Window

The qualitative phone interviews will be conducted with selected participants within the following timeframes:

- For selected Cohort 1 participants: Between the Week 4b and Week 12 visits (inclusive), or during LSFU visits.
- For selected Cohort 2A participants: Between the Week 24 and Week 96 visits (inclusive), or during LSFU visits.
- For selected Cohort 2B participants: Between the Week 20 and Week 92 visits (inclusive), or during LSFU visits.

11.3 Consenting Considerations and Scheduling Qualitative Phone Interviews

For all adolescent participants, consent (or assent, as applicable) for the possibility of being selected for a phone interview will be obtained from the adolescent and their parent/guardian as part of the informed consent process (or informed assent process, as applicable) for the IMPAACT 2017 study. The protocol interview team will notify site staff when participants are selected for an interview; see Section 11.1 above for details on the selection process.

Upon notification of selection by the protocol interview team, site staff will approach selected participants (either in person or by phone) to confirm willingness to take part in the phone interview. Willingness to take part in the phone interview does not affect overall study participation or other scheduled study visit procedures.

Upon confirmation of the selected participant being willing to take part in the phone interview, site staff will work with the protocol interview team and the selected participant to schedule the phone interview. Operational considerations and guidance, including coordinating the interview, are provided in the IMPAACT 2017 MOP.

11.4 Conducting Qualitative Phone Interviews

Once the phone interview is scheduled, site staff will provide the selected participant with detailed instructions and guidance on accessing the phone interview platform. Phone interviews may be completed either in the study clinic during a scheduled study visit, or from a phone outside the study clinic at a time that is convenient for the participant and within the interview procedural window. All phone interviews will be conducted by a protocol interview team member external to participating clinical research sites, following an interview guide, and will be audio recorded and transcribed.

Sites must source document notification by the protocol interview team of participant selection, and all attempts to contact the participant. Sites must source document and enter into eCRFs willingness to take part in the phone interview, whether they are able to conduct the interview in English, and the date the phone interview occurred. Operational and logistical details regarding communication with the protocol interview team members and site staff are provided in the IMPAACT 2017 MOP.

11.5 Disclosure of Harm

As described above, the purpose of conducting in-depth qualitative phone interviews with participants is to identify acceptability and tolerability concerns unique to the participant population, and to evaluate adolescent participant's experience of CAB LA and/or RPV LA. Conducting the interviews is not expected to increase the likelihood or risk of self-harm or harm to others.

During the consent (or assent, as applicable) process, participants will be informed that the information that they provide in the interview will be kept confidential, with the exception of disclosures of significant risk for harm, including being abused or experiencing violence, suicidality or homicidality.

If at any time during a qualitative phone interview, a participant divulges that s/he is at risk for harm, including but not limited to being abused or experiencing violence, if harm is suspected or likely, or if the participant states s/he is suicidal or homicidal, the following will occur to ensure his or her safety:

- The protocol interview team member conducting the interview will immediately contact the site IoR or designee and share any time-sensitive, potentially life-threatening information received from the study participant as part of the phone interview discussions.
- The IoR or designee contacted with this information will follow local policies for management of such situations including engaging immediate/first responders as applicable.
- The IoR or designee will also follow local reporting policies and legal statutes, including reporting to child protection or other appropriate agencies, as well as arranging referrals to appropriate support, counseling or treatment resources.

After the safety of the participant is addressed according to the steps above, the IoR or designee will notify the CMC and document the event, as applicable per Section 7.

To facilitate rapid communications, the IoR or designee is expected to provide up-to-date contact information to the protocol interview team while phone interviews are being scheduled and conducted with participants from the site.

11.6 Qualitative Phone Interview Data Analyses

This section provides an overview of the qualitative data analysis process, which will be a descriptive analysis without formal inference, with a more detailed description presented in the qualitative analysis plan. See Section 12 for details regarding data management responsibilities and source data of the in-depth qualitative phone interviews, audio files, and transcriptions.

Analysis will begin during data collection to allow for an iterative process through which questions and probes can be refined to enhance the depth of understanding elicited, so that topics for further exploration can be noted and incorporated into ongoing interviews. Contemporaneous analysis will also be used for determination of the achievement of thematic saturation. Thematic saturation is determined on the basis of analysis of the completed scripts by multiple investigators who agree that novel information has ceased to arise as new interviews are completed. The qualitative data analysis will utilize a thematic approach whereby the protocol interview team will

search for patterns in data and will conceptualize ideas that help explain the presence of those patterns (29). Analysis of textual data will consist of 5 main steps:

1) Reading for content: Analysis will begin with reading and rereading transcripts until content becomes intimately familiar (30). As data are reviewed, emergent themes will be noted;
2) Coding: A list of codes will be created based on both pre-specified and identified themes. Codes will then be assigned to specific sections of text so that the text can be easily and meaningfully searched (31). Code definitions will be documented in a code book and will include information about the code's central meaning and may also provide examples of text considered within and outside the code's parameters (30). To ensure inter-coder reliability, all transcripts will be double-coded (i.e. by two separate coders who will compare and reconcile coding results);
3) Displaying: Once transcripts have been coded, principle sub-themes will be identified within each code that reflect finer distinctions in the data;
4) Data Reduction: Matrices and tables that categorize and display data will be used to help the analysts understand the dimensions by which the data are categorized and facilitate comparisons (31);
5) Interpretation: Themes will be identified and explained. Relationships between themes and speakers (e.g. adolescents/parents, assigned male/female at birth, older/younger adolescents) will be mapped to highlight similarities and differences of perspective.

12 DATA HANDLING AND RECORD KEEPING

12.1 Data Management Responsibilities

As described in Section 4.7, 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 adolescent participants, and all enrolled 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 or DSMB) 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 Subject Enrollment System is available on the DMC portal at: https://www.frontierscience.org

For US sites: The protocol interview team at the Children's Hospital of Philadelphia (CHOP) will collect and manage qualitative phone interview data for the study. In-depth phone interview guides will be developed by the protocol interview team at CHOP and will receive IRB/EC review and approval. The protocol interview team at CHOP will conduct the phone interviews with participants (and parents/caregivers) using a secure teleconference platform. The phone interviews will be digitally-audio recorded, downloaded to a secure server, and subsequently transcribed by an external transcription service. The audio recordings and transcripts will be securely electronically transferred to the protocol interview team at CHOP. Transcripts will then be processed by the protocol interview team at CHOP for quality assurance, including ensuring that all personal identifiers have been removed. After completion of quality assurance processing, de-identified transcripts will be labeled as final source data of the phone interview. The audio recordings and transcripts generated by the external transcription service will be deleted from their secure server, as well as from any back-up servers. The audio recordings and finalized transcripts will be kept on a password-protected secure server at CHOP. At no time will study sites have access to the audio files or the transcripts.

For US sites: The finalized transcriptions of interviews will be uploaded and managed by the protocol interview team at CHOP using a qualitative software package (e.g. NVivo). The DMC will serve as a repository for the following data, which will be securely transferred by the protocol interview team at CHOP: finalized transcripts, codebook, and output data.

12.2 Essential and Source Documents and Access to Source Data

Study sites must comply with requirements for essential documents and source documentation specified in the DAIDS SCORE Manual. This includes establishing SOPs for maintaining essential and source documents in compliance with these policies. 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.

For U.S. sites: In-depth qualitative phone interviews will be digitally audio-recorded and transcribed. See Section 12.1 above regarding data management and processing of the audio files and transcripts.

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 it is 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, Janssen Pharmaceuticals, the US Food and Drug Administration, site drug regulatory authorities, site IRBs/ECs, the sIRB (for US sites), OHRP, 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. No study records may be removed to an off-site location or destroyed prior to receiving approval from NIAID.

12.3 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.

13 CLINICAL SITE MONITORING

Site monitors under contract to NIAID or NICHD will visit study sites to inspect study facilities and review participant study records including consent and/or 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. The monitors will also review essential document files to ensure compliance with all applicable regulatory requirements. Site investigators will make study facilities and documents available for inspection by the 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(32). Site investigators will make available study documents for site monitors to review utilizing a secure platform that is 21 CFR Part 11 and HIPAA compliant. Potential platform options include: Veeva SiteVault, Medidata Rave Imaging Solution, site-controlled SharePoint or cloud-based portal, and direct access to electronic medical records. Other secure platforms that are 21 CFR Part 11 and HIPAA compliant may be utilized, as allowed by DAIDS Office of Clinical Site Oversight (OCSO) or NICHD.

14 HUMAN SUBJECTS PROTECTIONS

14.1 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 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.

All IRB/EC policies and procedures must be followed and complete documentation of all correspondence to and from the 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 15.2).

14.2 Vulnerable Participants

It is NIH policy to ensure that children be included in clinical research when appropriate (33, 34). This study responds to that mandate and will provide clinical research data to inform oral CAB, CAB LA, RPV LA, as well as oral CAB + oral RPV, and CAB LA + RPV LA safety and dosing in children and adolescents. Nonetheless, the children and adolescents who take part in this study are considered vulnerable participants per the US Code of Federal Regulations, and IRBs/ECs must consider the potential risks and benefits to child and adolescent participants as described in 45 CFR 46 Subpart D (for children).

With respect to 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 15.2, and the risk category assigned by the IRB/EC further determines the parental informed consent requirements for the study at each site. Per 45 CFR 46.408 (b), the IRB/EC may find that the consent 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 consent, 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, and study sites should adapt the signature pages of their site-specific ICFs as needed to accommodate the parental consent requirements associated with the IRB/EC determination.

Study sites must comply with the requirements for enrolling minors in clinical research 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. In cases where multiple different sets of requirements apply, the most stringent requirements must be followed.

14.3 Informed Consent

This section provides details regarding informed consent and assent requirements and procedures for adolescents. Refer to Section 4.7 and the IMPAACT 2017 MOP for further information on informed consent and assent procedures for this study.

As indicated in Section 4.1.2, site investigators and their designees will be required to determine participant age and ability to provide independent informed consent for study participation consistent with IRB/EC policies and procedures. Each site must establish SOPs, roles, and responsibilities for completing these determinations, and study staff involved in completing these determinations must have documented training in the relevant policies and procedures prior to study initiation.

Written informed consent and written assent will be obtained for study participation as follows:

- *If the potential participant is not of legal age to provide independent informed consent as determined by site SOPs*: Parent, legal guardian, or other legally authorized representative must provide written informed consent for study participation and the potential participant must provide written assent for study participation.

Note: Refer to Section 14.2 for considerations related to parental consenting requirements; IRB/EC risk determinations will guide whether the consent of one or both parents may be required for this study. All IRB/EC requirements must be followed.

- *If the potential participant is of legal age and able to provide independent informed consent as determined by site SOPs*: The potential participant must provide written informed consent for study participation.

Written informed consent and assent (as applicable) for participation will be obtained before any study-specific procedures are performed. 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. The process will describe what is known about the safety and tolerability of the study products and participants and parents/guardians will be extensively counseled on the importance of adherence to the study product regimen, as well as to cART regimen (for Cohort 1 and LSFU). The informed assent process will include a similar process, with the amount of information and level of detail provided as part of assent processes tailored to the age of the potential participant, guided by IRB/EC policies and procedures.

As part of the informed consent and assent process, consenters will be asked whether they agree to storage and future research testing of biological specimens remaining after all protocol-specified testing has been performed. This storage and future use is optional and may be declined with no impact on other aspects of study participation. Likewise, genetic testing of residual specimens is optional and may be declined.

Appendix II provides sample informed consent forms, including a section of the form for indicating consent to storage and future research testing. Appendix III provides sample informed assent forms for adolescents who are unable to provide consent (i.e., require parent or legal guardian consent for study participation), including a section of the form for indicating assent to storage and future research testing. For the Cohort 2 assent forms, a section is also included to indicate the participant's choice of either Cohort 2A or Cohort 2B. All sample informed consent and assent forms provided in AppendicesAppendix II and Appendix III may be modified by sites to meet IRB/EC requirements. Study sites are permitted to develop separate assent and consent forms for this study, if required by site or IRB/EC policies and procedures; for example, sites may develop one assent form for children 12 years of age at lower reading and comprehension levels than another assent form for children 13 to less than 18 years of age.

If the participant, parent, or guardian (as applicable) is unable to read, the process for consenting illiterate participants, as defined or approved by the local IRB/EC, should be followed. Sites must also establish and maintain written procedures describing standards for obtaining informed assent, reflective of applicable IRB/EC guidance.

As indicated above, parental consenting requirements at each site will depend on the IRB/EC risk determination described in Section 14.2; all IRB/EC requirements will be followed. Participants enrolling in the study as minors will generally require consent from a parent or guardian.

In general, each participant is expected to take part in the informed consent process with their parent or legal guardian, and both the assent of the participant and the consent of the parent or legal guardian will be required for all consent decisions. For example, if the participant does not provide assent, or the parent or legal guardian does not provide consent, the participant will not be enrolled in the study. The same approach will be taken for consent for storage and future

research testing of biological specimens. However, should the participant be unaware of his/her HIV status, the informed consent process may be conducted with the parent or legal guardian separately and without the presence of the participant, per IRB/EC policies. In these circumstances, the assent process must be conducted with both the parent or legal guardian and the participant present. Per IRB/EC policies, sites may modify the consent and/or assent (as applicable) forms and processes to remove mentioning of HIV for participants who do not know their status.

Should the consenting parent (or guardian) of a participant die or no longer be available for any reason, sites should follow the guidelines and procedures in Section 8.8, in addition to those described by their IRBs/ECs. Study sites may continue to provide care for the participant as needed and appropriate (outside of the study), consistent with local standard of care. If a guardian cannot be identified, or if the guardian does not consent to continued study participation, the participant must be withdrawn from the study. In accordance with the DAIDS 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 guardian for an enrolled child or adolescent, reflective of applicable IRB/EC guidance for conduct of human subjects research within the context of available local law, regulation, or government policy.

Participants may also reach the legal age of consent during follow-up. In this case, written informed consent for continued participation and specimen storage and future use (Appendix II-A, Appendix II-B, or Appendix II-C, as applicable) will be obtained from participants once they reach legal age at their next study visit. If participants do not consent for continued study participation, they should be discontinued from the study; similarly, if they do not consent for specimen storage and future use, all specimens will be destroyed after all protocol-related testing is complete.

See Appendix IV for informed consent considerations for parent/caregivers who may enroll to the study to participate in a single in-depth qualitative phone interview.

14.4 Potential Benefits

There may be no direct benefit to participants who take part in this study although there is a potential benefit for improved understanding of, and engagement in, HIV care. Information learned in this study may be of benefit to participants and others in the future, particularly information that may lead to more treatment options for children and adolescents living with HIV. As mentioned in Section 1.4 there is also the potential risk-benefit of early access to Cohort 2 and its related benefits with the opportunity to stop oral cART and switch to an entirely long-acting injectable regimen. Lastly, participants may also appreciate the opportunity for themselves to contribute to HIV-related research.

14.5 Potential Risks

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

Most study procedures are routine medical procedures that are associated with minimal to no risk in participants. Blood collection may cause pain, bruising, swelling, or fainting. There is a very small chance of infection where the needle is inserted, though the injections may cause pain, swelling, reddening of the skin, and nodule formations where the needle is inserted.

Although there is already a great deal of robust safety, PK and efficacy data in adults, these drugs have not yet been studied in adolescents. There may also be additional risks associated with use of these study products in adolescence. Refer to Section 1.2.3 for a complete description of the potential risks associated with the use of these drugs.

A preliminary analysis of an ongoing birth outcome surveillance study in Botswana involving women exposed to DTG a different molecule in the same integrase class of medications as CAB, identified five cases (as of March 2019) of neural tube defects in 1,683 infants born to mothers who were exposed to DTG-containing regimens from the time of conception. In the same study, one infant born to a woman who started DTG during pregnancy had a neural tube defect, out of 3,840 women. More recent data from this same study suggest an even lower incidence of neural tube defects amongst women taking dolutegravir-containing regimens from the time of conception. A causal relationship of these events to the use of DTG has not been established. The incidence of neural tube defects in the general population ranges from 0.5-1 case per 1,000 live births. As neural tube defects occur within the first 4 weeks of fetal development (at which time the neural tubes are sealed) this potential risk would concern women exposed to DTG at the time of conception and in early pregnancy. Cabotegravir is not dolutegravir. While these medications share a common molecular backbone, and have a similar mechanism of activity, they are separate chemical compounds and have differences in antiviral activity, pharmacokinetics, metabolism and drug-drug interactions. It is not known if the safety signal identified with dolutegravir will be observed with cabotegravir. Cabotegravir was evaluated in a complete package of reproductive toxicology studies, including embryofetal development studies, and no safety findings suggestive of teratogenesis or neural tube defects were identified in the 17 December 2019 version of the Investigator's Brochure. Every effort will be made in this study to avoid the occurrence of pregnancies among participants.

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

For virologically suppressed, ART-experienced participants enrolling into Cohort 2, and dropping their background cART, there is the potential risk that the study products may not be as effective in maintaining viral suppression as participants' current regimen.

Despite all efforts to maintain confidentiality, involvement in the 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). For example, participants could be treated unfairly or discriminated against or could have problems being accepted by their families and/or communities. Refer to Section 14.7 for further information on privacy and confidentiality.

14.6 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 or other materials if applicable per IRC/EC policies and procedures.

14.7 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 from the parent/guardian, as well as the adolescent, to do so except as necessary for review, monitoring, and/or auditing as described in Section 12.2.

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) will be identified by PID only. Likewise, communications between study staff and protocol team members regarding individual participants will identify participants by PID only. Audio files and transcripts will be kept on a secure and password protected server with the protocol interview team, and will be identified by PID only when transmitted to contracting services (e.g., a transcription service provider).

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 obtained for this study from 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.

14.8 Communicable Disease Reporting

Study staff will comply with local requirements to report communicable diseases including HIV identified among study participants to health authorities. Participants will be made aware of all applicable reporting requirements as part of the study informed consent process.

14.9 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 results of HIV tests (if applicable), and hematology and chemistry tests. 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 informed consent and assent forms. When applicable, site clinicians will provide referrals to non-study sources of medical care for further evaluation and/or treatment of these findings.

14.10 Management of New Information Pertinent to Study Participation

Participants, and their parent (or other authorized guardians if applicable) will be provided any new information learned over the course of the study that may affect their willingness to allow their adolescent to continue receiving study product and/or remain in follow-up in the study.

14.11 Post-Trial Access to Study Product

Participants will be transitioned into care and treatment outside of the study at the end of their study participation. If CAB LA + RPV LA is not locally available for a participant in Cohort 2 completing the study, then the pharmaceutical company or their partners will provide access to CAB LA + RPV LA following the participant's completion of the study through a mechanism outside of the IMPAACT 2017 protocol until one or both of the following events occur:

- CAB LA + RPV LA is available from another source (e.g., government programs, aid programs, assistance programs, etc.); OR
- If development of CAB LA + RPV LA is terminated.

15 ADMINISTRATIVE PROCEDURES

15.1 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). Study products are provided by ViiV Healthcare; however, this organization is not involved in sponsorship or regulatory oversight of this study.

The Division of AIDS (DAIDS) within the NIAID 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 13. As part of these visits, monitors will inspect study-related documentation to ensure compliance with all applicable US, local, and international regulatory requirements.

15.2 Protocol Registration

Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol ICFs approved, as appropriate, by applicable IRBs/ECs, and any other applicable regulatory entity. 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 ICFs 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 ICFs 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 on the RSC website: https://rsc.niaid.nih.gov/clinical-research-sites/daids-protocol-registration-policy-and-procedures-manual

15.3 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 IMPAACT web site: www.impaactnetwork.org.

Study implementation at each site will also be guided by 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.

15.4 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 Network Manual of Procedures.

15.5 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.

16 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.

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Appendix I: Schedule of Evaluations
Appendix I-A: Schedule of Evaluations for Cohort 1 Adolescents (Cohort 1C and Cohort 1R)

Cohort 1 (CT 1)											
		Step 1 (oral phase)			Step 2 (injection phase)						
Study Visit[1]	**CT 1 Screen**	**CT 1 Entry**	**CT 1 Wk 2**	**CT 1 Wk 4a**	**CT 1 Wk 4b (Step 2 Entry)**	**CT 1 Wk 5**	**CT 1 Wk 8**	**CT 1 Wk 9**	**CT 1 Wk 12**	**CT 1 Wk 16**	**Confirmation of Virologic Failure**
Behavioral Evaluations											
Acceptability/Tolerability assessment[2]		X	*	*	X	*	X			X	
Qualitative Interview[3]					*	*	*	*	*		
Clinical Evaluations											
Medical history	X	X	X	X	X	X	X	X	X	X	X
Adherence assessment			X	X	X						
Complete physical examination	X			X						X	
Symptom-directed physical examination		X	X		X	X	X	X	X		X
Sexual Maturity Rating	X									X	
ECG[4]	X							X		X	
Study Product											
Dispense oral study product (for up to 6 wks)		X	*	*							
Administer injection study product					X		X				
Laboratory Evaluations											
hCG (females only)	X	X	X	X	X		X			X	X
Confirmation of HIV infection	0-6 mL*										
Hematology	2 mL	2 mL	2 mL	2 mL		2 mL	2 mL			2 mL	
Chemistries	3 mL	3 mL	3 mL	3 mL		3 mL	3 mL			3 mL	
CD4 count and percentage		3 mL								3 mL	
HIV-1 RNA	6 mL	6 mL	6 mL		6 mL		6 mL			6 mL	6 mL
Whole blood for genotypic resistance testing[5]		4 mL									
Plasma for genotypic and phenotypic resistance testing[5]			6 mL		6 mL		6 mL			6 mL	6 mL
Pharmacology Evaluations											
PK Sampling[6]			6-12 mL		4 mL	2 mL	2 mL	2 mL	2 mL	2 mL	2 mL
Total maximum blood volume	11-17 mL	18 mL	23-29 mL	5 mL	16 mL	7 mL	19 mL	2 mL	2 mL	22 mL	14 mL

Notes: X – required; * - if indicated

1) Target dates and visit windows may vary per visit. See Section 6.3 for Cohort 1 study visits, procedures, and target dates associated with each visit. See Section 6.1 for further details regarding target dates, target visit windows, and allowable visit windows. See Section 0 and Appendix I-D for details on conducting an Early Termination visit.
2) Acceptability/tolerability assessment questionnaires will be administered at the following Cohort 1 study visits (required): Step 1 Entry, Week 4b, Week 8, and Week 16. Additionally, acceptability/tolerability assessment questionnaires will be administered at indicated visits should premature permanent study product discontinuation be initiated (noted in the table as *if indicated*). See Section 6.15 and the IMPAACT 2017 MOP for further details on the specific questionnaires and timing of administration.
3) Only a sub-set of participants will be selected for the qualitative phone interview. For selected Cohort 1 participants, the qualitative phone interview may be conducted between and including the Week 4b and Week 12 visits (noted in the table as *if indicated*). See Section 11 for qualitative interview window and details on participant selection.
4) See Section 6.12 for details regarding performing an ECG/EKG.
5) HIV genotypic and phenotypic resistance samples (collected at the Confirmation of Virologic Failure visit and other visits) will be processed, stored, and shipped for testing per Section 6.16.2 and the LPC.
6) See Sections 6.3 and 6.6 for PK sample collection timepoints and windows.

Appendix I-B: Schedule of Evaluations for Cohort 2A Adolescents

Cohort 2A (CT 2A)															
Study Visit[1]	**CT 2A Screen**	**Step 3 (oral phase)**			**Step 4 (injection phase)**										**Confirmation of Virologic Failure**
		CT 2A Entry	**CT 2A Wk 2**	**CT 2A Wk 4a**	**CT 2A Wk 4b (Step 4 Entry)**	**CT 2A Wk 5**	**CT 2A Wks 8 and 16**	**CT 2A Wk 24**	**CT 2A Wk 25**	**CT 2A Wks 32 and 40**	**CT 2A Wk 48**	**CT 2A Wks 56, 64, 72, 80, and 88**	**CT 2A Wk 96**	**Interim Injection Visit[7]**	
Behavioral Evaluations															
Acceptability/ Tolerability assessment[2]		X	*	*	X	*	Wk 8 (X) Wk 16(*)	X	*	*	X	*	X		
Qualitative Interview[3]								*	*	*	*	*	*		
Clinical Evaluations															
Medical history	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adherence assessment			X	X	X										
Complete physical examination	X			X				X			X		X		
Symptom-directed physical examination		X	X		X	X	X		X	X		X		X	X
Sexual Maturity Rating	X							X					X		
ECG[4]	X				X										
Study Product															
Dispense oral study products (for up to 6 wks)		X	*	*											
Administer injection study products					X		X	X		X	X	X	X	X	
Laboratory Evaluations															
hCG (females only)	X	X	X	X	X		X	X		X	X	X	X	X	X
Confirmation of HIV infection	0-6 mL*														
Hematology	2 mL	2 mL	2 mL	2 mL		2 mL	2 mL	2 mL		2 mL	2 mL	2 mL	2 mL	2 mL	

Chemistries	3 mL	3 mL	3 mL	3 mL		3 mL	3 mL	3 mL		3 mL	3 mL	3 mL	3 mL	3 mL	
CD4 count and percentage		3 mL						3 mL			3 mL	Only Wk 72 (3 mL)	3 mL		
HIV-1 RNA	6 mL	6 mL	6 mL		6 mL		6 mL	6 mL		6 mL	6 mL	Only Wks 64 and 80 (6 mL)	6 mL	6 mL	6 mL
Whole blood for genotypic resistance testing[5]		4 mL													
Plasma for genotypic and phenotypic resistance testing[5]			6 mL		6 mL		6 mL	6 mL		6 mL	6 mL	Only Wks 64 and 80 (6 mL)	6 mL	6 mL	6 mL
Pharmacology Evaluations															
PK Sampling[6]			8 mL		8 mL	4 mL	4 mL	4 mL	4 mL	4 mL	4 mL	Only Wks 64, 80, and 88 (4 mL)	4 mL	4 mL	4 mL
Total maximum blood volume	11-17 mL	18 mL	25 mL	5 mL	20 mL	9 mL	21 mL	24 mL	4 mL	21 mL	24 mL	5-21 mL	24 mL	21 mL	16 mL

Notes: X – required; * - if indicated

1) Target dates and visit windows may vary per visit. See Section 6.4 for Cohort 2 study visits, procedures, and target dates associated with each visit. See Section 6.1 for further details regarding target dates, target visit windows, and allowable visit windows. See Section 0 and Appendix I-D for details on conducting an Early Termination visit.
2) Acceptability/tolerability assessment questionnaires will be administered at the following Cohort 2A study visits (required): Step 3 Entry, Week 4b, 8, 24, 48, and Week 96. Additionally, acceptability/tolerability assessment questionnaires will be administered at indicated visits should premature permanent study product discontinuation be initiated (noted in the table as *if indicated*). See Section 6.15 and the IMPAACT 2017 MOP for further details on the specific questionnaires and timing of administration
3) Only a sub-set of participants will be selected for the qualitative phone interview. For selected Cohort 2A participants, the qualitative phone interview may be conducted between and including the Week 24 and Week 96 visits (noted in the table as *if indicated*). See Section 11 for qualitative interview window and details on participant selection.
4) See Section 6.12 for details regarding performing an ECG/EKG.
5) HIV genotypic and phenotypic resistance samples (collected at the Confirmation of Virologic Failure visit and other visits) will be processed, stored, and shipped for testing per Section 6.16.2 and the LPC.
6) See Sections 6.4 and 6.6 for PK sample collection timepoints and windows.
7) See Section 6.4.14 for interim injection visit scheduling considerations and required procedures for Cohort 2 participants.

Appendix I-C: Schedule of Evaluations for Cohort 2B Adolescents

Cohort 2B (CT 2B)												
Study Visit[1]	CT 2B Screen	Step 5 (injection phase)										Confirmation of Virologic Failure
		CT 2B Entry (Step 5 Entry)	CT 2B Wk 1	CT 2B Wks 4 and 12	CT 2B Wk 20	CT 2B Wk 21	CT 2B Wks 28 and 36	CT 2B Wk 44	CT 2B Wks 52, 60, 68, 76, and 84	CT 2B Wk 92	Interim Injection Visit[7]	
Behavioral Evaluations												
Acceptability/ Tolerability assessment[2]		X	*	Wk 4 (X) Wk 12(*)	X	*	*	X	*	X		
Qualitative Interview[3]					*	*	*	*	*	*		
Clinical Evaluations												
Medical history	X	X	X	X	X	X	X	X	X	X	X	X
Complete physical examination	X				X			X		X		
Symptom-directed physical examination		X	X	X		X	X		X		X	X
Sexual Maturity Rating	X				X					X		
ECG[4]	X	X										
Study Product												
Administer injection study products		X		X	X		X	X	X	X	X	
Laboratory Evaluations												
hCG (females only)	X	X		X	X		X	X	X	X	X	X
Confirmation of HIV infection	0-6 mL*											
Hematology	2 mL	2 mL	2 mL	2 mL	2 mL		2 mL	2 mL	2 mL	2 mL	2 mL	
Chemistries	3 mL	3 mL	3 mL	3 mL	3 mL		3 mL	3 mL	3 mL	3 mL	3 mL	
CD4 count and percentage		3 mL			3 mL			3 mL	Only Wk 68 (3 mL)	3 mL		
HIV-1 RNA	6 mL	6 mL		6 mL	6 mL		6 mL	6 mL	Only Wks 60 and 76 (6 mL)	6 mL	6 mL	6 mL

Whole blood for genotypic resistance testing[5]		4 mL										
Plasma for genotypic and phenotypic resistance testing[5]				6 mL	6 mL		6 mL	6 mL	Only Wks 60 and 76 (6 mL)	6 mL	6 mL	6 mL
Pharmacology Evaluations												
PK Sampling[6]		4 mL	4 mL	4 mL	4 mL	4 mL	4 mL	4 mL	Only Wks 60, 76, and 84 (4 mL)	4 mL	4 mL	4 mL
Total maximum blood volume	11-17 mL	22 mL	9 mL	21 mL	24 mL	4 mL	21 mL	24 mL	5-21 mL	24 mL	21 mL	16 mL

Notes: X – required; * - if indicated

1) Target dates and visit windows may vary per visit. See Section 6.4 for Cohort 2 study visits, procedures, and target dates associated with each visit. See Section 6.1 for further details regarding target dates, target visit windows, and allowable visit windows. See Section 0 and Appendix I-D for details on conducting an Early Termination visit.
2) Acceptability/tolerability assessment questionnaires will be administered at the following Cohort 2B study visits (required): Step 5 Entry, 4, 20, 44, and Week 92. Additionally, acceptability/tolerability assessment questionnaires will be administered at indicated visits should premature permanent study product discontinuation be initiated (noted in the table as *if indicated*). See Section 6.15 and the IMPAACT 2017 MOP for further details on the specific questionnaires and timing of administration
3) Only a sub-set of participants will be selected for the qualitative phone interview. For selected Cohort 2B participants, the qualitative phone interview may be conducted between and including the Week 20 and Week 92 visits (noted in the table as *if indicated*). See Section 11 for qualitative interview window and details on participant selection.
4) See Section 6.12 for details regarding performing an ECG/EKG.
5) HIV genotypic and phenotypic resistance samples (collected at the Confirmation of Virologic Failure visit and other visits) will be processed, stored, and shipped for testing per Section 6.16.2 and the LPC.
6) See Sections 6.4 and 6.6 for PK sample collection timepoints and windows.
7) See Section 6.4.14 for interim injection visit scheduling considerations and required procedures for Cohort 2 participants.

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

Study Visit[1]	LSFU Week 8[2]	LSFU Week 24	LSFU Week 36	LSFU Week 48/ Early Termination[3]	Confirmation of Virologic Failure
Behavioral Evaluations					
Acceptability/ Tolerability assessment	X			X	
Qualitative Interview[4]	*	*	*	*	
Clinical Evaluations					
Medical history	X	X	X	X	X
Complete physical examination	X			X	
Symptom-directed physical examination		X	X		X
Sexual Maturity Rating				X	
Laboratory Evaluations					
hCG (females only)[5]	X	X	X	X	X
Hematology	2 mL	2 mL	2 mL	2 mL	
Chemistries	3 mL	3 mL	3 mL	3 mL	
HIV-1 RNA	6 mL	6 mL	6 mL	6 mL	6 mL
Plasma for genotypic and phenotypic resistance testing[6]	6 mL	6 mL	6 mL	6 mL (LSFU Week 48 only)	6 mL
Whole blood for genotypic resistance testing[3, 6]				4 mL (Early Termination visit only)	
Pharmacology					
PK Sampling[7]	2-4 mL	2-4 mL	2-4 mL	0-4 mL[3,7]	2-4 mL[7]
Total maximum blood volume	19-21 mL	19-21 mL	19-21 mL	15-21 mL	14-16 mL

Notes: X – required

1) Target dates and visit windows may vary per visit. See Section 6.5 for LSFU study visits, procedures, and target dates, and target visit windows associated with each visit.
2) Participants completing the Cohort 1 Step 2 Week 16 visit will not complete the LSFU Week 8 visit.
3) See Sections 0 and 6.7 for more details on conducting Early Termination visits. Participants completing an Early Termination visit will have whole blood collected for genotypic and phenotypic resistance testing. Cohort 1 Step 1 and Cohort 2 Step 3 participants completing an Early Termination visit will not have a PK evaluation performed and a PK sample will not be collected.
4) Only a sub-set of participants will be selected for the qualitative phone interview. For selected Cohort 1 or Cohort 2 participants being followed per the LSFU schedule, the qualitative phone interview may be conducted between and including the LSFU Week 8 and LSFU Week 48 visits (noted in the table as *if indicated*). See Section 11 for qualitative interview window and details on participant selection.
5) Pregnancy testing will not be required for participants who are currently pregnant.
6) HIV genotypic and phenotypic resistance samples (collected at the Confirmation of Virologic Failure visit and other visits) will be processed, stored, and shipped for testing per Section 6.16.2 and the LPC.
7) See Sections 6.5 and 6.6 for PK sample collection timepoints and windows. Cohort 1 Step 2 participants being followed per the LSFU visit schedule will have 2 mL collected for each PK sampling timepoint, whereas Cohort 2 Step 4 and Step 5 participants being followed per the LSFU visit schedule will have 4 mL collection for each PK sampling timepoint.

Appendix II: Sample Informed Consent Forms

Appendix II-A: Sample Informed Consent Form for Participation in Cohort 1

for adolescents who can provide independent informed consent for study participation and parents/legal guardians of adolescents

IMPAACT 2017
Phase I/II Study of the Safety, Acceptability, Tolerability, and Pharmacokinetics of Oral and Long-Acting Injectable Cabotegravir and Long-Acting Injectable Rilpivirine in Virologically Suppressed HIV-Infected Children and Adolescents

Version 4.0, dated 27 May 2022

[Throughout this form sites may modify to remove mentions of HIV and ARVs for participants who do not know their status].

If you are the parent or legal guardian of a child who may take part in this study, your permission and the permission of your child will be needed. When "you" appears in this form, it refers to your child except where it says otherwise.

Introduction

You are being asked to take part in the research study named above.

This form gives information about 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 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 medicines (ARVs), Cabotegravir (CAB) and Rilpivirine (RPV), taken as pills and given as long-acting shots in adolescents 12 to less than 18 years of age.
- Some of the study drugs are already approved in some countries for use in adolescents or adults, but more data is needed for use in adolescents.
- There are two parts to this study, Cohort 1 and Cohort 2. This form is about Cohort 1. Adolescents who participate in Cohort 1 may qualify for Cohort 2 of the study after completing Cohort 1.
- Participants in Cohort 1 will be in this part of the study for at least 4 months and up to 16 months.
- Adolescents in Cohort 1 will continue taking their usual ARVs while also taking the study medicine. After entering the study, adolescents will take daily CAB or RPV *pills* for 4 to 6 weeks while taking their usual ARVs. Adolescents will then switch to getting CAB or RPV *shots* 4 weeks apart (for a total of 2 shots) while continuing to take their usual ARVs.
- After the last shot, adolescents will be followed for up to 1 year for long-term safety follow-up. During this time, adolescents will not take any study medicine (shots or pills) but will continue taking their usual ARVs.
- While in the study, adolescents will have clinic visits with physical examinations and blood draws for laboratory tests. Some visits will include a review of adolescents' medical records and ECG tests to look at the adolescent's heart. Participants assigned female at birth will also be tested for pregnancy.
- If interested, participants in the U.S. may be eligible to do one in-depth phone interview where they will talk about their experience getting their ARV's as shots.

- There are some possible risks for adolescents in the study. One possible risk is that the pills or shots being tested could cause side effects. The most severe side effects include allergic reaction, liver problems, and mental health problems. These side effects are uncommon.
- There are some possible benefits for adolescents in the study. One possible benefit is a better understanding of your health and HIV care. Another possible benefit is early access to the Cohort 2 part of the study, if you qualify.
- Your decision on your participation in the study will have no effect on the medical care you receive at this clinic. Your access to services, and the benefits and rights you normally have, will not be affected. You may choose to leave the study at any time.

More information is given in this form about the study, its risks and benefits. You should feel that you understand the study before deciding whether to participate. If you decide to 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

This study is being done by the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) and *[insert site name]*. The person in charge of the study at *[insert site name]* is *[insert name of IoR]*.

The study is being done to test two anti-HIV medicines (antiretrovirals or ARVs) in adolescents 12 to less than 18 years old who have HIV. The study ARVs are called cabotegravir (CAB) and rilpivirine (RPV). HIV is the virus that can lead to AIDS.

The study will include up to 155 adolescents from the United States, Botswana, South Africa, Thailand and Uganda. There will be two groups of adolescents, called Cohort 1 and Cohort 2. This form is about Cohort 1. Participants in Cohort 1 will be in the study for at least 16 weeks (4 months) and then up to an additional 48 weeks (12 months) as part of long-term follow-up, for a total of 64 weeks (16 months).

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 adolescents.

People living with HIV usually take a combination of ARVs daily to stay healthy. There are not as many ARVs available for adolescents as for adults because many ARVs have not yet been tested in adolescents. ARVs can be made in different forms, such as liquids, pills, and injections (shots). The study will test CAB and RPV when taken as pills and when given as shots in adolescents. The pills are taken every day. The shots can be given every 4 weeks or every 8 weeks. The shots are being developed because it can be difficult to take pills every day, and some people may prefer to have the shots rather than taking pills.

RPV pills (25 mg), RPV shots (600mg and 900mg), CAB pills (30mg), and CAB shots (400mg and 600mg) are now approved by the U.S. Food and Drug Administration (FDA) for adults and adolescents living with HIV. The approvals are based on this study and studies in adults which showed that CAB and RPV were safe and well tolerated. The adult studies also showed that the shots worked well to control HIV. The study drugs are approved by the European Medicines Agency (EMA) for adults. Only the RPV pills (25mg taken once daily) are approved by the EMA for adolescents.

This will be the first study of RPV shots, CAB pills and CAB shots in adolescents. The testing in adults has shown that the study pills and study shots work as well as other ARVs that are approved. So far, the testing in this study has shown that the study pills and study shots also work well for adolescents. However, because these

ARVs are still being tested, there may be some effects that we do not know about yet. More information is needed from this study so that the study drugs can be approved for adolescents in more countries.

This study will test the effects of these ARVs in adolescents. The study will look at whether these ARVs:

- Are being given at the correct dose for adolescents
- Are safe and well-tolerated in adolescents
- Can control HIV in adolescents as well as other ARVs

The study will also look at how willing adolescents are to take these ARVs.

Cohort 1 of this study will be done first to test CAB and RPV pills when taken for about 1 month followed by CAB and RPV shots. Adolescents in Cohort 1 will take either CAB pills followed by CAB shots or RPV pills followed by RPV shots. They will keep taking their usual ARVs (see #4 below for more information).

Some adolescents who took part in Cohort 1 of this study received the study pills for about 1 month followed by 3 study shots given over 2 months. The RPV shots given at that time were 900mg for the first and second shots and then 600mg for the third RPV shot. The CAB shots given at that time were 600mg for the first and second shots and then 400mg for the third CAB shot.

Some adolescents who took part in Cohort 1, the study pills were taken for about 1 month and followed by 2 study shots given 1 month apart. These adolescents only received 2 study shots in Cohort 1. Both RPV study shots were 900mg, while both CAB study shots were 600mg. This is because the testing in adults has shown that fewer study shots can be given with these amounts.

If the results from Cohort 1 show that CAB pills, CAB shots and RPV shots are safe and that the dose is correct, Cohort 2 will start. Cohort 2 will test whether CAB and RPV pills taken together, followed by CAB and RPV shots taken together are safe and can control HIV when adolescents stop taking their previous ARVs. Some adolescents from Cohort 1 may be eligible to also take part in Cohort 2.

More information about the study, Cohort 1, and CAB and RPV is given in the rest of this form.

2. Only adolescents who are eligible can participate in the study.

If you decide to join the study, we will first do some tests to find out if you are eligible. More information about the tests is given in #5 (see below). If you are eligible, you will be entered in the study. If you are not eligible, you cannot be entered in the study.

3. It is your decision whether or not you join the study.

Deciding to join the study is voluntary (your choice). You may choose to join or not join. If you choose to join, you can change your mind and leave the study. Your choices will have no effect on the medical care you would normally receive. Your access to services, and the benefits and rights you normally have, will not be affected.

Take your time and consider your decision carefully. If you wish, you can talk to other people about the study. 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 you to keeping taking ARVs. This is the best known way for you to stay healthy.

4. There are three phases in Cohort 1.

For participants in Cohort 1, there are three phases of the study. All participants will take part in Cohort 1-Phase 1. Only those who are eligible will take part in Cohort 1-Phase 2. Participants who take part in Cohort 1-Phase 2 will also take part in Cohort 1-Phase 3, called the long-term safety follow-up phase.

In Cohort 1-Phase 1, you will keep taking your usual ARVs. You will also take either the CAB or the RPV pills. The type of usual ARVs you take will determine whether you will take CAB or RPV in this study. The pills must be swallowed whole. They cannot be broken or crushed. They should be taken with a meal. This phase lasts for about 4-6 weeks. After the study entry visit (see #8 below), you will have 2 more visits during Phase 1. At these visits, we will check to see how you are doing while taking the pills (see #9 for more information). We will also check to see if you are eligible for Cohort 1-Phase 2.

If you are eligible for Cohort 1-Phase 2, **you will keep taking your usual ARVs**. You will stop taking the CAB or RPV pills and start getting either the CAB or the RPV shots. The study ARV you get in the shot will be the same study ARV you were taking by pill. The shots are long-acting, meaning the medicine stays in the body for a long time. This phase lasts about 12 weeks. You will have 6 visits during this time, and you will get shots at two of these visits. Each shot is about 3mL (about 1 teaspoon). The shots are given in the buttocks (bottom "cheeks"). At each of these two visits, you will be given one shot of CAB or one shot of RPV. At all of the Phase 2 visits, we will check on how you are doing while getting the shots (see #11 for more information).

After Cohort 1-Phase 2, you will stop taking the study drugs and take part in the long-term safety follow-up phase of the study. This phase lasts about 48 weeks. We will check on how you are doing and the amount of study drugs in your blood after stopping the study drugs. You will keep taking your usual ARVs. There will be 3 or 4 visits during long-term follow-up (see #16 for more information).

Finding out if you are eligible for Cohort 1

5. We will ask questions, examine you, and discuss the study requirements with you.

To find out if you are eligible for the study, we will:

- Review your medical records.
- Ask questions about you, your health, and the medications you take.
- Talk with you about birth control (ways to prevent pregnancy).
- Talk with you about the study requirements and if you are able to meet these requirements.
- Do a physical exam. This will include looking at your genitals to see your stage of development. For participants assigned female at birth, this will also include looking at your breasts.
- Do an electrocardiogram (ECG). This is to test how well your heart is working.
- Draw between 11-17mL (about 2-3 teaspoons) of blood for tests. The tests will:
    - Check your blood cells.
    - Check how well your liver and kidneys are working.
    - Confirm that you have HIV. There are certain HIV tests that are required for this study. If the required tests are not in the medical records, we will do the tests that are needed.
    - Check the amount of HIV in your blood. This is called the HIV viral load.

These procedures will take about 4 hours *[here and throughout this form, sites may modify the expected visit duration as needed]*.

6. For participants assigned female at birth, we will also test for pregnancy.

Participants in this study cannot be pregnant. Participants should not join this study if they are pregnant or intend to become pregnant within 30 days after stopping the study ARV pills or within 48 weeks after stopping the study shots. Because the effects of the study ARVs on unborn babies are unknown, you should not become pregnant while in this study. For all participants assigned female at birth in the study, we will collect urine or blood to test for pregnancy.

There are certain effective methods of birth control that participants who are able to become pregnant must use while in this study. These effective methods must be continued for 30 days after stopping the study ARV pills, or for at least 48 weeks after stopping the study ARV shots. Participants who are able to become pregnant, must agree to use these methods in order to take part in the study. We will help make sure you can get effective methods by providing them here in the clinic or offering a referral. At study visits when you will receive study medicines (either the pill or shot), we will need to confirm that you are using effective birth control before giving you the study medicines.

Participants who become pregnant during the study will stop taking the study medicines and enter the long-term safety follow-up phase of the study (see #16 below). **You must continue taking your usual ARVs.** We will contact you to find out the outcome of the pregnancy even if the outcome occurs after leaving the study.

[Sites may modify the following paragraph to include locally appropriate language regarding disclosure of pregnancy results to parents or guardians: As soon as the pregnancy test result is available, we will go over it with you in private, without your parents/guardians present. You must give us permission before we can share these results with your parents/guardians. If the test shows that you are pregnant, we will give you information on where medical care and other services can be received.*]*

If you are pregnant, your doctor may report your pregnancy to the Antiretroviral Pregnancy Registry. The Antiretroviral Pregnancy Registry assists participants and doctors in gauging potential benefits and risks of treatment; however, the registry does not collect any identifying information about you, such as your name, initials, contact information, or date of birth.

7. We will tell you if you are eligible.

We will give you the results of all procedures and explain the results to you. We will tell you about getting care, treatment and any other services you may need. While waiting for the results, it is important for you to keep taking your usual ARVs.

If you are <u>not</u> eligible for the study for any reason, we will tell you this. You <u>will not</u> be entered in the study. You 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 you do not enter the study, we will still use some information collected about you (for example age, sex, and race). We will use this information to look at patterns or common reasons for not entering the study.

If you <u>are</u> eligible for the study, you <u>will</u> be entered into the study.

Entering the study

8. If you are eligible, you will enter the study.

On the day you enter the study we will:

- Review your medical records.
- Talk with you about your ARV use
- Talk with you about preventing pregnancy
- Ask you questions about what you think about CAB or RPV
- Do a physical exam.
- Draw about 18mL (about 4 teaspoons) of blood for tests. The tests will:
  - Check your blood cells.
  - Check how well your liver and kidneys are working.
  - Check how much the virus has affected your ability to fight the virus. This is called CD4 cell count.
  - The tests will check your 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.
- For participants assigned female at birth, we will collect urine or blood for a pregnancy test.
- Ask if you are willing to complete an in-depth phone interview. [*US sites only.*]

At this visit, you will start taking CAB or RPV pills. We will give you the pills and explain how to take them. You will take your first dose at the visit. **You will continue taking your usual ARVs.** This visit will take about 4 hours.

Being in the study

9. After entering the study, you will have two more visits in Cohort 1-Phase 1 (Weeks 2 and 4a).

The first visit in Cohort 1-Phase 1 will be the study entry visit and is described in #8 above. After that visit, you will have 2 more visits in Cohort 1-Phase 1. These visits will be scheduled 2 weeks apart. *[Sites to modify]* Each visit will take about 1-3 hours. At each of these visits, we will:

- Review your medical records.
- Talk with you about your ARV use
- Do a physical exam.
- For participants assigned female at birth, we will also collect urine or blood to test for pregnancy.
- Talk with you about preventing pregnancy.
- Remind you to bring the oral CAB or oral RPV to the study clinic.

At two of these visits (Week 2 and Week 4a), we will draw about 5mL (about 1 teaspoon) of blood for tests. These tests will check your blood cells and how well your liver and kidneys are working.

At the second visit (Week 2), we will also draw about 12mL (about 2-3 teaspoons) blood for tests. This test will check your HIV viral load. Some blood will be saved for later resistance testing.

At the second visit (Week 2), we will also do an intensive pharmacokinetic (PK) test. This is a test to look at the amount of CAB or RPV in your blood. At this visit, we will ask you when you took CAB or RPV in the past three days. [*Sites: modify language as appropriate to align the three prior doses with the timing (morning or evening) of the Week 4b pre-dose PK sample collection.]* For three days before this visit, you must be sure to take CAB or RPV on time and in the morning. <u>This is very important.</u> We will help you remember this before the visit.

If you are taking oral CAB, we will need to draw your blood six times during the visit, one time before and five times after taking CAB. We will also remind you **not** to take CAB before coming to this visit. When you come to the visit, we will draw your blood, then you will take CAB, and then we will draw your blood 5 more times, about

1, 2, 3, 4, and 8 hours later. Each time we will draw 2mL (less than 1 teaspoon), for a total of 12mL (about 3 teaspoons).

If you are taking oral RPV, we will need to draw your blood three times during the visit, before and after taking RPV. We will remind you **not** to take RPV before coming to this visit. When you come to the visit, we will draw your blood, then you will take RPV, and then we will draw your blood 2 more times, about 4, and 8 hours later. Each time we will draw 2mL (less than 1 teaspoon), for a total of 6mL (about 1 teaspoon).

[Sites: modify language as appropriate to indicate procedures for the intensive PK collection. For the intensive PK tests, a small plastic tube will be placed in your arm to draw blood samples. This tube is attached to a plastic needle so that we can draw blood several times. We will not need to stick you with a needle each time. The plastic tube may stay in place for the blood draws.]

[Sites: modify language as appropriate to indicate procedures for intensive PK visit and overnight stays – You may need to stay at the clinic or hospital for up to 8 hours. If the study clinic is able, you may be allowed to stay at the clinic the night before and during your first PK visit.*]*

[Sites to modify] On rare occasions, we may offer some of the visit activities off-site, or by phone. The study staff will discuss the location and best time to visit you so that the visit is at a convenient time and the visit is done at a place you feel comfortable and confidentiality can be maintained.

10. If you are eligible, you will enter Cohort 1-Phase 2 (Week 4b).

At the Week 4b visit, we will determine if you are eligible for Cohort 1-Phase 2. At this visit, we will:

- Review your medical records.
- Talk with you about your ARV use.
- Do a physical exam.
- Ask you questions about your experience with the study drug.
- Talk with you about preventing pregnancy.
- Draw about 12mL (about 2-3 teaspoons) blood for tests. These tests will check your HIV viral load. Some blood will be saved for later resistance testing.
- For participants assigned female at birth, we will also collect urine or blood to test for pregnancy.
- Remind you to bring the oral CAB or oral RPV to the study clinic.
- [*Sites: modify language as appropriate to align the three prior doses with the timing (morning or evening) of the Week 4b pre-dose PK sample collection*. Remind you to take your oral CAB or oral RPV in the morning for the three days before this visit.]

If you are **not** eligible, you will stop taking oral CAB or oral RPV and will complete a final study visit about 4 weeks after your last oral dose (see #15 for more information).

If you are eligible for Cohort 1-Phase 2, you will continue taking your usual ARVs. You will take your last dose of oral CAB or oral RPV at the Week 4b visit. We will also give you the first shot of CAB or the first shot of RPV at the Week 4b visit. We will remind you **not** to take oral CAB or oral RPV before coming to this visit. You will take oral CAB or oral RPV at the study clinic before the first shot of CAB or the first shot of RPV.

At this visit, we will also look closely at the amount of CAB or RPV in your blood. To do this, we will need to draw your blood two times during the visit, before taking oral CAB or RPV and after getting a shot of CAB or RPV. When you come to the visit, we will draw your blood, then you will take your oral CAB or RPV and get a shot of CAB or RPV, and then we will draw your blood again, about two hours later. Each time we will draw 2mL (less than 1 teaspoon), for a total of 4mL (less than 1 teaspoon).

[*Sites to include if combined Week 4a and Week 4b visits are planned.*] This visit may be combined with the previous study visit (Week 4a).

11. You will have 5 visits (Weeks 5-16) in Cohort 1-Phase 2.

The first visit in Cohort 1-Phase 2 will be the Week 4b visit, which is described in #10 above. After that visit, you will have 5 more visits in this phase. These visits will take place 1-4 weeks apart. *[Sites to modify]* Each visit will take about 1-3 hours.

At each of these visits, we will:
- Review your medical records.
- Talk with you about preventing pregnancy.
- Do a physical exam. At the Week 16 visit, this will include looking at your genitals to see your stage of development. For participants assigned female at birth, this will also include looking at your breasts
- Draw about 2mL of blood (less than 1 teaspoon) to look at the amount of CAB or RPV in your blood.

At 3 of these visits (Weeks 5, 8, and 16) we will also draw about 5mL of blood (about 1 teaspoon) to check your blood cells and how well your liver and kidneys are working.

At 2 of these visits (Weeks 8 and 16) we will also draw about 12mL of blood (about 2-3 teaspoons) to check your HIV viral load. Some blood will be saved for later resistance testing.

At 1 of these visits (Week 16), we will also draw about 3mL of blood (less than 1 teaspoon) for tests. These tests will check your blood cells and CD4 count.

At 2 of these visits (Weeks 9 and 16) we will also do an ECG to look at your heart.

At 1 of these visits (Week 8) we will also give you a shot of either CAB or RPV.

At 2 of these visits (Weeks 8 and 16) we will also talk with you about your experience with study ARVs.

For participants assigned female at birth, at 2 of these visits (Weeks 8 and 16) we will also collect urine or blood to test for pregnancy.

12. In-depth phone interview *[for U.S. sites only]*

We are very interested to understand what adolescents think about getting their ARV's as shots. You may be asked if you would like to complete an in-depth phone interview. If you would like to take part in the interview, then you may be contacted to have the interview after getting the first shot of CAB or RPV. Not all participants will be contacted for the interview. You do not have to do the interview to take part in this study.

If contacted, an interviewer will talk to you for about 1-2 hours and will ask how you feel about having shots of CAB or RPV. This information will help us understand if CAB shots and RPV shots have any side effects for adolescents. It will also help us understand how adolescents and families feel about the shots. The interview may take place at or in between the Week 4b, 5, 6, 8, and 12 study visits, or during the long-term follow-up safety phase. The interview will only take place once. The interview will be audio recorded and written down in a report. Your name will not be included in the report.

We may also ask your parent or caregiver to complete an in-depth interview. This interview would ask them how they felt about you having shots of CAB or RPV.

13. We will tell you if you are eligible for Cohort 2.

After your last visit in Cohort 1-Phase 2, we will tell you if are eligible for Cohort 2 or if you need additional tests to see if you qualify for Cohort 2.

If you are not eligible for Cohort 2, or if Cohort 2 is not ready to take participants, you will stop getting shots of CAB or RPV and will enter Cohort 1-Phase 3, also called the long-term safety follow-up phase (see #16 below for more information). We will let you know when Cohort 2 is ready and if you need additional tests to see if you qualify for Cohort 2.

If you are eligible for Cohort 2 and Cohort 2 is ready to take participants, you can enter into Cohort 2.

14. Adolescents may have an extra visit if their HIV is not controlled.

Participants will have viral load tests at almost all visits to check the amount of HIV in the blood. If tests show that the viral load is higher than expected (200 copies/mL or more) you will have repeat testing. This may occur as part of another study visit or may occur as an extra study visit.

The extra visit will take about 1-2 hours. At this visit we will:
- Review your medical records.
- Do a physical exam.
- Draw about 14mL (about 3 teaspoons) of blood for tests. The tests will:
    - Check your HIV viral load.
    - Check the amount of CAB or RPV in the blood.
    - We will save some blood for later resistance testing.
- Talk with you about preventing pregnancy.
- For participants assigned female at birth, we will also collect urine or blood to check for pregnancy.

If the repeat test also shows an increased amount of HIV in your blood, you will stop taking the study product. If you were getting shots of CAB or RPV, you will enter long-term follow-up (more information in #16 below).

15. If you are not eligible to receive shots of CAB or RPV you will stop the study early.

If you are not eligible to get shots of CAB or RPV in Cohort 1-Phase 2, you will stop taking oral CAB or oral RPV and will complete a final study visit about 4 weeks after your last oral dose.

During this visit, we will:
- Review your medical records.
- Do a physical exam. This will include looking at your genitals to see the stage of development. For participants assigned female at birth, this will also include looking at the breasts.
- Draw blood for tests. This would be about 15-20mL of blood (about 3-4 teaspoons) for these tests. These tests will check:
    - Your blood cells.
    - How well your liver and kidneys are working.
    - Your HIV viral load.
    - Some blood will be saved for future resistance testing.
- Talk with you about preventing pregnancy.

- For participants assigned female at birth, we will also collect urine or blood to check for pregnancy.
- Ask you questions about what it is like taking CAB or RPV.
- We will also talk with you about your ARV use.

16. If you stop the shots of CAB or RPV early, or if you are not eligible to enroll in Cohort 2, or if Cohort 2 is not yet ready, you will enter Cohort 1-Phase 3 (long-term safety follow-up phase).

You will enter Cohort 1-Phase 3 (long-term safety follow-up phase) after the last shot of study product, if you:
- Stop the shots of CAB or RPV during Cohort 1-Phase 2 early, or
- Are not eligible to enroll in Cohort 2, or
- If Cohort 2 is not yet ready for participants

If you become pregnant, you will enter this phase of the study after your positive confirmatory pregnancy test result, whether you are taking the pill or the shot.

You will keep taking your usual ARVs. There will be 3 or 4 visits during the long-term safety follow-up phase. These visits will be scheduled 8, 24, 36 and 48 weeks after your last shot of CAB or RPV (or after a positive confirmatory pregnancy test result). *[Sites to modify]* Each of these visits will take about 1-3 hours. At these visits, we will:
- Review your medical records.
- Do a physical exam. At the final long-term follow-up visit, this will include examination of your genitals to see the stage of development. For participants assigned female at birth, this will also include looking at your breasts.
- Talk with you about preventing pregnancy.
- Draw blood for tests. This would be about 19mL of blood (about 4 teaspoons) for these tests. These tests will check:
    - Your blood cells.
    - How well your liver and kidneys are working.
    - Your HIV viral load.
    - The amount of CAB or RPV in the blood.
    - Some blood will also be saved for future resistance testing.
- For participants assigned female at birth, we will also collect urine or blood to check for pregnancy.
- At two of these visits (8 weeks and 48 weeks after your last shot of CAB or RPV) we will talk with you about your ARV use.
- At two of the visits (8 weeks and 48 weeks after your last shot of CAB or RPV), we will also ask you questions about getting shots of CAB or RPV.

For participants who complete the Week 16 visit in Cohort 1-Phase 2, the first long-term follow-up visit will be skipped entirely. The Week 16 visit and the first long-term follow-up visit are very similar and do not need to be conducted twice.

17. Different tests will be done at different laboratories.

We will do most of the tests of blood or urine here at our laboratory. We will give you the results of most of these tests at the next scheduled visit, or sooner, if necessary. We will explain the results and give you counseling and referrals as needed.

We will also draw blood to check the amount of CAB or RPV in your blood. This is called a pharmacokinetic (PK) test. The PK test will be done at a laboratory in the United States. We will not usually give you the results of this PK test during the study.

If you need a test for resistance (see #14 above), that test will be done at a laboratory in the United States. You will be given the results of this resistance test and referrals if needed.

18. We may take you off of the study.

We may take you off the study ARVs if:

- You are not able to come to the study visits or we determine that you cannot meet the study requirements.
- You are not able to take the study ARVs.
- The study ARVs are not controlling the HIV in your blood.
- Continuing the study ARVs may be harmful to you.
- You request to stop the study ARVs.
- You are not able to follow the birth control requirements of this study.
- You become pregnant.

If you stop the oral study ARVs early, we will ask you to come back to the clinic about four weeks after you stop the oral study ARVs (see #15 above). You will not have any other visits after this.

If you stop the ARV shots early, we will ask you to come back to the clinic for four additional study visits for long-term safety follow-up (see #16 above). You will not have any other visits after these four visits.

We may also take you off the study early if the study is stopped for any reason.

The study cannot provide other types of ARVs, but we will give you information, counseling, and referrals to where you can get care and treatment needed. We will help make sure you can get ARVs from outside of the study. If the study stops early, every effort will be made to make certain that there is no interruption in your therapy.

19. Please tell us if you want to leave the study.

You are free to leave the study at any time for any reason. The care that you receive at this clinic will not be affected, but it is important for us to know about your decision.

If you stop the study ARVs, we may ask you to return to the study clinic for additional study visits described in #15 and #16 above. If you stop the study early, we may ask you to return to the study clinic for one final study visit, like the last study visit described in #16 above.

We will answer any questions you may have and give you information on how to contact us in the future, if you wish.

Risks of the study

Taking part in this study may involve some risks and discomfort. The risks are different for each phase of the study. Cohort 1-Phase 1 risks include: risks from blood draws, risk from the study pills (CAB or RPV), and risks to your privacy.

Cohort 1-Phase 2 risks include: risks from blood draws, risks from receiving the injection, risks from the study pills (CAB or RPV) and the study shots (long-acting CAB or RPV) and risks to your privacy.

Cohort 1-Phase 3 risks include: risks from blood draws, and risks to your privacy.

20. Risk from blood draws

Drawing blood can cause pain, swelling, bruising, or bleeding where the needle is inserted. Rarely, drawing blood can cause fainting or infection.

21. Risk from receiving the injection

People in other studies who have received the CAB and RPV shots said they had pain, skin irritation, skin redness, bumps, swelling, itching, bruising at the spot where they got the shot. Most reactions go away in a week or less but sometimes they can last longer. Most people usually do well with them and rarely need to stop the drug.

The shots will be given in the muscles of your buttocks. The injection could be given too deeply or not deeply enough, missing the muscle and entering your skin, blood, or a nerve.

The risks of this are not well understood but could make CAB or RPV levels too low or too high. If too low the drug may not work against your HIV. If RPV is too high, there could be a change in your heartbeat, which in severe cases can be life-threatening. In rare cases, symptoms such as feeling lightheaded, numbness or tingling, difficulty breathing, chest or stomach discomfort, sweating, rash, pain (e.g., back and chest), nausea and/or feeling anxious have occurred after an injection with RPV LA. In these cases, high blood levels of RPV have been observed, which may be due to an accidental injection of part of the medication into a blood vessel instead of the muscle. Not all participants in whom an accidental injection in a blood vessel was suspected reported such symptoms. Most of the symptoms resolved within minutes. Your doctor may need to administer treatment to help resolve these symptoms. Everything possible will be done to decrease this risk, including watching you for problems during the study. If your doctor thinks that the injection was not given the right way, you might be asked to stay in the clinic up to 3 hours after the injection to watch how you are doing and extra tests may be needed to be sure you are safe. We will also draw blood (less than 1 teaspoon) about 2 hours after the study shot to look at the amount of study drugs in your blood. If you are worried about this risk, talk to your doctor.

Receiving injections can cause some people to feel lightheaded or feel like they might pass out. Fainting can also occur. This reaction, called a 'vasovagal reaction', has been reported with other injectable medicines, and resolves quickly.

22. There are risks from the study ARVs

All ARVs can cause side effects. This includes the ARVs you are currently taking and the ARVs that are given in the study. Some side effects are minor; others can be severe. Some side effects are common; others are rare. Some people who take ARVs have some of the side effects. Other people have different side effects, or no side effects.

The most common and most serious side effects of the study ARVs, CAB and RPV, are listed below. This is based on what we know now about CAB and RPV used in adults. There may be other side effects that we do not know about now. This may be especially true for adolescents, because this is the first study of CAB and RPV in adolescents.

This form does not list all possible side effects of all ARVs. If you join the study, we will tell you more about the ARVs you will be taking. At each study visit, we will check on whether the ARVs 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.

23. Some side effects from the CAB pills and the CAB

Many people have received CAB pills or the CAB shot in other studies. The table below lists side effects from other studies of CAB with people who have HIV. It is not known if CAB, other drugs or the participant's other health problems caused or affected these. Some of these are the same side effects as RPV (see #24 below).

Common and Uncommon Side Effects of CAB

Very Common Side Effects of CAB	Common Side Effects of CAB	Uncommon Side Effects of CAB
• Headache • Pyrexia (fever), feeling hot, body temperature increase • Injection Site Reactions (pain and discomfort, a hardened mass or lump)	• 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 • Injection Site Reactions (swelling, redness, itching, bruising, warmth or discoloration)	• Somnolence (sleepiness or Drowsiness) • Vasovagal reactions (light-headedness or fainting, during or following an injection) • Hepatotoxicity (liver problems) • Transaminase increase (blood test may show increase in the level of liver enzymes) • Injection Site Reactions (cellulitis [heat, swelling or redness], abscess [collection of pus], numbness, minor bleeding, discoloration)

The following effects have also been seen in some of the people who received CAB pills or the CAB shot in other studies:

Abnormal liver tests:

A small number of people across all studies (just over 1% of 1644 participants as of April 2017) 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 liver will be done during the study. Your study doctor will tell you if you need to stop taking the study drugs or if other actions are needed. If you stop taking the study drug, you may be able to re-start the study drug or you may need to change your usual 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 about them.

In other studies, two people without HIV had a history of seizures (epilepsy), and had a seizure about 3 months and 9 months after starting CAB. One other person with HIV but without a history of seizures, had seizures about one year after starting CAB. This participant had a long period of seizures without medical treatment and died. It is not known if CAB was part of the reason for seizures in these people. If you have a history of seizures, please let your study doctor know.

24. Some side effects from the RPV pills and the RPV shot

Oral RPV (Edurant) is a marketed drug which many people throughout the world have received to manage HIV. We know more about the side effects of Edurant than we do about CAB or RPV shots. The following side effects have been seen in studies in people with HIV taking RPV.

Common and Uncommon Side Effects of RPV

Common Side Effects of RPV	Uncommon Side Effects of RPV
• Dry mouth • Feeling less hungry (decreased appetite) • Sleep disorders	• 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 • Abdominal discomfort (belly ache)

The following effects have also been seen in some people who received RPV in other studies:

Abnormal blood tests:

Other changes in blood tests have also 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, like the liver, and cause liver problems which can lead to liver failure. Contact your study doctor right away if you have 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*

Blood tests to check the health of your liver will be done regularly during the study. Your study doctor will tell you if you need to stop taking the study drugs or if other action is needed. If you stop taking the study drug, you may be able to re-start the study drug or you may need to change your usual ARVs.

Skin Rash:

Most rashes were mild or moderate, and happened within the first 4 weeks of taking RPV. Most of 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 you, you will need to come for extra study visits to monitor your health. Some people with rash may also have other signs and symptoms of allergic reaction.

If you have any type of rash or other skin problems during the study you must tell your study doctor right away, and the doctor may tell you to stop taking CAB and/or RPV.

25. There may be other possible risks from the study ARVs.

The study ARV shots stay in your body for a long time

The shots you get in this study are long acting, meaning they stay in your body for a long time. In most people the drugs will no longer be in the body one year after an injection, while in some people low levels of CAB and RPV may still be in the body after one year. If you develop a side effect to the study drug after the shot, there will be no way to remove the drug from your body. If you get a shot of CAB or RPV, we will monitor your health for 48 weeks after your last shot. If you develop a symptom from these drugs while the drugs are still in your body, every effort will be made to treat the side effects. The amount of drug will decrease overtime and will eventually disappear.

While the amount of study drugs in your body decrease slowly over time after you stop getting shots, the study drugs could stop working against your HIV. When stopping long acting HIV drugs, it will be very important to start taking other HIV medications, as your study doctor tells you, so your HIV medications do not stop working against your HIV.

Risk of resistance

All ARVs can cause some resistance if not taken correctly. Resistance means that the ARVs may not work against HIV if these ARVs are taken again in the future. To stop resistance, it is important that you take and/or receive the ARVs as instructed, and do not miss any doses.

Effects on other ARVs

We do not expect the study ARVs to change the way other ARVs work in the body. For example, if you were to join the study, we would expect the ARVs you are currently taking to keep working to control the amount of HIV in your body. We also do not expect the study ARVs to cause more or worse side effects from other ARVs. However, this study is being done to learn more about these kinds of possible effects.

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 called integrase inhibitors [INIs] for HIV like CAB, have had suicidal thoughts and actions, particularly participants with a prior history of depression or mental health illness.

Tell the study doctor if you have a history of mental health illness. If you have thoughts of hurting or killing yourself or have any other unusual or uncomfortable thoughts or feelings during this study, you should tell the study doctor or go to the nearest hospital right away.

Possible effects on pregnancy or unborn babies

HIV and ARVs may lead to some pregnancy complications, like early delivery or low weight of the baby at birth. We do not know if some ARVs are more likely to cause these effects than others. We do not yet know if CAB is safe in pregnancy. RPV does not appear to be a risk to pregnancy and the developing baby based on the information we know now, but additional data are still being collected.

There are few data from humans on the effects of CAB in pregnancy. Most of the information we have comes from animal studies. In studies done in pregnant rats and their newborns, using very high amounts of CAB, there were more baby rats that died when they were born or right after they were born. This did not happen to the baby rats when the mother got lower amounts of the drug, or no drug. The amount of CAB that we are giving in this study is expected to be more than 7-times lower than the amount given to the pregnant rats. Birth defects have not been found in any animal studies of CAB so far. We do not know whether what happened to the baby rats has any impact on what will happen in pregnant humans taking this drug.

Early results from one large study in Botswana showed that the ARV called dolutegravir (DTG) may increase the risk of serious birth defects of the brain or spine in the new baby. The increased risk was seen among babies whose mothers were taking DTG when they became pregnant. These birth defects happen during the first few weeks of pregnancy, before mothers may know they are pregnant. These birth defects have not been seen among babies whose mothers started taking DTG later in pregnancy.

CAB is not the same drug as DTG. We do know that CAB and DTG belong to the same class of medications and work in a similar way to treat HIV infection. We do not know if CAB can cause brain or spine defects in babies.

Participants who are able to become pregnant must agree to use certain effective methods of birth control to be in this study (see #6 above). If you become pregnant during the study, please let us know right away.

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 but can also occur later. Some of these symptoms may be life threatening. If you start having new symptoms, or if you notice that any existing symptoms are getting worse after starting the ARVs, tell your doctor immediately.

Abnormal placement of body fat and wasting

The use of potent antiretroviral drug combinations may be associated with an abnormal placement of body fat and wasting. Some of the body changes include:

- Increase in fat around the waist and stomach area
- Increase in fat on the back of the neck
- Thinning of the face, legs, and arms
- Breast enlargement

26. There could be risks of disclosure of your information.

We will make every effort to keep your information private and confidential. Study records and specimens will be kept in secure, locked locations. All specimens and most records will be labeled only with a code number. However, your name will be written on some records.

Despite our best efforts to keep your information private, it is possible that the information could be obtained by someone who should not have it. If this were to happen, you could be treated badly or unfairly. You could feel stress or embarrassment.

To help us protect your privacy, we have obtained a Certificate of Confidentiality that protects us from 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 US federal government or from the US Food and Drug Administration. Regardless of the certificate, you can release information about your participation in the study to others, if you wish.

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 or adolescents 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 you may be used, but your name will not be shared.

Benefits of the study

27. There may be a direct benefit to you from being in the study.

By joining the study, you will be part of the search for ARVs that may be better for adolescents. We do not know if being in the study will benefit you in any way. There may be a direct benefit to you by taking part in this study, but no guarantee can be made. For example, you may gain a better understanding of your health and HIV care. Another possible benefit is early access to the Cohort 2 part of the study, if you qualify. There may also be benefit if the results from this study lead to a safe and effective dose of the study drugs for adolescents. It is also possible that you may receive no direct benefit from this study. Information learned from this study may help other adolescents who have HIV.

You will have regular visits here and frequent checks on your health, including tests for amount of HIV in your blood, called viral load. It is possible that the study ARVs will slow your HIV infection. Information learned from this study may help other adolescents with HIV.

Other information about the study

28. There are no costs from being in the study.

There are no costs to you for study visits, CAB, RPV or procedures.

[Insert information about compensation/reimbursement here, e.g., You will be reimbursed for the cost of transport to study visits. For each visit, you will be given (specify amount).*]*

29. Study records may be reviewed by study staff and groups that oversee the study.

Groups that oversee the study include:
- *[insert name of site IRB/EC]*
- *[insert name of site drug regulatory authority]*
- *[insert name of other site 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
- ViiV Healthcare (the company that makes CAB)
- Janssen Pharmaceuticals (the company that makes RPV)

The study staff and these groups are required 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 personally.

A description of this study will be available on ClinicalTrials.gov as required by U.S. law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

Your study information may be given to other authorities if required by law. *[Sites add more specific detail here as needed; example follows:]* For example, we are required to report any significant risk of harm to you or others.

30. If you get sick or injured, contact us immediately.

Your health is important to us. We will make every effort to protect your well-being and minimize risks. It is possible, however, that you could have an illness or injury that is study-related. This means that the illness or injury occurred as a direct result of the study procedures.

[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 treatment. The cost for this treatment may be charged to you or your insurance company. There is no program for compensation either through *[site name or]* the U.S. National Institutes of Health.

Whom to contact

31. If you have questions, concerns, or problems at any time, use these contacts.

- If you have questions about the study:
  [insert name and telephone number of investigator or other study staff]

- If you have questions about your rights as research participants or concerns about how you are being treated in the study:
  [insert name and telephone number of IRB/EC contact person or other appropriate person/organization]

- If you have any health or other problems that may be related to study participation:
  [insert name and telephone number of investigator or other study staff]

- If you want to leave the study:
  [insert name and telephone number of investigator or other study staff]

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.

If you decide to join, we will tell you any new information from this study or other studies that may affect your willingness to stay in the study. You are welcome to ask questions or request more information at any time. If you want the results from this study, please tell the study staff.

You do not give up any rights by signing this form.
[Insert signature blocks as required by site IRB/EC policies.]

Signature blocks for participants of legal age to provide independent informed consent

_____	_____
Participant's Name (print)	Participant's Signature and Date
_____	_____
Study Staff Conducting Consent Discussion (print)	Study Staff Signature and Date
_____	_____
Witness's Name (print) (As appropriate)	Witness's Signature and Date

Signature blocks for parent/legal guardian of adolescent:

_____	_____
Name of Parent/Legal Guardian (print)	Signature of Parent/Legal Guardian and Date
_____	_____
Study Staff Conducting Consent Discussion (print)	Study Staff Signature and Date
_____	_____
Witness's Name (print) (As appropriate)	Witness's Signature and Date

Appendix II-B: Sample Informed Consent Form for Participation in Cohort 2A

for adolescents who can provide independent informed consent for study participation and parents/legal guardians of adolescents

IMPAACT 2017
Phase I/II Study of the Safety, Acceptability, Tolerability, and Pharmacokinetics of Oral and Long-Acting Injectable Cabotegravir and Long-Acting Injectable Rilpivirine in Virologically Suppressed HIV-Infected Children and Adolescents

Version 4.0, dated 27 May 2022

[Throughout this form sites may modify to remove mentions of HIV and ARVs for participants who do not know their status].

If you are the parent or legal guardian of a child who may take part in this study, your permission and the permission of your child will be needed. When "you" appears in this form, it refers to your child except where it says otherwise.

Introduction

You are being asked to take part in the research study named above.

This form gives information about 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 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 medicines (ARVs), Cabotegravir (CAB) and Rilpivirine (RPV), taken as pills and given as long-acting shots in adolescents 12 to less than 18 years of age.
- Some of the study drugs are already approved in some countries for use in adolescents or adults, but more data is needed for use in adolescents.
- There are two parts to this study, Cohort 1 and Cohort 2. The Cohort 2 part to this study also has two groups: Cohort 2A and Cohort 2B. **This form is about Cohort 2A**.
- Adolescents in Cohort 2 will switch from their usual ARVs to the study medicine and will be in this part of the study for at least 2 years up to 3 years.
- In Cohort 2, you will have the option to either take the study pills and then get the study shots (this is called Cohort 2A) or skip the study pills and only get the study shots (this is called Cohort 2B).
- After entering the study, adolescents in Cohort 2A will stop taking their usual ARVs and start taking daily CAB and RPV *pills* for 4 to 6 weeks. Adolescents will then switch to CAB and RPV *shots* every 8 weeks for about 2 years.
- Adolescents in Cohort 2B will stop taking their usual ARVs and start CAB and RPV *shots* every 8 weeks for about 2 years.
- We will discuss Cohort 2A and Cohort 2B with you and together make a decision that is best for you.
- After the 2 years of getting the CAB and RPV shots, all Cohort 2 adolescents might be able to continue getting the same CAB and RPV shots outside of the study. We will explain the options to you and help ensure your access to ARVs outside the study.

- Adolescents 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, adolescents will not take any study medicine (shots or pills) but will take ARVs.
- While in the study, adolescents will have clinic visits with physical examinations and blood draws for laboratory tests. Some visits will include a review of adolescents' medical records and ECG tests to look at the adolescent's heart. Participants assigned female at birth will also be tested for pregnancy.
- If interested, participants in the U.S. may be eligible to do one in-depth phone interview where they will talk about their experience getting their ARVs as shots.
- There are some possible risks for adolescents in the study. One possible risk is that the pills or shots being tested could cause side effects. The most severe side effects include allergic reaction, liver problems, and mental health problems. These side effects are uncommon.
- There are some possible benefits for adolescents in the study. One possible benefit is not taking daily pills while getting the CAB and RPV shots. Another possible benefit is that the shots being tested will be better for your health and HIV care than the usual ARV pills.
- Your decision on your participation in the study will have no effect on the medical care you receive at this clinic. Your access to services, and the benefits and rights you normally have, will not be affected. You may choose to leave the study at any time.

More information is given in this form about the study, its risks and benefits. You should feel that you understand the study before deciding whether you will participate. If you decide to 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

This study is being done by the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) and *[insert site name]*. The person in charge of the study at *[insert site name]* is *[insert name of IoR]*.

The study is being done to test two anti-HIV medicines (antiretrovirals or ARVs) in adolescents 12 to less than 18 years old who have HIV. The study ARVs are called cabotegravir (CAB) and rilpivirine (RPV). HIV is the virus that can lead to AIDS.

The study will include up to 155 adolescents from the United States, Botswana, South Africa, Thailand and Uganda. There will be two groups of adolescents, called Cohort 1 and Cohort 2. This form is about Cohort 2. Participants in Cohort 2 will be in the study for 2 to 3 years. In Cohort 2, participants will get study product for 92 or 96 weeks (about 2 years). After this time, participants will leave the study and may continue getting the study medicines outside of the study. If you stop getting the study shots early, you will enter long-term safety follow-up and continue having study visits for an additional 48 weeks (about 1 year).

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 adolescents.

People living with HIV usually take a combination of ARVs daily to stay healthy. There are not as many ARVs available for adolescents as for adults because many ARVs have not yet been tested in adolescents. ARVs can be made in different forms, such as liquids, pills, and injections (shots). The study will test CAB and RPV when taken as pills and when given as shots in adolescents. The pills are taken every day. The shots can be given every 4 weeks or every 8 weeks. The shots are being developed because it can be difficult to take pills every day, and some people may prefer to have the shots rather than taking pills.

RPV pills (25 mg), RPV shots (600mg and 900mg), CAB pills (30mg), and CAB shots (400mg and 600mg) are now approved by the U.S. Food and Drug Administration (FDA) for adults and adolescents living with HIV. The approvals are based on this study and studies in adults which showed that CAB and RPV were safe and well tolerated. The adult studies also showed that the shots worked well to control HIV. The study drugs are approved by the European Medicines Agency (EMA) for adults. Only the RPV pills (25mg taken once daily) are approved by the EMA for adolescents.

This will be the first study of RPV shots, CAB pills and CAB shots in adolescents. The testing in adults has shown that the study pills and study shots work as well as other ARVs that are approved. So far, the testing in this study has shown that the study pills and study shots also work well for adolescents. However, because these ARVs are still being tested, there may be some effects that we do not know about yet. More information is needed from this study so that the study drugs can be approved for adolescents in more countries.

This study will test the effects of these ARVs in adolescents. The study will look at whether these ARVs:

- Are being given at the correct dose for adolescents
- Are safe and well-tolerated in adolescents
- Can control HIV in adolescents as well as other ARVs

The study will also look at how willing adolescents are to take these ARVs.

Cohort 1 of this study was done first to test CAB and RPV pills when taken for about 1 month followed by 2 or 3 CAB and RPV shots when taken 1 month apart. Cohort 2 is now being done to test CAB and RPV when taken together. There are two groups within Cohort 2:

- Adolescents in the **Cohort 2A** group will take CAB and RPV pills together for about 1 month, followed by getting the CAB and RPV shots together.
- Adolescents in the **Cohort 2B** group will only get the CAB and RPV shots. This group will not take the CAB and RPV pills.

Both CAB and RPV shots will be given together about every 8 weeks for up to two years. Each time the shots are given, the RPV shot will be 900mg and the CAB shot will be 600mg. Cohort 2 will look at whether these study ARVs are safe and can control HIV when adolescents stop taking their previous ARVs.

We will discuss both Cohort 2A and Cohort 2B groups with you to make the decision of which group you will enter. If you decide to participate in the study, your signature or mark on this form will also document the decision of which Cohort 2 group. You can ask any questions about the groups at any time. You will not be able to switch to the other group after they have entered the study.

More information about the study, the Cohort 2A group, and CAB and RPV is given in the rest of this form.

2. Only adolescents who are eligible can participate in the study.

If you decide to join the study, we will first do some tests to find out if you are eligible. More information about the tests is given in #5 (see below). If you are eligible, you will be entered in the study. If you are not eligible, you cannot be entered in the study.

3. It is your decision whether or not you join the study.

Deciding to join the study is voluntary (your choice). You may choose to join or not join. If you choose to join, you can change your mind and leave the study. Your choices will have no effect on the medical care you would normally receive. Your access to services, and the benefits and rights you normally have, will not be affected.

Take your time and consider your decision carefully. If you wish, you can talk to other people about the study. 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 you to keeping taking ARVs. This is the best known way for you to stay healthy.

4. There are three phases in Cohort 2: the study pills, the study shots, and the long-term safety follow-up.

For participants in Cohort 2, there are three phases of the study:

- The CAB and RPV pills
- The CAB and RPV shots
- The long-term safety follow-up phase with no study medicines

Not all participants will be in all three phases of the study. Participants in the Cohort 2A group will first take part in the CAB and RPV pills and then take part in the CAB and RPV shots phases of the study. In Cohort 2B, participants will also stop taking their usual ARVs but will skip the CAB and RPV pills phase and go straight to the CAB and RPV shots phase of the study.

Any participant who takes part in the CAB and RPV shot phase but must stop the study shots early will take part in the long-term safety follow-up phase.

In Cohort 2A, you will stop taking your usual ARVs and take CAB and RPV pills. The pills must be swallowed whole. They cannot be broken or crushed. They should be taken with a meal. This phase lasts for about 4-6 weeks. After the study entry visit (see #8 below), you will have 2 more visits during this phase. At these visits, we will check to see how you are doing while taking the pills (see #9 for more information). We will also check to see if you are eligible to get the CAB and RPV shots. If you are eligible then, you will stop taking the CAB and the RPV pills and start getting CAB and RPV shots.

For both Cohort 2A and Cohort 2B participants, the study shots phase lasts 2-3 years. You will have 15 visits over about two years. At 13 of these visits you will be given one shot of CAB and one shot of RPV. Each shot is about 3mL (about 1 teaspoon). The shots are given in the buttocks (bottom "cheeks"). The shots may be given on the same side of the buttocks or on different sides. The shots are long-acting, meaning the medicine stays in your body for a long time. The first two visits with the CAB and RPV shots are 4 weeks apart. Then the CAB and RPV shots are given every 8 weeks. At all of these study visits, we will check on how you are doing while getting the shots (see #11 for more information).

After the CAB and RPV shots, you might have the option to continue getting the long-acting injections outside of the study (see #19 for more information).

If you no longer want to get the injections, or have to stop the study shots early, you will stop taking the study drugs and take part in the long-term safety follow-up phase of the study. This phase lasts about 48 weeks. We will check on how you are doing and the amount of study drugs in your blood after stopping the study drugs. You will also go back to taking your usual (pre-study) ARVs. There will be 4 visits during long-term follow up (see #15 for more information).

Finding out if you are eligible for Cohort 2

5. We will ask questions, examine you, and discuss the study requirements with you.

To find out if you are eligible for the study, we will:

- Review your medical records.
- Ask questions about you, your health, and the medications you take.
- Talk with you about birth control (ways to prevent pregnancy).
- Talk with you about the study requirements and if you are able to meet these requirements.
- Talk with you about which group is best for you to join (Cohort 2A or Cohort 2B)
- Do a physical exam. This will include looking at your genitals to see your stage of development. For participants assigned female at birth, this will also include looking at your breasts.
- Do an electrocardiogram (ECG). This is to test how well your heart is working.
- Draw about 11-17mL (about 2-3 teaspoons) of blood for tests. The tests will:
    - Check your blood cells.
    - Check how well your liver and kidneys are working.
    - Confirm that you have HIV. There are certain HIV tests that are required for this study. If the required tests are not in the medical records, we will do the tests that are needed.
    - Check the amount of HIV in your blood. This is called your HIV viral load.

These procedures will take about 4 hours *[here and throughout this form, sites may modify the expected visit duration as needed]*.

6. For participants assigned female at birth, we will also test for pregnancy.

Participants in this study cannot be pregnant. Participants should not join this study if they are pregnant or intend to become pregnant within 30 days after stopping the study ARV pills or within 48 weeks after stopping the study shots. Because the effects of the study ARVs on unborn babies are unknown, you should not become pregnant while in this study. For all participants assigned female at birth in the study, we will collect urine or blood to test for pregnancy.

There are certain effective methods of birth control that participants who are able to become pregnant must use while in this study. These effective methods must be continued for 30 days after stopping the study ARV pills, or for at least 48 weeks after stopping the study ARV shots. Participants who are able to become pregnant, must agree to use these methods in order to take part in the study. We will help make sure you can get effective methods by providing them here in the clinic or offering a referral. At study visits when you will receive study medicines (either the pill or shot), we will need to confirm that you are using effective birth control before giving you the study medicines.

Participants who become pregnant during the study will stop taking the study medicines and enter the long-term safety follow-up phase of the study (see #15 below). **They must continue taking their usual ARVs.** We will also contact you to find out the outcome of the pregnancy even if the outcome occurs after leaving the study.

[Sites may modify the following paragraph to include locally appropriate language regarding disclosure of pregnancy results to parents or guardians: As soon as the pregnancy test result is available, we will go over it with you in private, without your parents/guardians present. You must give us permission before we can share these results with your parents/guardians. If the test shows that you are pregnant, we will give you information on where medical care and other services can be received.*]*

If you are pregnant, your doctor may report your pregnancy to the Antiretroviral Pregnancy Registry. The Antiretroviral Pregnancy Registry assists participants and doctors in gauging potential benefits and risks of treatment; however, the registry does not collect any identifying information about you, such as your name, initials, contact information, or date of birth.

7. We will tell you if you are eligible.

We will give you the results of all procedures and explain the results to you. We will tell you about getting care, treatment and any other services you may need. While waiting for the results, it is important for you to keep taking your usual ARVs.

If you are not eligible for the study for any reason, we will tell you this. You will not be entered in the study. You 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 you do not enter the study, we will still use some information collected about you (for example age, sex, and race). We will use this information to look at patterns or common reasons for not entering the study.

If you are eligible for the study, you will be entered into the study.

Entering the study

8. If you are eligible, you will enter the study

On the day you enter the study we will:

- Review your medical records.
- Talk with you about your ARV use.
- Talk with you about preventing pregnancy.
- Talk with you about the study visit schedule and taking the study medicines correctly
- Ask you questions about what you think about CAB and RPV
- Do a physical exam.
- Draw about 18mL (about 4 teaspoons) of blood for tests. The tests will:
  - Check your blood cells.
  - Check how well your liver and kidneys are working.
  - Check how much the virus has affected your ability to fight the virus. This is called CD4 cell count.
  - The tests will check your 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.
- For participants assigned female at birth, we will collect urine or blood for a pregnancy test
- Ask if you are willing to complete an in-depth phone interview. [*US sites only.*]

At this visit we will again talk with you about which group is best for you to join (Cohort 2A or Cohort 2B). You will not be able to switch to the other group after you have entered the study.

If it is decided that you will enter Cohort 2A, then at this visit, you will stop taking your usual ARVs and start taking CAB and RPV pills. We will give you the pills and explain how to take them. You will take your first dose at the visit.

This visit will take about 4 hours.

Being in the study

9. After entering the study in the Cohort 2A group, you will have two more visits in the study pills phase (Weeks 2 and 4a).

The first visit in Cohort 2A will be the study entry visit and is described in #8 above. After that visit, you will have 2 more visits in the study pill phase. These visits will be scheduled 2 weeks apart. *[Sites to modify]* Each visit will take about 1-3 hours. At each of these visits, we will:

- Review your medical records.
- Talk with you about your ARV use
- Do a physical exam.
- Talk with you about preventing pregnancy.
- For participants assigned female at birth, we will collect urine or blood to test for pregnancy.
- Remind you to bring the oral CAB and oral RPV to the study clinic.

At two of these visits (Week 2 and Week 4a), we will draw about 5mL (about 1 teaspoon) of blood for tests. These tests will check your blood cells and how well your liver and kidneys are working.

At the second visit (Week 2), we will draw about 12mL (about 2-3 teaspoons) blood for tests. This test will check your HIV viral load. Some blood will be saved for later resistance testing.

At the Week 2 visit we will also test the amount of CAB and RPV in your blood. This is called a pharmacokinetic (PK) test. At this visit, we will ask you when you took CAB or RPV in the past three days. [*Sites: modify language as appropriate to align the three prior doses with the timing (morning or evening) of the Week 4b pre-dose PK sample collection.]* For three days before this visit, you must be sure to take CAB and RPV on time and in the morning. <u>This is very important.</u> We will help you remember this before the visit.

We will need to draw your blood two times during the Week 2 visit, before and after taking CAB and RPV. We will remind you to **not** to take CAB or RPV before coming to this visit. When you come to the visit, we will draw your blood, then you will take CAB and RPV, and then we will draw your blood again, about three hours later. Each time we will draw 4mL (less than 1 teaspoon), for a total of 8mL (about 2 teaspoons).

Study staff will let you know when these procedures will occur ahead of time.

[Sites to modify] On rare occasions, we may offer some of the visit activities off-site, or by phone. The study staff will discuss the location and best time to visit you so that the visit is at a convenient time and the visit is done at a place you feel comfortable and confidentiality can be maintained.

10. If you are eligible, you will enter the study shots phase (Week 4b).

At the Week 4b visit, we will determine if you are eligible to get the CAB and RPV study shots. At this visit we will:

- Review your medical records.
- Talk with you about your ARV use.
- Do a physical exam.
- Ask you questions about your experience with the study drugs.
- Talk with you about preventing pregnancy.
- Draw about 12mL (about 2-3 teaspoons) blood for tests. These tests will check your HIV viral load. Some blood will be saved for later resistance testing.

- Do an electrocardiogram (ECG). This is to test how well your heart is working.
- For participants assigned female at birth, we will also collect urine or blood to test for pregnancy.
- Remind you to bring the oral CAB and oral RPV to the study clinic.
- [*Sites: modify language as appropriate to align the three prior doses with the timing (morning or evening) of the Week 4b pre-dose PK sample collection*. Remind you to take the oral CAB and oral RPV in the morning for the three days before this visit.]

If you are not eligible, you will stop taking oral CAB and oral RPV and will start taking your previous ARVs again. If you did not participate in Cohort 1, you will complete a final study visit about 4 weeks after your last oral CAB and RPV dose (see #14 for more information). If you received shots of CAB or RPV before in Cohort 1 but are not eligible to get the shots of CAB and RPV in Cohort 2, you will stop taking the study pills and will take part in the long-term safety follow-up phase (see #15 below).

If you are eligible, you will take your last dose of oral CAB and oral RPV at the Week 4b visit. At this visit, we will also give you the first shot of CAB and the first shot of RPV. We will remind you **not** to take oral CAB and RPV before coming to this visit. You will take oral CAB and RPV at the study clinic before the first shot of CAB and the first shot of RPV.

At this visit, we will also look closely at the amount of CAB and RPV in your blood. To do this, we will need to draw your blood two times during the visit, before taking oral CAB and RPV and after getting the CAB and RPV shots. When you come to the visit, we will draw your blood, then you will take oral CAB and RPV and get CAB and RPV shots, and then we will draw your blood again, about two hours later. Each time we will draw 4mL (less than 1 teaspoon) for a total of 8mL (about 2 teaspoons). At this visit, about 2 hours after you get a shot of CAB and a shot of RPV, we will also do an ECG to look at your heart.

[*Sites to include if combined Week 4a and Week 4b visits are planned.*] This visit may be combined with the previous study visit (Week 4a).

11. You will have 14 more visits (Weeks 5-96) in the study shots phase.

The first visit in the study shots phase will be the Week 4b visit, which is described in #10 above. After that visit, you will have 14 more visits in this phase. Most of these visits will take place about 8 weeks apart, and some of these visits will take place 1 week apart. *[Sites to modify]* Each visit will take about 1-3 hours. At each of these visits, we will:
- Review your medical records.
- Talk with you about preventing pregnancy.
- Do a physical exam. At two of these visits (Weeks 24 and 96), this exam will include examination of your genitals to see the stage of development. For participants assigned female at birth, this will also include looking at the breasts.

At 12 of these visits (Weeks 8-24 and 32-96) you will:
- Get a shot of CAB and a shot of RPV.
- For participants assigned female at birth, we will also collect urine or blood to check for pregnancy.

At 13 of these visits (Weeks 5, 8-24, and 32-96) we will draw about 5mL of blood (about 1 teaspoon) for tests. These tests will check:
- Your blood cells
- How well your liver and kidneys are working

At 9 of these visits (Weeks 8-24, 32-48, 64, 80, and 96) we will draw about 12mL of blood (about 2-3 teaspoons) for tests. These tests will check:

- Your HIV viral load.
- Some blood will be saved for later resistance testing.

At 12 of these visits (Weeks 5, 8-48, 64, 80, 88, and 96), we will also draw about 4mL of blood (less than 1 teaspoon) of blood to look at the amount of CAB and RPV in the blood.

At 4 of these visits (Weeks 24, 48, 72 and 96) we will draw about 3mL of blood (about 1 teaspoon) to check your CD4 count.

At 4 of these visits (Weeks 8, 24, 48, and 96) we will ask you questions about getting the shots of CAB and RPV.

At 5 of these visits (Weeks 8, 24, 48, 72, and 96) we may also talk with you about how you are doing with the visit schedule.

Study staff may ask you to return to the clinic for a study shot before your next visit. If so, then many of the procedures described above would also be done again.

If you cannot come to the clinic to receive the CAB and RPV shots, then you may have the option to take the CAB and RPV pills until you are able to get the shots again. If this happens, you may need more frequent CAB and RPV shots outside of the scheduled visit days for a few months. If you cannot return to the clinic to get the CAB and RPV shots soon, then you may need to stop taking the study ARVs and enter the long-term safety follow-up phase (see #15 below). This is not preferred, and it is important to get the shots on the scheduled visit day and not miss any CAB and RPV shots.

Study staff will let you know when these procedures will occur ahead of time.

12. In-depth phone interviews [*for U.S. sites only*]

We are very interested to understand what adolescents think about getting their ARV's as shots. You may be asked if you would like to complete an in-depth phone interview. If you would like to take part in the interview, then you may be contacted to have the interview after getting the fourth shot of CAB and RPV. Not all participants will be contacted for the interview. You do not have to do the interview to take part in this study.

If contacted, an interviewer will talk to you for about 1-2 hours and will ask how you feel about having shots of CAB and RPV. This information will help us understand if CAB shots and RPV shots have any bad side effects for adolescents. It will also help us understand how adolescents and families feel about the shots. The interview may take place at or in between the Week 24 through 96 visits or during the long-term follow-up safety phase. The interview will only take place once. The interview will be audio recorded and written down in a report. Your name will not be included in the report.

We may also ask your parent or caregiver to complete an in-depth interview. This interview would ask them how they felt about you having shots of CAB and RPV.

13. Adolescents may have an extra visit if their HIV is not controlled.

Participants will have viral load tests at almost all visits to check the amount of HIV in the blood. If tests show that the viral load is higher than expected (200 copies/mL or more) you will have repeat testing. This may occur as part of another study visit or may occur as an extra study visit.

The extra visit will take about 1-2 hours. At this visit we will:
- Review your medical records.
- Do a physical exam.
- Draw about 16mL (about 3 teaspoons) of blood for tests. The tests will:
    - Check your HIV viral load.
    - Check the amount of CAB and RPV in the blood.
    - We will save some blood for later resistance testing.
- Talk with you about preventing pregnancy.
- For participants assigned female at birth, we will also collect urine or blood to check for pregnancy.

If the repeat test also shows an increased amount of HIV in your blood, you will stop taking the study product and start taking your previous ARVs again. If you were getting shots of CAB and RPV, you will enter long-term safety follow-up (more information in #15 below).

14. If you are not eligible to receive shots of CAB and RPV you will stop the study early.

If you are not eligible to get shots of CAB and RPV then you will stop taking oral CAB and oral RPV and will complete a final study visit about 4 weeks after your last oral dose.

During this visit, we will:
- Review your medical records.
- Do a physical exam. This will include looking at your genitals to see the stage of development. For participants assigned female at birth, this will also include looking at the breasts.
- Draw blood for tests. This would be about 15-20mL of blood (about 3-4 teaspoons) for these tests. These tests will check:
    - Your blood cells.
    - How well your liver and kidneys are working.
    - Your HIV viral load.
    - Some blood will also be saved for later resistance testing.
- Talk with you about preventing pregnancy.
- For participants assigned female at birth, we will also collect urine or blood to check for pregnancy.
- Ask you questions about what it is like to take the oral CAB and oral RPV.
- We will talk with you about your ARV use.

If you also participated in Cohort 1 and received shots of CAB or RPV in Cohort 1, but are not eligible to get the shots of CAB and RPV in Cohort 2, you will stop taking oral CAB and oral RPV and will enter into the Cohort 2 long-term safety follow-up phase (see #15 below).

15. If you stop the shots of CAB and RPV early or after the Week 96 study visit, you will enter the long-term safety follow-up phase.

You will enter the long-term safety follow-up phase after the last shot of study product if you:
- Stop the shots of CAB and RPV early, or
- Do not wish to continue to get the shots of CAB and RPV after the final Cohort 2 visit (Week 96)

If you become pregnant, you will enter this phase of the study after your positive confirmatory pregnancy test result, whether you are taking the pill or the shot.

During the long-term safety follow-up phase, you will stop getting shots of CAB and RPV. You will start taking your previous ARVs again. There will be 4 visits during the long-term safety follow-up phase.

These visits will be scheduled 8, 24, 36 and 48 weeks after your last shot of CAB and RPV (or after a positive confirmatory pregnancy test result). *[Sites to modify]* Each of these visits will take about 1-3 hours. At these visits, we will:

- Review your medical records.
- Talk with you about preventing pregnancy.
- Do a physical exam. At the final long-term safety follow-up visit, this will include examination of your genitals to see the stage of development. For participants assigned female at birth, this will also include looking at your breasts.
- Draw blood for tests. This would be about 21mL of blood (about 4 teaspoons) for these tests. These tests will check:
    - Your blood cells.
    - How well your liver and kidneys are working.
    - Your HIV viral load.
    - The amount of CAB and RPV in the blood.
    - Some blood will also be saved for future resistance testing.
- For participants assigned female at birth, we will also collect urine or blood to check for pregnancy.
- At two of these visits (8 weeks and 48 weeks after your last shot of CAB and RPV) we will talk with you about your ARV use.
- At two of these visits (8 weeks and 48 weeks after your last shot of CAB and RPV), we will also ask you questions about getting shots of CAB and RPV.

16. Different tests will be done at different laboratories.

We will do most of the tests of blood or urine here at our laboratory. We will give you the results of most of these tests at the next scheduled visit, or sooner, if necessary. We will explain the results and give you counseling and referrals as needed.

We will also draw blood to check the amount of CAB and RPV in your blood. This is called a pharmacokinetic (PK) test. The PK test will be done at a laboratory in the United States. We will not usually give you the results of this test during the study.

If you need a test for resistance (see #13 above), that test will be done at a laboratory in the United States. You will be given the results of this resistance test and referrals if needed.

17. We may take you off of the study.

We may take you off the study ARVs if:

- You are not able to come to the study visits or we determine that you cannot meet the study requirements.
- You are not able to take the study ARVs.
- The study ARVs are not controlling the HIV in your blood.
- Continuing the study ARVs may be harmful to you.
- You request to stop the study ARVs.
- You are not able to follow the birth control requirements of this study.
- You become pregnant

If you stop the oral study ARVs early, we will ask you to come back to the clinic about four weeks after you stop the oral study ARVs (see #14 above). You will not have any other visits after this.

If you stop the ARV shots early, we will ask you to come back to the clinic for four additional study visits for long-term follow-up (see #15 above). You will not have any other visits after these four visits.

We may also take you off the study early if the study is stopped for any reason.

The study cannot provide other types of ARVs, but we will give you information, counseling, and referrals to where you can get care and treatment needed. We will help make sure you can get ARVs from outside of the study. If the study stops early, every effort will be made to make certain that there is no interruption in your therapy.

18. Please tell us if you want to leave the study.

You are free to leave the study at any time for any reason. The care that you receive at this clinic will not be affected, but it is important for us to know about your decision.

If you stop the study ARVs, we may ask you to return to the study clinic for additional study visits described in #14 and #15 above. If you stop the study early, we may ask you to return to the study clinic for one final study visit, like the last study visit described in #15 above.

We will answer any questions you may have and give you information on how to contact us in the future, if you wish.

After the study

19. Receiving the study ARVs after the study is over.

As you come to the end of the study, we will work with you to plan for your care and treatment outside the study. It is important that we plan for this in advance, so that there is no gap in your taking ARVs as you finish the study. Taking ARVs without interruption is the best-known way for you to stay healthy.

We will tell you where you can go to receive needed care and treatment after you finish the study. If you are gaining benefit from the study ARV shots given in the study, the companies that are providing these ARVs (ViiV Healthcare and Janssen Pharmaceuticals) will try to provide these ARV shots to you. They will be provided until they are otherwise available locally, until you are no longer gaining benefit, or if the company decides to stop studying the ARVs. However, there is no guarantee this will be possible. If this is <u>not</u> possible, you will need to switch to other oral ARVs that are available locally. We will explain the options to you and help ensure your access to ARVs outside the study. We will also contact you again within the first four or eight weeks after you finish the study to confirm that you are getting ARVs.

Risks of the study

Taking part in this study may involve some risks and discomfort. The risks are different for each phase of the study. Risks during the study pills phase include: risks from blood draws, risks from the study pills (CAB and RPV), risks of switching ARVs, and risks to your privacy.

Risks during the study shots phase include: risks from blood draws, risks from receiving the injection, risks from the study pills (CAB and RPV) and the study shots (long-acting CAB and RPV), and risks to your privacy.

Risks during the long-term safety and follow-up phase include: risks from blood draws, risks of switching ARVs, and risks to your privacy.

20. Risk from blood draws

Drawing blood can cause pain, swelling, bruising, or bleeding where the needle is inserted. Rarely, drawing blood can cause fainting or infection.

21. Risk from receiving the injection

People in other studies who have received the CAB and RPV shots said they had pain, skin irritation, skin redness, bumps, swelling, itching, bruising at the spot where they got the shot. Most reactions go away in a week or less but sometimes they can last longer. Most people usually do well with them and rarely need to stop the drug.

The shots will be given in the muscles of your buttocks. The injection could be given too deeply or not deeply enough, missing the muscle and entering your skin, blood, or a nerve.

The risks of this are not well understood but could make CAB or RPV levels too low or too high. If too low the drug may not work against your HIV. If RPV is too high, there could be a change in your heartbeat, which in severe cases can be life-threatening. In rare cases, symptoms such as feeling lightheaded, numbness or tingling, difficulty breathing, chest or stomach discomfort, sweating, rash, pain (e.g., back and chest), nausea and/or feeling anxious have occurred after an injection with RPV LA. In these cases, high blood levels of RPV have been observed, which may be due to an accidental injection of part of the medication into a blood vessel instead of the muscle. Not all participants in whom an accidental injection in a blood vessel was suspected reported such symptoms. Most of the symptoms resolved within minutes. Your doctor may need to administer treatment to help resolve these symptoms. Everything possible will be done to decrease this risk, including watching you for problems during the study. If your doctor thinks that the injection was not given the right way, you might be asked to stay in the clinic up to 3 hours after the injection to watch how you are doing and extra tests may be needed to be sure you are safe. We will also draw blood (less than 1 teaspoon) about 2 hours after the study shot to look at the amount of study drugs in your blood. If you are worried about this risk, talk to your doctor.

Receiving injections can cause some people to feel lightheaded or feel like they might pass out. Fainting can also occur. This reaction, called a ‘vasovagal reaction’, has been reported with other injectable medicines, and resolves quickly.

22. There are risks from the study ARVs

All ARVs can cause side effects. This includes the ARVs you are currently taking and the ARVs that are given in the study. Some side effects are minor; others can be severe. Some side effects are common; others are rare. Some people who take ARVs have some of the side effects. Other people have different side effects, or no side effects.

The most common and most serious side effects of the study ARVs, CAB and RPV, are listed below. This is based on what we know now about CAB and RPV used in adults. There may be other side effects that we do not know about now. This may be especially true for adolescents, because this is the first study of CAB and RPV in adolescents.

This form does not list all possible side effects of all ARVs. If you join the study, we will tell you more about the ARVs you will be taking. At each study visit, we will check on whether the ARVs 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.

23. Some side effects from the CAB pills and the CAB shot

Many people have received CAB pills or the CAB shot in other studies. The table below lists side effects from other studies of CAB with people who have HIV. It is not known if CAB, other drugs or the participant's other health problems caused or affected these. Some of these are the same side effects as RPV (see #24 below).

Common and Uncommon Side Effects of CAB

Very Common Side Effects of CAB	Common Side Effects of CAB	Uncommon Side Effects of CAB
• Headache • Pyrexia (fever), feeling hot, body temperature increase • Injection Site Reactions (pain and discomfort, a hardened mass or lump)	• 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 • Injection Site Reactions (swelling, redness, itching, bruising, warmth or discoloration)	• Somnolence (sleepiness or Drowsiness) • Vasovagal reactions (light-headedness or fainting, during or following an injection) • Hepatotoxicity (liver problems) • Transaminase increase (blood test may show increase in the level of liver enzymes) • Injection Site Reactions (cellulitis [heat, swelling or redness], abscess [collection of pus], numbness, minor bleeding, discoloration)

The following effects have also been seen in some of the people who received CAB pills or the CAB shot in other studies:

Abnormal liver tests:

A small number of people across all studies (just over 1% of 1644 participants as of April 2017) 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 liver will be done during the study. Your study doctor will tell you if you need to stop taking the study drugs or if other actions are needed. If you stop taking the study drug, you may be able to re-start the study drug or you may need to change your usual 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 about them.

In other studies, two people without HIV had a history of seizures (epilepsy), and had a seizure about 3 months and 9 months after starting CAB. One other person with HIV but without a history of seizures, had seizures about one year after starting CAB. This participant had a long period of seizures without medical treatment and died. It is not known if CAB was part of the reason for seizures in these people. If you have a history of seizures, please let your study doctor know.

24. Some side effects from the RPV pills and the RPV shot

Oral RPV (Edurant) is a marketed drug which many people throughout the world have received to manage HIV. We know more about the side effects of Edurant than we do about CAB or RPV shots. The following side effects have been seen in studies in people with HIV taking RPV.

Common and Uncommon Side Effects of RPV

Common Side Effects of RPV	Uncommon Side Effects of RPV
• Dry mouth • Feeling less hungry (decreased appetite) • Sleep disorders	• 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 • Abdominal discomfort (belly ache)

The following effects have also been seen in some people who received RPV in other studies:

Abnormal blood tests:

Other changes in blood tests have also 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, like the liver and cause liver problems which can lead to liver failure. Contact your study doctor right away if you have 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*

Blood tests to check the health of your liver will be done regularly during the study. Your study doctor will tell you if you need to stop taking the study drugs or if other action is needed. If you stop taking the study drug, you may be able to re-start the study drug or you may need to change your usual ARVs.

Skin Rash:
Most rashes were mild or moderate, and happened within the first 4 weeks of taking RPV. Most of 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 you, you will need to come for extra study visits to monitor your health. Some people with rash may also have other signs and symptoms of allergic reaction.

If you have any type of rash or other skin problems during the study you must tell your study doctor right away, and the doctor may tell you to stop taking CAB and/or RPV.

25. There may be other possible risks from the study ARVs.

The study ARV shots stay in your body for a long time

The shots you get in this study are long acting, meaning they stay in your body for a long time. In most people the drugs will no longer be in the body one year after an injection, while in some people low levels of CAB and RPV may still be in the body after one year. If you develop a side effect to the study drug after the shot, there will be no way to remove the drug from your body. If you get a shot of CAB or RPV, we will monitor your health for 48 weeks after your last shot. If you develop a symptom from these drugs while the drugs are still in your body, every effort will be made to treat the side effects. The amount of drug will decrease overtime and will eventually disappear.

While the amount of study drugs in your body decrease slowly over time after you stop getting shots, the study drugs could stop working against your HIV. When stopping long acting HIV drugs, it will be very important to start taking other HIV medications, as your study doctor tells you, so your HIV medications do not stop working against your HIV.

Risk of switching ARVs

If you join this study, you will stop taking the ARVs you are currently taking, and start taking ARVs given by the study. The study ARVs could cause side effects that you would not have from the ARVs you are currently taking. The study ARVs also may not work as well as the ARVs you are currently taking. For example, the study ARVs may not work as well to control the amount of HIV in your body. We will test your HIV viral load at most study visits to check on this. If your viral load is higher than expected, you will have repeat testing, and your use of the study ARVs may be stopped (see #13 above).

Risk of resistance

By stopping your previous ARVs and switching to the study ARVs, you could develop resistance. This could happen if the study ARVs don't work as well to control the amount of HIV in your body. Resistance means that the ARVs may not work against HIV if these ARVs are taken again in the future. To stop resistance, it is important that you take and/or receive the ARVs as instructed, and do 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 called integrase inhibitors [INIs] for HIV like CAB, have had suicidal thoughts and actions, particularly participants with a prior history of depression or mental health illness.

Tell the study doctor if you have a history of mental health illness. If you have thoughts of hurting or killing yourself or have any other unusual or uncomfortable thoughts or feelings during this study, you should tell the study doctor or go to the nearest hospital right away.

Possible effects on pregnancy or unborn babies

HIV and ARVs may lead to some pregnancy complications, like early delivery or low weight of the baby at birth. We do not know if some ARVs are more likely to cause these effects than others. We do not yet know if CAB is safe in pregnancy. RPV does not appear to be a risk to pregnancy and the developing baby based on the information we know now, but additional data are still being collected.

There are few data from humans on the effects of CAB in pregnancy. Most of the information we have comes from animal studies. In studies done in pregnant rats and their newborns, using very high amounts of CAB, there were more baby rats that died when they were born or right after they were born. This did not happen to the baby rats when the mother got lower amounts of the drug, or no drug. The amount of CAB that we are giving in this study is expected to be more than 7-times lower than the amount given to the pregnant rats. Birth defects have not been found in any animal studies of CAB so far. We do not know whether what happened to the baby rats has any impact on what will happen in pregnant humans taking this drug.

Early results from one large study in Botswana showed that the ARV called dolutegravir (DTG) may increase the risk of serious birth defects of the brain or spine in the new baby. The increased risk was seen among babies whose mothers were taking DTG when they became pregnant. These birth defects happen during the first few weeks of pregnancy, before mothers may know they are pregnant. These birth defects have not been seen among babies whose mothers started taking DTG later in pregnancy.

CAB is not the same drug as DTG. We do know that CAB and DTG belong to the same class of medications and work in a similar way to treat HIV infection. We do not know if CAB can cause brain or spine defects in babies.

Participants who are able to become pregnant must agree to use certain effective methods of birth control to be in this study (see #6 above). If you become pregnant during the study, please let us know right away.

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 but can also occur later. Some of these symptoms may be life threatening. If you start having new symptoms, or if you notice that any existing symptoms are getting worse after starting the ARVs, tell your doctor immediately.

Abnormal placement of body fat and wasting

The use of potent antiretroviral drug combinations may be associated with an abnormal placement of body fat and wasting. Some of the body changes include:

- Increase in fat around the waist and stomach area
- Increase in fat on the back of the neck
- Thinning of the face, legs, and arms
- Breast enlargement

26. There could be risks of disclosure of your information.

We will make every effort to keep your information private and confidential. Study records and specimens will be kept in secure, locked locations. All specimens and most records will be labeled only with a code number. However, your name will be written on some records.

Despite our best efforts to keep your information private, it is possible that the information could be obtained by someone who should not have it. If this were to happen, you could be treated badly or unfairly. You could feel stress or embarrassment.

To help us protect your privacy, we have obtained a Certificate of Confidentiality that protects us from 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 US federal government or from the US Food and Drug Administration. Regardless of the certificate, you can release information about your participation in the study to others, if you wish.

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 or adolescents 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 you may be used but your name will not be shared.

Benefits of the study

27. There may be a direct benefit to you from being in the study.

By joining the study, you will be part of the search for ARVs that may be better for adolescents. We do not know if being in the study will benefit you in any way. There may be a direct benefit to you by taking part in this study, but no guarantee can be made. For example, if you get shots of CAB and RPV, you might prefer having monthly shots instead of taking daily pills. The study ARVs may have fewer side effects than the previous ARVs you were taking. There may also be benefit if the results from this study lead to a safe and effective dose of the study drugs for adolescents. It is also possible that you may receive no direct benefit from this study. Information learned from this study may help other adolescents who have HIV.

You will have regular visits here and frequent checks on your health, including tests for amount of HIV in your blood, called viral load. It is possible that the study ARVs will slow your HIV infection. Information learned from this study may help other adolescents with HIV.

Other information about the study

28. There are no costs from being in the study.

There are no costs to you for study visits, CAB, RPV or procedures.

[Insert information about compensation/reimbursement here, e.g., You will be reimbursed for the cost of transport to study visits. For each visit, you will be given (specify amount).*]*

29. Study records may be reviewed by study staff and groups that oversee the study.

Groups that oversee the study include:
- *[insert name of site IRB/EC]*
- *[insert name of site drug regulatory authority]*
- *[insert name of other site 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
- ViiV Healthcare (the company that makes CAB)
- Janssen Pharmaceuticals (the company that makes RPV)

The study staff and these groups are required 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 personally.

A description of this study will be available on ClinicalTrials.gov as required by U.S. law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

Your study information may be given to other authorities if required by law. *[Sites add more specific detail here as needed; example follows:]* For example, we are required to report any significant risk of harm to you or others.

30. If you get sick or injured, contact us immediately.

Your health is important to us. We will make every effort to protect your well-being and minimize risks. It is possible, however, that you could have an illness or injury that is study-related. This means that the illness or injury occurred as a direct result of the study procedures.

[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 treatment. The cost for this treatment may be charged to you or your insurance company. There is no program for compensation either through *[site name or]* the U.S. National Institutes of Health.

Whom to contact

31. If you have questions, concerns, or problems at any time, use these contacts.

- If you have questions about the study:
  [insert name and telephone number of investigator or other study staff]

- If you have questions about your rights as research participants or concerns about how you are being treated in the study:
  [insert name and telephone number of IRB/EC contact person or other appropriate person/organization]

- If you have any health or other problems that may be related to study participation:
  [insert name and telephone number of investigator or other study staff]

- If you want to leave the study:
  [insert name and telephone number of investigator or other study staff]

Signatures

If you agree to participate in Cohort 2A of 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.

If you decide to join, we will tell you any new information from this study or other studies that may affect your health, welfare, or willingness to stay in the study. You are welcome to ask questions or request more information at any time. If you want the results from this study, please tell the study staff.

You do not give up any rights by signing this form.
[Insert signature blocks as required by site IRB/EC policies.]

Signature blocks for participants of legal age to provide independent informed consent

_____	_____
Participant's Name (print)	Participant's Signature and Date
_____	_____
Study Staff Conducting Consent Discussion (print)	Study Staff Signature and Date
_____	_____
Witness's Name (print) (As appropriate)	Witness's Signature and Date

Signature blocks for parent/legal guardian of adolescent:

_____ Name of Parent/Legal Guardian (print)	_____ Signature of Parent/Legal Guardian and Date
_____ Study Staff Conducting Consent Discussion (print)	_____ Study Staff Signature and Date
_____ Witness's Name (print) (As appropriate)	_____ Witness's Signature and Date

Appendix II-C: Sample Informed Consent Form for Participation in Cohort 2B

for adolescents who can provide independent informed consent for study participation and parents/legal guardians of adolescents

IMPAACT 2017
Phase I/II Study of the Safety, Acceptability, Tolerability, and Pharmacokinetics of Oral and Long-Acting Injectable Cabotegravir and Long-Acting Injectable Rilpivirine in Virologically Suppressed HIV-Infected Children and Adolescents

Version 4.0, dated 27 May 2022

[Throughout this form sites may modify to remove mentions of HIV and ARVs for participants who do not know their status].

If you are the parent or legal guardian of a child who may take part in this study, your permission and the permission of your child will be needed. When "you" appears in this form, it refers to your child except where it says otherwise.

Introduction

You are being asked to take part in the research study named above.

This form gives information about 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 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 medicines (ARVs), Cabotegravir (CAB) and Rilpivirine (RPV), taken as pills and given as long-acting shots in adolescents 12 to less than 18 years of age.
- Some of the study drugs are already approved in some countries for use in adolescents or adults, but more data is needed for use in adolescents.
- There are two parts to this study, Cohort 1 and Cohort 2. The Cohort 2 part to this study also has two groups: Cohort 2A and Cohort 2B. **This form is about Cohort 2B**.
- Adolescents in Cohort 2 will switch from their usual ARVs to the study medicine and will be in this part of the study for at least 2 years up to 3 years.
- In Cohort 2, you will have the option to either take the study pills and then get the study shots (this is called Cohort 2A) or skip the study pills and only get the study shots (this is called Cohort 2B).
- After entering the study, adolescents in Cohort 2A will stop taking their usual ARVs and start taking daily CAB and RPV *pills* for 4 to 6 weeks. Adolescents will then switch to CAB and RPV *shots* every 8 weeks for about 2 years.
- Adolescents in Cohort 2B will stop taking their usual ARVs and start CAB and RPV *shots* every 8 weeks for about 2 years.
- We will discuss Cohort 2A and Cohort 2B with you and together make a decision that is best for you.
- After the 2 years of getting the CAB and RPV shots, all Cohort 2 adolescents might be able to continue getting the same CAB and RPV shots outside of the study. We will explain the options to you and help ensure your access to ARVs outside the study.

- Adolescents 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, adolescents will not take any study medicine (shots or pills) but will take ARVs.
- While in the study, adolescents will have clinic visits with physical examinations and blood draws for laboratory tests. Some visits will include a review of adolescents' medical records and ECG tests to look at the adolescent's heart. Participants assigned female at birth will also be tested for pregnancy.
- If interested, participants in the U.S. may be eligible to do one in-depth phone interview where they will talk about their experience getting their ARVs as shots.
- There are some possible risks for adolescents in the study. One possible risk is that the pills or shots being tested could cause side effects. The most severe side effects include allergic reaction, liver problems, and mental health problems. These side effects are uncommon.
- There are some possible benefits for adolescents in the study. One possible benefit is not taking daily pills while getting the CAB and RPV shots. Another possible benefit is that the shots being tested will be better for your health and HIV care than the usual ARV pills.
- Your decision on your participation in the study will have no effect on the medical care you receive at this clinic. Your access to services, and the benefits and rights you normally have, will not be affected. You may choose to leave the study at any time.

More information is given in this form about the study, its risks and benefits. You should feel that you understand the study before deciding whether you will participate. If you decide to 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

This study is being done by the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) and *[insert site name]*. The person in charge of the study at *[insert site name]* is *[insert name of IoR]*.

The study is being done to test two anti-HIV medicines (antiretrovirals or ARVs) in adolescents 12 to less than 18 years old who have HIV. The study ARVs are called cabotegravir (CAB) and rilpivirine (RPV). HIV is the virus that can lead to AIDS.

The study will include up to 155 adolescents from the United States, Botswana, South Africa, Thailand and Uganda. There will be two groups of adolescents, called Cohort 1 and Cohort 2. This form is about Cohort 2. Participants in Cohort 2 will be in the study for 2 to 3 years. In Cohort 2, participants will get study product for 92 or 96 weeks (about 2 years). After this time, participants will leave the study and may continue getting the study medicines outside of the study. If you stop getting the study shots early, you will enter long-term safety follow-up and continue having study visits for an additional 48 weeks (about 1 year).

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 adolescents.

People living with HIV usually take a combination of ARVs daily to stay healthy. There are not as many ARVs available for adolescents as for adults because many ARVs have not yet been tested in adolescents. ARVs can be made in different forms, such as liquids, pills, and injections (shots). The study will test CAB and RPV when taken as pills and when given as shots in adolescents. The pills are taken every day. The shots can be given every 4 weeks or every 8 weeks. The shots are being developed because it can be difficult to take pills every day, and some people may prefer to have the shots rather than taking pills.

RPV pills (25 mg), RPV shots (600mg and 900mg), CAB pills (30mg), and CAB shots (400mg and 600mg) are now approved by the U.S. Food and Drug Administration (FDA) for adults and adolescents living with HIV. The approvals are based on this study and studies in adults which showed that CAB and RPV were safe and well tolerated. The adult studies also showed that the shots worked well to control HIV. The study drugs are approved by the European Medicines Agency (EMA) for adults. Only the RPV pills (25mg taken once daily) are approved by the EMA for adolescents.

This will be the first study of RPV shots, CAB pills and CAB shots in adolescents. The testing in adults has shown that the study pills and study shots work as well as other ARVs that are approved. So far, the testing in this study has shown that the study pills and study shots also work well for adolescents. However, because these ARVs are still being tested, there may be some effects that we do not know about yet. More information is needed from this study so that the study drugs can be approved for adolescents in more countries.

This study will test the effects of these ARVs in adolescents. The study will look at whether these ARVs:

- Are being given at the correct dose for adolescents
- Are safe and well-tolerated in adolescents
- Can control HIV in adolescents as well as other ARVs

The study will also look at how willing adolescents are to take these ARVs.

Cohort 1 of this study was done first to test CAB and RPV pills when taken for about 1 month followed by 2 or 3 CAB and RPV shots when taken 1 month apart. Cohort 2 is now being done to test CAB and RPV when taken together. There are two groups within Cohort 2:

- Adolescents in the **Cohort 2A** group will take CAB and RPV pills together for about 1 month, followed by getting the CAB and RPV shots together.
- Adolescents in the **Cohort 2B** group will only get the CAB and RPV shots. This group will not take the CAB and RPV pills.

Both CAB and RPV shots will be given together about every 8 weeks for up to two years. Each time the shots are given, the RPV shot will be 900mg and the CAB shot will be 600mg. Cohort 2 will look at whether these study ARVs are safe and can control HIV when adolescents stop taking their previous ARVs.

We will discuss both Cohort 2A and Cohort 2B groups with you to make the decision of which group you will enter. If you decide to participate in the study, your signature or mark on this form will also document the decision of which Cohort 2 group. You can ask any questions about the groups at any time. You will not be able to switch to the other group after they have entered the study.

More information about the study, the Cohort 2B group, and CAB and RPV is given in the rest of this form.

2. Only adolescents who are eligible can participate in the study.

If you decide to join the study, we will first do some tests to find out if you are eligible. More information about the tests is given in #5 (see below). If you are eligible, you will be entered in the study. If you are not eligible, you cannot be entered in the study.

3. It is your decision whether or not you join the study.

Deciding to join the study is voluntary (your choice). You may choose to join or not join. If you choose to join, you can change your mind and leave the study. Your choices will have no effect on the medical care you would normally receive. Your access to services, and the benefits and rights you normally have, will not be affected.

Take your time and consider your decision carefully. If you wish, you can talk to other people about the study. 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 you to keeping taking ARVs. This is the best known way for you to stay healthy.

4. There are three phases in Cohort 2: the study pills, the study shots, and the long-term safety follow-up.

For participants in Cohort 2, there are three phases of the study:

- The CAB and RPV pills
- The CAB and RPV shots
- The long-term safety follow-up phase with no study medicines

Not all participants will be in all three phases of the study. Participants in the Cohort 2A group will first take part in the CAB and RPV pills and then take part in the CAB and RPV shots phases of the study. In Cohort 2B, participants will also stop taking their usual ARVs but will skip the CAB and RPV pills phase and go straight to the CAB and RPV shots phase of the study.

Any participant who takes part in the CAB and RPV shot phase but must stop the study shots early will take part in the long-term safety follow-up phase.

In Cohort 2A, participants will stop taking their usual ARVs and take CAB and RPV pills. The study pills phase lasts for about 4-6 weeks. These participants will be checked to see if they are eligible to get the CAB and RPV shots. If eligible then, they will stop taking the CAB and the RPV pills and start getting CAB and RPV shots.

Both Cohort 2A and Cohort 2B participants will have the study shots. The study shots phase lasts 2-3 years.

For Cohort 2B participants, you will not have the study pills phase but go straight to the study shots phase. You will have 15 visits over about two years in the study shots phase. At 13 of these visits you will be given one shot of CAB and one shot of RPV. Each shot is about 3mL (about 1 teaspoon). The shots are given in the buttocks (bottom "cheeks"). The shots may be given on the same side of the buttocks or on different sides. The shots are long-acting, meaning the medicine stays in your body for a long time. The first two visits with the CAB and RPV shots are 4 weeks apart. Then the CAB and RPV shots are given every 8 weeks. At all of these study visits, we will check on how you are doing while getting the shots (see #9 for more information).

After the CAB and RPV shots, you might have the option to continue getting the long-acting injections outside of the study (see #17 for more information).

If you no longer want to get the injections, or have to stop the study shots early, you will stop taking the study drugs and take part in the long-term safety follow-up phase of the study. This phase lasts about 48 weeks. We will check on how you are doing and the amount of study drugs in your blood after stopping the study drugs. You will also go back to taking your usual (pre-study) ARVs. There will be 4 visits during long-term follow up (see #12 for more information).

Finding out if you are eligible for Cohort 2

5. We will ask questions, examine you, and discuss the study requirements with you.

To find out if you are eligible for the study, we will:

- Review your medical records.
- Ask questions about you, your health, and the medications you take.
- Talk with you about birth control (ways to prevent pregnancy).
- Talk with you about the study requirements and if you are able to meet these requirements.
- Talk with you about which group is best for you to join (Cohort 2A or Cohort 2B)
- Do a physical exam. This will include looking at your genitals to see your stage of development. For participants assigned female at birth, this will also include looking at your breasts.
- Do an electrocardiogram (ECG). This is to test how well your heart is working.
- Draw about 11-17mL (about 2-3 teaspoons) of blood for tests. The tests will:
  - Check your blood cells.
  - Check how well your liver and kidneys are working.
  - Confirm that you have HIV. There are certain HIV tests that are required for this study. If the required tests are not in the medical records, we will do the tests that are needed.
  - Check the amount of HIV in your blood. This is called your HIV viral load.

These procedures will take about 4 hours *[here and throughout this form, sites may modify the expected visit duration as needed]*.

6. For participants assigned female at birth, we will also test for pregnancy.

Participants in this study cannot be pregnant. Participants should not join this study if they are pregnant or intend to become pregnant within 30 days after stopping the study ARV pills or within 48 weeks after stopping the study shots. Because the effects of the study ARVs on unborn babies are unknown, you should not become pregnant while in this study. For all participants assigned female at birth in the study, we will collect urine or blood to test for pregnancy.

There are certain effective methods of birth control that participants who are able to become pregnant must use while in this study. These effective methods must be continued for 30 days after stopping the study ARV pills, or for at least 48 weeks after stopping the study ARV shots. Participants who are able to become pregnant, must agree to use these methods in order to take part in the study. We will help make sure you can get effective methods by providing them here in the clinic or offering a referral. At study visits when you will receive study medicines (either the pill or shot), we will need to confirm that you are using effective birth control before giving you the study medicines.

Participants who become pregnant during the study will stop taking the study medicines and enter the long-term safety follow-up phase of the study (see #12 below). **They must continue taking their usual ARVs.** We will also contact you to find out the outcome of the pregnancy even if the outcome occurs after leaving the study.

[Sites may modify the following paragraph to include locally appropriate language regarding disclosure of pregnancy results to parents or guardians: As soon as the pregnancy test result is available, we will go over it with you in private, without your parents/guardians present. You must give us permission before we can share these results with your parents/guardians. If the test shows that you are pregnant, we will give you information on where medical care and other services can be received.*]*

If you are pregnant, your doctor may report your pregnancy to the Antiretroviral Pregnancy Registry. The Antiretroviral Pregnancy Registry assists participants and doctors in gauging potential benefits and risks of treatment; however, the registry does not collect any identifying information about you, such as your name, initials, contact information, or date of birth.

7. We will tell you if you are eligible.

We will give you the results of all procedures and explain the results to you. We will tell you about getting care, treatment and any other services you may need. While waiting for the results, it is important for you to keep taking your usual ARVs.

If you are not eligible for the study for any reason, we will tell you this. You will not be entered in the study. You 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 you do not enter the study, we will still use some information collected about you (for example age, sex, and race). We will use this information to look at patterns or common reasons for not entering the study.

If you are eligible for the study, you will be entered into the study.

Entering the study

8. If you are eligible, you will enter the study.

On the day you enter the study we will:

- Review your medical records.
- Talk with you about your ARV use.
- Talk with you about preventing pregnancy.
- Talk with you about the study visit schedule and taking the study medicines correctly
- Ask you questions about what you think about CAB and RPV
- Do a physical exam.
- Draw about 18mL (about 4 teaspoons) of blood for tests. The tests will:
  - Check your blood cells.
  - Check how well your liver and kidneys are working.
  - Check how much the virus has affected your ability to fight the virus. This is called CD4 cell count.
  - The tests will check your 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.
- For participants assigned female at birth, we will collect urine or blood for a pregnancy test
- Ask if you are willing to complete an in-depth phone interview. [*US sites only.*]

At this visit we will again talk with you about which group is best for you to join (Cohort 2A or Cohort 2B). You will not be able to switch to the other group after you have entered the study.

If it is decided that you will enter Cohort 2B, then at this visit, you will stop taking your usual ARVs and get one shot of CAB and one shot of RPV. We will also draw about 4mL of blood (less than 1 teaspoon) to look at the amount of CAB or RPV in your blood. We will also do an ECG to look at your heart.

This visit will take about 4 hours.

Being in the study

9. After entering the study in the Cohort 2B group, you will have 14 more visits (Weeks 1-92) in the study shots phase.

The first visit in Cohort 2B will be the study entry visit and is described in #8 above. After that visit, you will have 14 more visits in the study shots phase. Most of these visits will take place about 8 weeks apart, and some of these visits will take place 1 week apart. *[Sites to modify]* Each visit will take about 1-3 hours. At each of these visits, we will:

- Review your medical records.
- Talk with you about preventing pregnancy.
- Do a physical exam. At two of these visits (Weeks 20 and 92), this exam will include examination of your genitals to see the stage of development. For participants assigned female at birth, this will also include looking at the breasts.

At 12 of these visits (Weeks 4-20 and 28-92) you will:

- Get a shot of CAB and a shot of RPV.
- For participants assigned female at birth, we will also collect urine or blood to check for pregnancy.

At 13 of these visits (Weeks 1, 4-20, and 28-92) we will draw about 5mL of blood (about 1 teaspoon) for tests. These tests will check:

- Your blood cells
- How well your liver and kidneys are working

At 9 of these visits (Weeks 4-20, 28-44, 60, 76, and 92) we will draw about 12mL of blood (about 2-3 teaspoons) for tests. These tests will check:

- Your HIV viral load.
- Some blood will be saved for later resistance testing.

At 12 of these visits (Weeks 1, 4-44, 60, 76, 84, and 92), we will also draw about 4mL of blood (less than 1 teaspoon) of blood to look at the amount of CAB and RPV in the blood.

At 4 of these visits (Weeks 20, 44, 68, and 92) we will draw about 3mL of blood (about 1 teaspoon) to check your CD4 count.

At 4 of these visits (Weeks 4, 20, 44, and 92) we will ask you questions about getting the shots of CAB and RPV.

At 5 of these visits (Weeks 4, 20, 44, 68, and 92) we may also talk with you about how you are doing with the visit schedule.

Study staff may ask you to return to the clinic for a study shot before your next visit. If so, then many of the procedures described above would also be done again.

If you cannot come to the clinic to receive the CAB and RPV shots, then you may have the option to take the CAB and RPV pills until you are able to get the shots again. If this happens, you may need more frequent CAB and RPV shots outside of the scheduled visit days for a few months. If you cannot return to the clinic to get the CAB and RPV shots soon, then you may need to stop taking the study ARVs and enter the long-term safety follow-up phase (see #12 below). This is not preferred, and it is important to get the shots on the scheduled visit day and not miss any CAB and RPV shots.

[Sites to modify] On rare occasions, we may offer some of the visit activities off-site, or by phone. The study staff will discuss the location and best time to visit you so that the visit is at a convenient time and the visit is done at a place you feel comfortable and confidentiality can be maintained.

Study staff will let you know when these procedures will occur ahead of time.

10. In-depth phone interviews [*for U.S. sites only*]

We are very interested to understand what adolescents think about getting their ARV's as shots. You may be asked if you would like to complete an in-depth phone interview. If you would like to take part in the interview, then you may be contacted to have the interview after getting the fourth shot of CAB and RPV. Not all participants will be contacted for the interview. You do not have to do the interview to take part in this study.

If contacted, an interviewer will talk to you for about 1-2 hours and will ask how you feel about having shots of CAB and RPV. This information will help us understand if CAB shots and RPV shots have any bad side effects for adolescents. It will also help us understand how adolescents and families feel about the shots. The interview may take place at or in between the Week 20 through 92 visits or during the long-term follow-up safety phase. The interview will only take place once. The interview will be audio recorded and written down in a report. Your name will not be included in the report.

We may also ask your parent or caregiver to complete an in-depth interview. This interview would ask them how they felt about you having shots of CAB and RPV.

11. Adolescents may have an extra visit if their HIV is not controlled.

Participants will have viral load tests at almost all visits to check the amount of HIV in the blood. If tests show that the viral load is higher than expected (200 copies/mL or more) you will have repeat testing. This may occur as part of another study visit or may occur as an extra study visit.

The extra visit will take about 1-2 hours. At this visit we will:

- Review your medical records.
- Do a physical exam.
- Draw about 16mL (about 3 teaspoons) of blood for tests. The tests will:
    - Check your HIV viral load.
    - Check the amount of CAB and RPV in the blood.
    - We will save some blood for later resistance testing.
- Talk with you about preventing pregnancy.
- For participants assigned female at birth, we will also collect urine or blood to check for pregnancy.

If the repeat test also shows an increased amount of HIV in your blood, you will stop taking the study product and start taking your previous ARVs again. If you were getting shots of CAB and RPV, you will enter long-term safety follow-up (more information in #12 below).

12. If you stop the shots of CAB and RPV early or after the Week 92 study visit, you will enter long-term safety follow-up phase.

You will enter the long-term safety follow-up phase after the last shot of study product if you:

- Stop the shots of CAB and RPV early, or
- Do not wish to continue to get the shots of CAB and RPV after the final Cohort 2 visit (Week 92)

If you become pregnant, you will enter this phase of the study after your positive confirmatory pregnancy test result, whether you are taking the pill or the shot.

During the long-term safety follow-up phase, you will stop getting shots of CAB and RPV. You will start taking your previous ARVs again. There will be 4 visits during the long-term safety follow-up phase.

These visits will be scheduled 8, 24, 36 and 48 weeks after your last shot of CAB and RPV (or after a positive confirmatory pregnancy test result). *[Sites to modify]* Each of these visits will take about 1-3 hours. At these visits, we will:

- Review your medical records.
- Talk with you about preventing pregnancy.
- Do a physical exam. At the final long-term safety follow-up visit, this will include examination of your genitals to see the stage of development. For participants assigned female at birth, this will also include looking at your breasts.
- Draw blood for tests. This would be about 21mL of blood (about 4 teaspoons) for these tests. These tests will check:
    - Your blood cells.
    - How well your liver and kidneys are working.
    - Your HIV viral load.
    - The amount of CAB and RPV in the blood.
    - Some blood will also be saved for future resistance testing.
- For participants assigned female at birth, we will also collect urine or blood to check for pregnancy.
- At two of these visits (8 weeks and 48 weeks after your last shot of CAB and RPV) we will talk with you about your ARV use.
- At two of these visits (8 weeks and 48 weeks after your last shot of CAB and RPV), we will also ask you questions about getting shots of CAB and RPV.

13. If you leave the study early, you will complete a final study visit.

If you need to leave the study early, then you will complete a final study visit about 4 weeks after your last CAB and RPV shots.

During this visit, we will:

- Review your medical records.
- Do a physical exam. This will include looking at your genitals to see the stage of development. For participants assigned female at birth, this will also include looking at the breasts.
- Draw blood for tests. This would be about 15-20mL of blood (about 3-4 teaspoons) for these tests. These tests will check:
    - Your blood cells.
    - How well your liver and kidneys are working.
    - Your HIV viral load.
    - Some blood will also be saved for later resistance testing.
- Talk with you about preventing pregnancy.
- For participants assigned female at birth, we will also collect urine or blood to check for pregnancy.
- Ask you questions about what it is like to take the oral CAB and oral RPV.
- We will talk with you about your ARV use.

14. Different tests will be done at different laboratories.

We will do most of the tests of blood or urine here at our laboratory. We will give you the results of most of these tests at the next scheduled visit, or sooner, if necessary. We will explain the results and give you counseling and referrals as needed.

We will also draw blood to check the amount of CAB and RPV in your blood. This is called a pharmacokinetic (PK) test. The PK test will be done at a laboratory in the United States. We will not usually give you the results of this test during the study.

If you need a test for resistance (see #11 above), that test will be done at a laboratory in the United States. You will be given the results of this resistance test and referrals if needed.

15. We may take you off of the study.

We may take you off the study ARVs if:

- You are not able to come to the study visits or we determine that you cannot meet the study requirements.
- You are not able to take the study ARVs.
- The study ARVs are not controlling the HIV in your blood.
- Continuing the study ARVs may be harmful to you.
- You request to stop the study ARVs.
- You are not able to follow the birth control requirements of this study.
- You become pregnant

If you stop the ARV shots early, we will ask you to come back to the clinic for four additional study visits for long-term follow-up (see #12 above). You will not have any other visits after these four visits.

We may also take you off the study early if the study is stopped for any reason.

The study cannot provide other types of ARVs, but we will give you information, counseling, and referrals to where you can get care and treatment needed. We will help make sure you can get ARVs from outside of the study. If the study stops early, every effort will be made to make certain that there is no interruption in your therapy.

16. Please tell us if you want to leave the study.

You are free to leave the study at any time for any reason. The care that you receive at this clinic will not be affected, but it is important for us to know about your decision.

If you stop the study early, we may ask you to return to the study clinic for one final study visit, like the last study visit described in #13 above.

We will answer any questions you may have and give you information on how to contact us in the future, if you wish.

After the study

17. Receiving the study ARVs after the study is over.

As you come to the end of the study, we will work with you to plan for your care and treatment outside the study. It is important that we plan for this in advance, so that there is no gap in your taking ARVs as you finish the study. Taking ARVs without interruption is the best-known way for you to stay healthy.

We will tell you where you can go to receive needed care and treatment after you finish the study. If you are gaining benefit from the study ARV shots given in the study, the companies that are providing these ARVs (ViiV Healthcare and Janssen Pharmaceuticals) will try to provide these ARV shots to you. They will be provided until

they are otherwise available locally, until you are no longer gaining benefit, or if the company decides to stop studying the ARVs. However, there is no guarantee this will be possible. If this is not possible, you will need to switch to other oral ARVs that are available locally. We will explain the options to you and help ensure your access to ARVs outside the study. We will also contact you again within the first four or eight weeks after you finish the study to confirm that you are getting ARVs.

Risks of the study

Taking part in this study may involve some risks and discomfort. The risks are different for each phase of the study. Cohort 2B risks include: risks from blood draws, risks from receiving the injection, risks from the study shots (long-acting CAB and RPV), and risks to your privacy. Some participants may need to take the study pills even during Cohort 2B (see #9 above). When this happens there is also risks from the study pills (CAB and RPV).

Risks during the long-term safety follow-up phase include: risks from blood draws, risks of switching ARVs, and risks to your privacy.

18. Risk from blood draws

Drawing blood can cause pain, swelling, bruising, or bleeding where the needle is inserted. Rarely, drawing blood can cause fainting or infection.

19. Risk from receiving the injection

People in other studies who have received the CAB and RPV shots said they had pain, skin irritation, skin redness, bumps, swelling, itching, bruising at the spot where they got the shot. Most reactions go away in a week or less but sometimes they can last longer. Most people usually do well with them and rarely need to stop the drug.

The shots will be given in the muscles of your buttocks. The injection could be given too deeply or not deeply enough, missing the muscle and entering your skin, blood, or a nerve.

The risks of this are not well understood but could make CAB or RPV levels too low or too high. If too low the drug may not work against your HIV. If RPV is too high, there could be a change in your heartbeat, which in severe cases can be life-threatening. In rare cases, symptoms such as feeling lightheaded, numbness or tingling, difficulty breathing, chest or stomach discomfort, sweating, rash, pain (e.g., back and chest), nausea and/or feeling anxious have occurred after an injection with RPV LA. In these cases, high blood levels of RPV have been observed, which may be due to an accidental injection of part of the medication into a blood vessel instead of the muscle. Not all participants in whom an accidental injection in a blood vessel was suspected reported such symptoms. Most of the symptoms resolved within minutes. Your doctor may need to administer treatment to help resolve these symptoms. Everything possible will be done to decrease this risk, including watching you for problems during the study. If your doctor thinks that the injection was not given the right way, you might be asked to stay in the clinic up to 3 hours after the injection to watch how you are doing and extra tests may be needed to be sure you are safe. We will also draw blood (less than 1 teaspoon) about 2 hours after the study shot to look at the amount of study drugs in your blood. If you are worried about this risk, talk to your doctor.

Receiving injections can cause some people to feel lightheaded or feel like they might pass out. Fainting can also occur. This reaction, called a ‘vasovagal reaction’, has been reported with other injectable medicines, and resolves quickly.

20. There are risks from the study ARVs

All ARVs can cause side effects. This includes the ARVs you are currently taking and the ARVs that are given in the study. Some side effects are minor; others can be severe. Some side effects are common; others are rare. Some people who take ARVs have some of the side effects. Other people have different side effects, or no side effects.

The most common and most serious side effects of the study ARVs, CAB and RPV, are listed below. This is based on what we know now about CAB and RPV used in adults. There may be other side effects that we do not know about now. This may be especially true for adolescents, because this is the first study of CAB and RPV in adolescents.

This form does not list all possible side effects of all ARVs. If you join the study, we will tell you more about the ARVs you will be taking. At each study visit, we will check on whether the ARVs 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.

21. Some side effects from the CAB pills and the CAB shot

Many people have received CAB pills or the CAB shot in other studies. The table below lists side effects from other studies of CAB with people who have HIV. It is not known if CAB, other drugs or the participant's other health problems caused or affected these. Some of these are the same side effects as RPV (see #22 below).

Common and Uncommon Side Effects of CAB

Very Common Side Effects of CAB	Common Side Effects of CAB	Uncommon Side Effects of CAB
• Headache • Pyrexia (fever), feeling hot, body temperature increase • Injection Site Reactions (pain and discomfort, a hardened mass or lump)	• 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 • Injection Site Reactions (swelling, redness, itching, bruising, warmth or discoloration)	• Somnolence (sleepiness or Drowsiness) • Vasovagal reactions (light-headedness or fainting, during or following an injection) • Hepatotoxicity (liver problems) • Transaminase increase (blood test may show increase in the level of liver enzymes) • Injection Site Reactions (cellulitis [heat, swelling or redness], abscess [collection of pus], numbness, minor bleeding, discoloration)

The following effects have also been seen in some of the people who received CAB pills or the CAB shot in other studies:

Abnormal liver tests:

A small number of people across all studies (just over 1% of 1644 participants as of April 2017) 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 liver will be done during the study. Your study doctor will tell you if you need to stop taking the study drugs or if other actions are needed. If you stops taking the study drug, you may be able to re-start the study drug or you may need to change your usual 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 about them.

In other studies, two people without HIV had a history of seizures (epilepsy), and had a seizure about 3 months and 9 months after starting CAB. One other person with HIV but without a history of seizures, had seizures about one year after starting CAB. This participant had a long period of seizures without medical treatment and died. It is not known if CAB was part of the reason for seizures in these people. If you have a history of seizures, please let your study doctor know.

22. Some side effects from the RPV pills and the RPV shot

Oral RPV (Edurant) is a marketed drug which many people throughout the world have received to manage HIV. We know more about the side effects of Edurant than we do about CAB or RPV shots. The following side effects have been seen in studies in people with HIV taking RPV.

Common and Uncommon Side Effects of RPV

Common Side Effects of RPV	Uncommon Side Effects of RPV
• Dry mouth • Feeling less hungry (decreased appetite) • Sleep disorders	• 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 • Abdominal discomfort (belly ache)

The following effects have also been seen in some people who received RPV in other studies:

Abnormal blood tests:

Other changes in blood tests have also 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, like the liver and cause liver problems which can lead to liver failure. Contact your study doctor right away if you have 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*

Blood tests to check the health of your liver will be done regularly during the study. Your study doctor will tell you if you need to stop taking the study drugs or if other action is needed. If you stop taking the study drug, you may be able to re-start the study drug or you may need to change your usual ARVs.

Skin Rash:

Most rashes were mild or moderate, and happened within the first 4 weeks of taking RPV. Most of 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 you, you will need to come for extra study visits to monitor your health. Some people with rash may also have other signs and symptoms of allergic reaction.

If you have any type of rash or other skin problems during the study you must tell your study doctor right away, and the doctor may tell you to stop taking CAB and/or RPV.

23. There may be other possible risks from the study ARVs.

The study ARV shots stay in your body for a long time

The shots you get in this study are long acting, meaning they stay in your body for a long time. In most people the drugs will no longer be in the body one year after an injection, while in some people low levels of CAB and RPV may still be in the body after one year. If you develop a side effect to the study drug after the shot, there will be no way to remove the drug from your body. If you get a shot of CAB or RPV, we will monitor your health for 48 weeks after your last shot. If you develop a symptom from these drugs while the drugs are still in your body, every effort will be made to treat the side effects. The amount of drug will decrease overtime and will eventually disappear.

While the amount of study drugs in your body decrease slowly over time after you stop getting shots, the study drugs could stop working against your HIV. When stopping long acting HIV drugs, it will be very important to start taking other HIV medications, as your study doctor tells you, so your HIV medications do not stop working against your HIV.

Risk of switching ARVs

If you join this study, you will stop taking the ARVs you are currently taking, and start taking ARVs given by the study. The study ARVs could cause side effects that you would not have from the ARVs you are currently taking. The study ARVs also may not work as well as the ARVs you are currently taking. For example, the study ARVs may not work as well to control the amount of HIV in your body. We will test your HIV viral load at most study visits to check on this. If your viral load is higher than expected, you will have repeat testing, and your use of the study ARVs may be stopped (see #11 above).

Risk of resistance

By stopping your previous ARVs and switching to the study ARVs, you could develop resistance. This could happen if the study ARVs don't work as well to control the amount of HIV in your body. Resistance means that the ARVs may not work against HIV if these ARVs are taken again in the future. To stop resistance, it is important that you take and/or receive the ARVs as instructed, and do 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 called integrase inhibitors [INIs] for HIV like CAB, have had suicidal thoughts and actions, particularly participants with a prior history of depression or mental health illness.

Tell the study doctor if you have a history of mental health illness. If you have thoughts of hurting or killing yourself or have any other unusual or uncomfortable thoughts or feelings during this study, you should tell the study doctor or go to the nearest hospital right away.

Possible effects on pregnancy or unborn babies

HIV and ARVs may lead to some pregnancy complications, like early delivery or low weight of the baby at birth. We do not know if some ARVs are more likely to cause these effects than others. We do not yet know if CAB is safe in pregnancy. RPV does not appear to be a risk to pregnancy and the developing baby based on the information we know now, but additional data are still being collected.

There are few data from humans on the effects of CAB in pregnancy. Most of the information we have comes from animal studies. In studies done in pregnant rats and their newborns, using very high amounts of CAB, there were more baby rats that died when they were born or right after they were born. This did not happen to the baby rats when the mother got lower amounts of the drug, or no drug. The amount of CAB that we are giving in this study is expected to be more than 7-times lower than the amount given to the pregnant rats. Birth defects have not been found in any animal studies of CAB so far. We do not know whether what happened to the baby rats has any impact on what will happen in pregnant humans taking this drug.

Early results from one large study in Botswana showed that the ARV called dolutegravir (DTG) may increase the risk of serious birth defects of the brain or spine in the new baby. The increased risk was seen among babies whose mothers were taking DTG when they became pregnant. These birth defects happen during the first few weeks of pregnancy, before mothers may know they are pregnant. These birth defects have not been seen among babies whose mothers started taking DTG later in pregnancy.

CAB is not the same drug as DTG. We do know that CAB and DTG belong to the same class of medications and work in a similar way to treat HIV infection. We do not know if CAB can cause brain or spine defects in babies.

Participants who are able to become pregnant must agree to use certain effective methods of birth control to be in this study (see #6 above). If you become pregnant during the study, please let us know right away.

Immune reconstitution syndrome

In some people with advanced HIV infection, signs and symptoms from other infections or certain diseases (for example a liver condition called autoimmune hepatitis) may occur soon after starting combination ARVs but can also occur later. Some of these symptoms may be life threatening. If you start having new symptoms, or if you notice that any existing symptoms are getting worse after starting the ARVs, tell your doctor immediately.

Abnormal placement of body fat and wasting

The use of potent antiretroviral drug combinations may be associated with an abnormal placement of body fat and wasting. Some of the body changes include:

- Increase in fat around the waist and stomach area
- Increase in fat on the back of the neck
- Thinning of the face, legs, and arms
- Breast enlargement

24. There could be risks of disclosure of your information.

We will make every effort to keep your information private and confidential. Study records and specimens will be kept in secure, locked locations. All specimens and most records will be labeled only with a code number. However, your name will be written on some records.

Despite our best efforts to keep your information private, it is possible that the information could be obtained by someone who should not have it. If this were to happen, you could be treated badly or unfairly. You could feel stress or embarrassment.

To help us protect your privacy, we have obtained a Certificate of Confidentiality that protects us from 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 US federal government or from the US Food and Drug Administration. Regardless of the certificate, you can release information about your participation in the study to others, if you wish.

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 or adolescents 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 you may be used but your name will not be shared.

Benefits of the study

25. There may be a direct benefit to you from being in the study.

By joining the study, you will be part of the search for ARVs that may be better for adolescents. We do not know if being in the study will benefit you in any way. There may be a direct benefit to you by taking part in this study, but no guarantee can be made. For example, if you get shots of CAB and RPV, you might prefer having monthly shots instead of taking daily pills. The study ARVs may have fewer side effects than the previous ARVs you were taking. There may also be benefit if the results from this study lead to a safe and effective dose of the study drugs for adolescents. It is also possible that you may receive no direct benefit from this study. Information learned from this study may help other adolescents who have HIV.

You will have regular visits here and frequent checks on your health, including tests for amount of HIV in your blood, called viral load. It is possible that the study ARVs will slow your HIV infection. Information learned from this study may help other adolescents with HIV.

Other information about the study

26. There are no costs from being in the study.

There are no costs to you for study visits, CAB, RPV or procedures.

[Insert information about compensation/reimbursement here, e.g., You will be reimbursed for the cost of transport to study visits. For each visit, you will be given (specify amount)*.]*

27. Study records may be reviewed by study staff and groups that oversee the study.

Groups that oversee the study include:

- *[insert name of site IRB/EC]*
- *[insert name of site drug regulatory authority]*
- *[insert name of other site 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
- ViiV Healthcare (the company that makes CAB)
- Janssen Pharmaceuticals (the company that makes RPV)

The study staff and these groups are required 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 personally.

A description of this study will be available on ClinicalTrials.gov as required by U.S. law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

Your study information may be given to other authorities if required by law. *[Sites add more specific detail here as needed; example follows:]* For example, we are required to report any significant risk of harm to you or others.

28. If you get sick or injured, contact us immediately.

Your health is important to us. We will make every effort to protect your well-being and minimize risks. It is possible, however, that you could have an illness or injury that is study-related. This means that the illness or injury occurred as a direct result of the study procedures.

[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 treatment. The cost for this treatment may be charged to you or your insurance company. There is no program for compensation either through *[site name or]* the U.S. National Institutes of Health.

Whom to contact

29. If you have questions, concerns, or problems at any time, use these contacts.

- If you have questions about the study:
  [insert name and telephone number of investigator or other study staff]

- If you have questions about your rights as research participants or concerns about how you are being treated in the study:
  [insert name and telephone number of IRB/EC contact person or other appropriate person/organization]

- If you have any health or other problems that may be related to study participation:
  [insert name and telephone number of investigator or other study staff]

- If you want to leave the study:
  [insert name and telephone number of investigator or other study staff]

Signatures

If you agree to participate in Cohort 2B of 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.

If you decide to join, we will tell you any new information from this study or other studies that may affect your health, welfare, or willingness to stay in the study. You are welcome to ask questions or request more information at any time. If you want the results from this study, please tell the study staff.

You do not give up any rights by signing this form.
[Insert signature blocks as required by site IRB/EC policies.]

Signature blocks for participants of legal age to provide independent informed consent

_____ Participant's Name (print)	_____ Participant's Signature and Date
_____ Study Staff Conducting Consent Discussion (print)	_____ Study Staff Signature and Date
_____ Witness's Name (print) (As appropriate)	_____ Witness's Signature and Date

Signature blocks for parent/legal guardian of adolescent:

_____ Name of Parent/Legal Guardian (print)	_____ Signature of Parent/Legal Guardian and Date
_____ Study Staff Conducting Consent Discussion (print)	_____ Study Staff Signature and Date
_____ Witness's Name (print) (As appropriate)	_____ Witness's Signature and Date

Appendix II-D: Sample Informed Consent Form for Specimen Storage and Future Use

for adolescents who can provide independent informed consent for study participation and parents/legal guardians of adolescents

IMPAACT 2017
Phase I/II Study of the Safety, Acceptability, Tolerability, and Pharmacokinetics of Oral and Long-Acting Injectable Cabotegravir and Long-Acting Injectable Rilpivirine in Virologically Suppressed HIV-Infected Children and Adolescents

Version 4.0, dated 27 May 2022

[Throughout this form sites may modify to remove mentions of HIV and ARVs for participants who do not know their status].

If you are the parent or legal guardian of a child who may take part in this study, your permission and the permission of your child will be needed. When "you" appears in this form, it refers to your child except where it says otherwise.

You have decided to join the study named above. As part of the study, you will have blood and urine collected. After these samples are tested for the study, some samples may be 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.

This form gives information about use of extra samples. Please read it, or have it read to you, and ask any questions you may have. After we discuss the information with you, you will record your decisions on use of extra samples at the end of the form.

1. It is your decision whether or not to allow the extra samples to be used.

You are free to say yes or no, and to change your mind at any time. Your decision will not affect your participation in the study. If you say no, all extra samples will be destroyed.

2. If you agree, your extra samples will be kept in a repository.

A repository is a secure facility that is used to store samples. The IMPAACT Network repository is in the United States. If you agree to have 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 insert time limits or additional site-specific requirements here if required by local authorities]*.

3. Extra samples could be used for different types of research.

Extra samples may be used for research on HIV, the immune system, and other diseases. The research may be done in the United States or in other locations.

If you agree, the extra samples could also be used for research that looks at your 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 samples would only be used to look at genes related to HIV and the immune system. Testing of all your genes, which is sometimes called whole genome sequencing, will not be done.

Any research done with the extra samples must be reviewed and approved by the IMPAACT Network. The research must also be approved by an ethics committee. The role of an ethics committee is to review the research plan and protect the rights and well-being of the people whose samples will be used.

The research done with extra samples is not expected to give any information relevant to your health. Therefore, the results will not be given to the study staff or to you. The results also will not be placed in your study records.

4. There is little risk to you.

When extra samples are used for research, they are labeled with a code number only. To protect your privacy, no names are used. However, information such as age, sex, HIV status, and other health information may be linked to the samples. Information on the ARVs you received in the study may also be linked to the samples. The only link between the code number and your name is kept here at [*site name*]. Your name will not be given to other researchers.

There may be some risks from tests of your genes. If others found out the results of these tests, they could treat you badly or unfairly. However, this is almost impossible because the results will not be given to the study staff, or to you, and will not be in your study records.

5. There may be no benefit to you.

By allowing extra samples to be used for research, you will be part of the search for new information that may benefit people with HIV in the future. However, the research done with the extra samples is not expected to directly benefit you in any way.

6. You will not be paid for use of your samples.

There is no cost to you for use of your extra samples. The samples will not be sold, and you will not be paid for use of the samples. It is possible that research done with the samples could lead to a new discovery or a new product. If this happens, there is no plan to share any money with you.

7. Information from research using extra samples may be reviewed by groups that oversee the research.

These groups include:
- The IMPAACT Network
- The ethics committees that review and approve the research
- Government and other agencies that pay for the research
- Government and other agencies that monitor the research
- Other local, US, or international regulatory entities

The people who do research with the extra samples and the groups listed above are required to make efforts to keep information private and confidential.

The results of research done with the extra samples may be presented publicly or published. However, no presentation or publication will use your name or identify you personally.

8. If you have questions, concerns, or problems at any time, use these contacts.

- If you have questions about use of your extra samples:
  [insert name and telephone number of investigator or other study staff].

- If you later change your mind about use of your extra samples:
  [insert name and telephone number of investigator or other study staff].

- If you have questions about your rights as a research participant or concerns about how you are being treated in the study:
  [insert name and telephone number of IRB/EC contact person or other appropriate person/organization].

Signatures

Before deciding whether your extra samples to be used for research, make sure you have read this form, or had it read to you. Make sure all of your questions have been answered. You should feel that you understand your options and the possible risks and benefits before making your decision.

You do not give up any rights by signing this form.

[Insert initial and signature blocks as required by site IRB/EC policies and the IRB/EC determination if the level of risk to children in the categories specified in 45 CFR 46.404-407. Separate consent decisions must be documented for genetic testing].

For YOUR extra samples, write your initials or make your mark next to your choice.

_____ I allow my extra samples to be used for research on HIV, the immune system, ARVs, and other diseases. I also allow my samples to be used for tests of my genes.

_____ I allow my extra samples to be used for research on HIV, the immune system, ARVs, and other diseases. I do not allow my samples to be used for tests of my genes.

_____ I do not allow my extra samples to be used for any research.

Signature blocks for participants of legal age to provide independent informed consent

_____	_____
Participant's Name (print)	Participant's Signature and Date
_____	_____
Study Staff Conducting Consent Discussion (print)	Study Staff Signature and Date
_____	_____
Witness's Name (print) (As appropriate)	Witness's Signature and Date

Signature blocks for parent/legal guardian of adolescent:

_____	_____
Name of Parent/Legal Guardian (print)	Signature of Parent/Legal Guardian and Date
_____	_____
Study Staff Conducting Consent Discussion (print)	Study Staff Signature and Date
_____	_____
Witness's Name (print) (As appropriate)	Witness's Signature and Date

Appendix III: Sample Informed Assent Forms

Appendix III-A: Sample Informed Assent Form for Participation in Cohort 1

for adolescents who cannot provide independent informed consent for study participation

IMPAACT 2017
Phase I/II Study of the Safety, Acceptability, Tolerability, and Pharmacokinetics of Oral and Long-Acting Injectable Cabotegravir and Long-Acting Injectable Rilpivirine in Virologically Suppressed HIV-Infected Children and Adolescents

Version 4.0, dated 27 May 2022

[Throughout this form sites may modify to remove mentions of HIV and ARVs for participants who do not know their status].

Introduction

You are being asked to take part in a research study. To take part in this study, you must give your permission. Your parent/guardian must also give their permission.

This form gives information about 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 you need to understand the study. We will ask you questions to see if we have explained the study clearly.

After you understand the study, if you decide to take part, you will sign or make your mark on this form. You will be offered a copy to keep.

About the study

This study is for 12 to 17-year-olds who are living with HIV. The study will test two anti-HIV medicines (antiretrovirals or ARVs). The ARVs are called cabotegravir (CAB) and rilpivirine (RPV).

People living with HIV take a combination of ARVs to stay healthy. There are not as many ARVs available for children and teenagers as for adults, because many ARVs have only been tested in adults. ARVs can be made in different forms, such as liquids, pills, and injections (shots). The study will test CAB and RPV pills and shots. The pills are taken every day. The shots are given every 4 or 8 weeks. The shots are being developed because it can be difficult to take pills every day, and some people may prefer having shots instead of taking pills.

The study drugs have approved by the US Food and Drug Administration (FDA) for adults and adolescents living with HIV. The FDA is the part of the government that regulates medicines in the United States. The approvals are based on information learned from this study and from studies which showed that CAB and RPV were safe and well tolerated in adults. The adult studies also showed that the CAB and RPV shots worked well to control HIV. So far, the testing in this study has shown that the study drugs also work well for adolescents. However, because these are still being tested, there may be some effects that we do not know about yet. More information is needed from this study so that the study drugs can be approved for adolescents in more countries.

There will be three groups in the study, called Cohort 1, Cohort 2A and Cohort 2B. **This form is about Cohort 1.**

What happens in the study

If you decide to take part in the study, we will check your medical records and examine you to see if you qualify. This will include looking at your genitals to see how developed you are. We will ask you and your parent/guardian questions about your health and the medications you take. We will collect blood for tests. We will also do a test of your heart called an ECG.

For participants assigned female at birth, we will do a pregnancy test. If you are pregnant, you cannot take part in the study. Participants who are able to become pregnant must agree to use certain methods of birth control in order to take part in the study. If you become pregnant during the study, you will stop getting CAB or RPV pills or shots and will enter the long-term follow-up safety phase of the study. We will also contact you to find out the outcome of the pregnancy, even if the outcome occurs after leaving the study.

[Sites may modify the following paragraph to include locally appropriate language regarding disclosure of pregnancy results to parents or guardians: As soon as the pregnancy test result is available, we will go over it with you in private, without your parents/guardians present. We will not share these results with your parents/guardians unless you tell us it is okay to share the results. If the test shows that you are pregnant, we will give you information on where medical care and other services can be received.*]*

We give you your test results and explain them to you. If you qualify, you can join the study. If you do not join the study, we will still use some information collected about you (for example age, sex, and race). We will use this information to look at patterns or common reasons for not entering the study.

First phase of the study

The study has three phases. If you join, you will start in the first phase. You will be given CAB or RPV pills to take <u>in addition to</u> the other ARVs you are already taking. The RPV pills should be taken with a meal. It is important to keep taking <u>all</u> your ARVs as instructed.

You will have 3 study visits over 4-6 weeks (about one month). At these visits, we will:

- Collect information from your medical records.
- Ask questions about your health, ARVs, and other medications.
- Give you a physical exam.
- Collect blood for tests. This will be done using a needle in your arm.
- For participants assigned female at birth, collect blood or urine for a pregnancy test.

Each visit will take about 1-3 hours.

At the second visit, we will look very closely at the amount of CAB or RPV in your blood. To do this, we will collect your blood different times over 8 hours (one full day). If you are taking CAB, we will collect your blood 6 times. If you are taking RPV, we will collect your blood 3 times. *[Sites: modify language as appropriate to indicate procedures for the intensive PK collection:* A small tube will be placed in your arm and attached to a plastic needle to draw your blood, so we do not need to stick you with a needle each time. The plastic tube may stay in place for 8 hours. You may need to stay at the clinic or hospital for up to 8 hours. If the study clinic is able, you may be able to stay at the clinic the night before and during this visit.*]*

Second phase of the study

At the fourth study visit, we will review all your test results to see if you qualify for the second phase of the study. This visit could be combined with your third visit.

- If you do not qualify, you will stop taking CAB or RPV pills. You will have one more visit about 4 weeks later. This visit will be like the other visits described above.
- If you qualify, you can enter the second phase of the study

In the second phase of the study you will have 5 more study visits over 12 weeks (about 3 months). At these visits, we will:
- Collect information from your medical records.
- Ask questions about your health, ARVs, and other medications.
- Give you a physical exam. At the last visit, we will also look at your genitals again to see how developed you are.
- Collect blood for tests. This will be done using a needle in your arm.
- For participants assigned female at birth, collect blood or urine for a pregnancy test.
- At two of these visits, we may do an ECG test to look at your heart.

Each visit will take about 1-3 hours.

During the second phase of the study, you will not take CAB or RPV pills. Instead, you will be given shots of CAB or RPV. The shots will be given 2 times (4 weeks apart). You will get one shot in the buttocks (bottom, "cheeks") each time. You will keep taking your other ARVs while getting the shots.

[U.S. sites only] You may also be contacted to answer questions over the phone about how you feel about the shots.

After 12 weeks, we will review your tests to see if you are eligible for Cohort 2.
- If you do not qualify, or if Cohort 2 isn't ready yet, you will stop getting shots of CAB or RPV. You will enter into the third phase, which is also called the long-term safety follow-up phase of the study. This is described below.
- If you qualify, and when Cohort 2 is ready, you can enter Cohort 2.

[Sites to modify] Some visit activities may be offered off-site or by phone. This might only happen if you are unable to come the clinic. The study staff will discuss this with you if it is an option. They will also discuss the location and time to visit you so that the visit is at a time and place when you feel comfortable and confidentiality can be maintained.

Long-term safety follow-up phase of the study

You will have 3 or 4 study visits over 48 weeks (about 1 year). The visits will be like the visits described above.

You will not be given CAB or RPV pills or shots. You will keep taking your other ARVs.

Risks of the study

Having blood collected may cause pain, bleeding, bruising, swelling, or infection where the needle goes in your arm.

Having shots of CAB or RPV may cause pain, irritation, redness, bumps, swelling, itching, or bruising on the buttocks (where the shot is given). When CAB and RPV are given as shots, they stay in the body for much longer than when CAB and RPV are taken as pills.

The shots will be given in the muscles of your buttocks. The shot could be given too deeply or not deeply enough, missing the muscle and entering your skin, blood, or a nerve. The side effects of shot missing the muscle are not well understood but could make CAB or RPV levels too low or too high. If too low the drug may not work against your HIV. If RPV is too high, there could be a change in your heartbeat, which in severe cases can be life-threatening. In rare cases, symptoms such as feeling lightheaded, numbness or tingling, difficulty breathing, chest or stomach discomfort, sweating, rash, pain (e.g., back and chest), nausea and/or feeling anxious have occurred after RPV shot. Not all participants reported such symptoms. Most of the symptoms resolved within minutes. Your doctor may need to administer treatment to help resolve these symptoms. Everything possible will be done to decrease this risk, including watching you for problems during the study. We will also draw blood (less than 1 teaspoon) about 2 hours after the study shot to look at the amount of study drugs in your blood.

CAB and RPV can cause other side effects. These side effects are common, but not everyone will have them. You may have pain, feel sick to your stomach, or vomit (throw up). You may have diarrhea. You may have a headache, fever, runny nose, sore throat, dry mouth, or rash. You may have trouble sleeping or a lack of energy. You may not want to eat as much as you usually do. You may feel lightheaded or sad. You may have problems in other parts of the body, such as your liver.

We do not yet know if CAB or RPV are safe in pregnancy. Early results from one study showed that the ARV called dolutegravir (DTG) may increase the risk of serious birth defects in the new baby. These mothers were taking the drug before they knew they were pregnant. The birth defects have not been seen when mothers started taking DTG later in pregnancy. CAB is not the same drug as DTG. We do not know if CAB can cause the same defects in babies.

Participants who are able to become pregnant must agree to use certain methods of birth control to be in this study. If you become pregnant during the study, please let us know right away.

We will check for side effects at each study visit. Please tell us if you have any side effects or don't feel well. We will also check the amount of HIV in your blood. If you have side effects, or if the amount of HIV in your blood is higher than expected, you may have extra visits. We will talk with you and your parent/guardian about this, and tell you what to do about any side effects. We will also tell you if you can keep taking CAB or RPV. In some cases, you may have to stop taking CAB or RPV.

All information collected for this study will be kept private and confidential. However, it is possible that information could be obtained by someone who should not have it. If this were to happen, you could be treated badly or unfairly. You could feel stressed or embarrassed.

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:

- *[insert name of site IRB/EC]*
- *[insert name of site drug regulatory authority]*
- *[insert name of other site 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
- ViiV Healthcare (the company that makes CAB)

- Janssen Pharmaceuticals (the company that makes RPV)

The study staff and these groups are required 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 personally.

A description of this study will be available on ClinicalTrials.gov as required by U.S. law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

[Sites may modify this paragraph to reflect local reporting requirements and legal statues: Your study information may be shared with other authorities if required by law. Public health authorities are required by law to receive information for the prevention or control of disease, injury or disability. (We must follow laws requiring the reporting of suspected child abuse and neglect).]

Benefits of the study

By joining the study, you will be part of the search for new ARVs for adolescents. The information learned in this study could someday lead to better ARVs for adolescents. However, being in this study may not be of any benefit to you.

Your rights

Taking part in this study is voluntary. You can say yes or no. If you say yes now, you can change your mind later. Your decision will have no effect on the medical care you normally receive.

Who to contact

If you have questions about the study:
[insert name and telephone number of investigator or other study staff]

If you have questions about your rights or how you are treated in the study:
[insert name and telephone number of IRB/EC contact person or other appropriate person/organization]

If you have problems related to being in the study:
[insert name and telephone number of investigator or other study staff]

If you want to leave the study:
[insert name and telephone number of investigator or other study staff]

Signatures

If you want to take part in this study, sign or make your mark below.

Before deciding whether to take part in 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 if you decide to take part.

We will tell you and your parent/guardian any new information that may affect your willingness to stay in the study. You can ask questions or ask for more information at any time.

You do not give up any rights by signing this form.

[Insert signature blocks as required by site IRB/EC policies.]

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 III-B: Sample Informed Assent Form for Participation in Cohort 2
for adolescents who cannot provide independent informed consent for study participation

IMPAACT 2017
Phase I/II Study of the Safety, Acceptability, Tolerability, and Pharmacokinetics of Oral and Long-Acting Injectable Cabotegravir and Long-Acting Injectable Rilpivirine in Virologically Suppressed HIV-Infected Children and Adolescents

Version 4.0, dated 27 May 2022

[Throughout this form sites may modify to remove mentions of HIV and ARVs for participants who do not know their status].

Introduction

You are being asked to take part in a research study. To take part in this study, you must give your permission. Your parent/guardian must also give their permission.

This form gives information about 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 you need to understand the study. We will ask you questions to see if we have explained the study clearly.

After you understand the study, if you decide to take part, you will sign or make your mark on this form. You will be offered a copy to keep.

About the study

This study is for 12 to 17-year-olds who are living with HIV. The study will test two anti-HIV medicines (antiretrovirals or ARVs). The ARVs are called cabotegravir (CAB) and rilpivirine (RPV).

People living with HIV take a combination of ARVs to stay healthy. There are not as many ARVs available for children and teenagers as for adults, because many ARVs have only been tested in adults. ARVs can be made in different forms, such as liquids, pills, and injections (shots). The study will test CAB and RPV pills and shots. The pills are taken every day. The shots are given every 4 or 8 weeks. The shots are being developed because it can be difficult to take pills every day, and some people may prefer having shots instead of taking pills.

The study drugs have approved by the US Food and Drug Administration (FDA) for adults and adolescents living with HIV. The FDA is the part of the government that regulates medicines in the United States. The approvals are based on information learned from this study and from studies which showed that CAB and RPV were safe and well tolerated in adults. The adult studies also showed that the CAB and RPV shots worked well to control HIV. So far, the testing in this study has shown that the study drugs also work well for adolescents. However, because these are still being tested, there may be some effects that we do not know about yet. More information is needed from this study so that the study drugs can be approved for adolescents in more countries.
There will be three groups in the study, called Cohort 1, Cohort 2A and Cohort 2B. **This form is about Cohort 2A and Cohort 2B.**

What happens in the study

If you decide to take part in the study, we will check your medical records and examine you to see if you qualify. This will include looking at your genitals to see how developed you are. We will ask you and your

parent/guardian questions about your health and the medications you take. We will collect blood for tests. We will also do a test of your heart called an ECG. We will also talk with you about whether you should join Cohort 2A or Cohort 2B. Participants in Cohort 2A take the study pills and then get the study shots. Participants in Cohort 2B will only get the study shots. Once you have entered the study, you cannot switch to the other group.

For participants assigned female at birth, we will do a pregnancy test. If you are pregnant, you cannot take part in the study. Participants who are able to become pregnant must agree to use certain methods of birth control in order to take part in the study. If you become pregnant during the study, you will stop getting CAB and RPV pills or shots and will enter the long-term follow-up safety phase of the study. We will also contact you to find out the outcome of the pregnancy, even if the outcome occurs after leaving the study.

[Sites may modify the following paragraph to include locally appropriate language regarding disclosure of pregnancy results to parents or guardians: As soon as the pregnancy test result is available, we will go over it with you in private, without your parents/guardians present. We will not share these results with your parents/guardians unless you tell us it is okay to share the results. If the test shows that you are pregnant, we will give you information on where medical care and other services can be received.*]*

We give you your test results and explain them to you. If you qualify, you can join the study. If you do not join the study, we will still use some information collected about you (for example age, sex, and race). We will use this information to look at patterns or common reasons for not entering the study.

The first phase of the study is only for the Cohort 2A group

The study has three phases. If you join, you will start in the first phase. You will be given CAB and RPV pills to start taking. The pills should be taken with a meal. You will stop taking the other ARVs you were taking before.

You will have 3 study visits over 4-6 weeks (about one month). At these visits, we will:

- Collect information from your medical records.
- Ask questions about your health, ARVs, and other medications.
- Give you a physical exam.
- Collect blood for tests. This will be done using a needle in your arm.
- For participants assigned female at birth, collect blood or urine for a pregnancy test.

Each visit will take about 1-3 hours.

At the second visit, we will look at the amount of CAB and RPV in your blood. To do this, we will collect your blood once before you take CAB and RPV and again about 3 hours after you have taken CAB and RPV. *[Sites: modify language as appropriate to indicate procedures for the intensive PK collection:* A small tube will be placed in your arm and attached to a plastic needle to draw your blood, so we do not need to stick you with a needle each time. The plastic tube may stay in place for 3 hours.*]*

If you join in the Cohort 2A group, then at the fourth study visit we will review all your test results to see if you qualify for the second phase of the study. This visit could be combined with your third visit.

- If you do <u>not</u> qualify for the second phase of the study, you will stop taking CAB or RPV pills. You will have one more visit about 4 weeks later. This visit will be like the other visits described above.
- If you qualify, you can enter the second phase of the study

The second phase of the study is for both the Cohort 2A and the Cohort 2B groups

In the second phase of the study, you will have 14 study visits over about 2 years. The visits will be like the visits described above. At two of these visits, we will also look at your genitals again to see how developed you are.

During the second phase of the study, you will be given shots of CAB and RPV. The shots will be given at 13 of the study visits (4 weeks and then 8 weeks apart). You will get one shot of CAB and one shot of RPV each time. The shots will be in the buttocks (bottom, "cheeks"). The shots may be given on the same side of the buttocks or on different sides.

[U.S. sites only] You may also be contacted to answer questions over the phone about how you feel about the shots.

If you join in the Cohort 2A group, then you will need to complete the first phase of the study (the study pills phase) before starting this second phase of the study.

If you join in the Cohort 2B group, then you will skip the first phase and go directly to the second phase of the study (the study shots phase). At the first visit, we will also do an ECG test of your heart.

After you finish the study visits in Cohort 2, you might be able to keep getting shots of CAB and RPV. If you do not want to keep getting shots of CAB and RPV at your last study visit, or if you have to stop the shots early during your study visits, then you will enter the third phase. This phase is described below.

[Sites to modify] Some visit activities may be offered off-site or by phone. This might only happen if you are unable to come the clinic. The study staff will discuss this with you if it is an option. They will also discuss the location and time to visit you so that the visit is at a time and place when you feel comfortable and confidentiality can be maintained.

Study staff may ask you to return to the clinic for a study shot before your next visit. If so, then many of the procedures described above would also be done again.

If you cannot come to the clinic for a visit when you need the study shots, then you might have the option to take the study pills again. You would take the study pills until you are able to come back to the clinic to get the study shot. If this happens, then you may need to get the study shots 4 weeks apart and then 8 weeks apart. If you cannot return to the clinic to get the study shots soon, then you may need to stop taking the study ARVs and enter the long-term safety follow-up phase. This is not preferred, and it is important to get the study shots on the scheduled day and not miss any visits.

The third phase of the study is called the long-term safety follow-up phase

The third phase of the study is for participants who have to stop the study shots early in the Cohort 2A or Cohort 2B groups. Participants who become pregnant will also stop their study medicines and join the third phase of the study. This phase is also called the long-term safety follow-up phase. You will have 4 study visits over 48 weeks (about 1 year). The visits will be like the visits described above.

You will <u>not</u> be given CAB and RPV pills or shots. You will go back to taking your other ARVs.

Risks of the study

Having blood collected may cause pain, bleeding, bruising, swelling, or infection where the needle goes in your arm.

Having shots of CAB or RPV may cause pain, irritation, redness, bumps, swelling, itching, or bruising on the buttocks (where the shot is given). When CAB and RPV are given as shots, they stay in the body for much longer than when CAB and RPV are taken as pills.

The shots will be given in the muscles of your buttocks. The shot could be given too deeply or not deeply enough, missing the muscle and entering your skin, blood, or a nerve. The side effects of shot missing the muscle are not well understood but could make CAB or RPV levels too low or too high. If too low the drug may not work against your HIV. If RPV is too high, there could be a change in your heartbeat, which in severe cases can be life-threatening. In rare cases, symptoms such as feeling lightheaded, numbness or tingling, difficulty breathing, chest or stomach discomfort, sweating, rash, pain (e.g., back and chest), nausea and/or feeling anxious have occurred after RPV shot. Not all participants reported such symptoms. Most of the symptoms resolved within minutes. Your doctor may need to administer treatment to help resolve these symptoms. Everything possible will be done to decrease this risk, including watching you for problems during the study. We will also draw blood (less than 1 teaspoon) about 2 hours after the study shot to look at the amount of study drugs in your blood.

CAB and RPV can cause other side effects. These side effects are common, but not everyone will have them. You may have pain, feel sick to your stomach, or vomit (throw up). You may have diarrhea. You may have a headache, fever, runny nose, sore throat, dry mouth, or rash. You may have trouble sleeping or a lack of energy. You may not want to eat as much as you usually do. You may feel lightheaded or sad. You may have problems in other parts of the body, such as your liver.

We do not yet know if CAB or RPV are safe in pregnancy. Early results from one study showed that the ARV called dolutegravir (DTG) may increase the risk of serious birth defects in the new baby. These mothers were taking the drug before they knew they were pregnant. The birth defects have not been seen when mothers started taking DTG later in pregnancy. CAB is not the same drug as DTG. We do not know if CAB can cause the same defects in babies.

Participants who are able to become pregnant must agree to use certain methods of birth control to be in this study. If you become pregnant during the study, please let us know right away.

We will check for side effects at each study visit. Please tell us if you have any side effects or don't feel well. There is also a risk that the CAB and RPV pills and shots won't control the HIV as well as the ARVs you were taking before. We will check the amount of HIV in your blood at each study visit. If you have side effects, or if the amount of HIV in your blood is higher than expected, you may have extra visits. We will talk with you and your parent/guardian about this, and tell you what to do about any side effects. We will also tell you if you can keep taking CAB and RPV. In some cases, you may have to stop taking CAB and RPV.

All information collected for this study will be kept private and confidential. However, it is possible that information could be obtained by someone who should not have it. If this were to happen, you could be treated badly or unfairly. You could feel stressed or embarrassed.

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:

- *[insert name of site IRB/EC]*
- *[insert name of site drug regulatory authority]*
- *[insert name of other site 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
- ViiV Healthcare (the company that makes CAB)
- Janssen Pharmaceuticals (the company that makes RPV)

The study staff and these groups are required 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 personally.

A description of this study will be available on ClinicalTrials.gov as required by U.S. law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

[Sites may modify this paragraph to reflect local reporting requirements and legal statues: Your study information may be shared with other authorities if required by law. Public health authorities are required by law to receive information for the prevention or control of disease, injury or disability. (We must follow laws requiring the reporting of suspected child abuse and neglect).]

Benefits of the study

By joining the study, you will be part of the search for new ARVs for adolescents. The information learned in this study could someday lead to better ARVs for adolescents. However, being in this study may not be of any benefit to you.

Your rights

Taking part in this study is voluntary. You can say yes or no. If you say yes now, you can change your mind later. Your decision will have no effect on the medical care you normally receive.

Who to contact

If you have questions about the study:
[insert name and telephone number of investigator or other study staff]

If you have questions about your rights or how you are treated in the study:
[insert name and telephone number of IRB/EC contact person or other appropriate person/organization]

If you have problems related to being in the study:
[insert name and telephone number of investigator or other study staff]

If you want to leave the study:
[insert name and telephone number of investigator or other study staff]

Signatures

If you want to take part in this study, sign or make your mark below.

Before deciding whether to take part in 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 if you decide to take part.

We will tell you and your parent/guardian any new information that may affect your willingness to stay in the study. You can ask questions or ask for more information at any time.

You do not give up any rights by signing this form.

[Insert initial and signature blocks as required by site IRB/EC policies.]

Please write your initials or make your mark next to your choice of either the Cohort 2A or the Cohort 2B group:

_____ I agree 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 I cannot switch the group after entering the study.

_____ I agree 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 I cannot switch the group after entering the study.

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 III-C: Sample Informed Assent Form for Specimen Storage and Future Use for Participants *who cannot provide independent informed consent*

IMPAACT 2017
Phase I/II Study of the Safety, Acceptability, Tolerability, and Pharmacokinetics of Oral and Long-Acting Injectable Cabotegravir and Long-Acting Injectable Rilpivirine in Virologically Suppressed HIV-Infected Children and Adolescents

Version 4.0, dated 27 May 2022

[Throughout this form sites may modify to remove mentions of HIV and ARVs for participants who do not know their status].

Introduction

As part of the study, you will have blood and urine collected. After these samples are tested for the study, some samples may be 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.

You are being asked for permission to keep your extra samples and use them for other research in the future. Your parent/guardian will also be asked for permission.

This form gives information about extra samples. Please read it, or have it read to you, and ask any questions you may have. After we talk about the information with you, you will record your decisions at the end of the form.

What happens with extra samples

If you allow your extra samples to be kept, there is no limit on how long they will be kept.

The samples may be used for research on HIV, the immune system, and other diseases.

If you agree, the samples could be used for research that looks at your 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 samples would only be used to look at genes related to HIV and the immune system. All your genes will not be tested.

The results of tests done with your samples will not be given to you or your parent/guardian.

Risks and benefits

When extra samples are kept for research, they are labeled with a code number only. No names are used. Therefore, there is very little risk to your privacy. Your name will not be given to other researchers.

By allowing extra samples to be used for research, you will be part of the search for new information that may benefit people with HIV in the future. However, the research done with extra samples is not expected to be of benefit to you.

Information from research using extra samples may be reviewed by groups that oversee the research

These groups include:

- The IMPAACT Network
- The ethics committees that review and approve the research
- Government and other agencies that pay for the research
- Government and other agencies that monitor the research
- Other local, US, or international regulatory entities

The people who do research with the extra samples and the groups listed above are required to make efforts to keep information private and confidential.

The results of research done with the extra samples may be presented publicly or published. However, no presentation or publication will use your name or identify you personally.

Your rights

It is up to you and your parent/guardian to decide if your extra samples can be used for research. You can say yes or no. If you say yes now, you can change your mind later. Your decision will have no effect on your participation in the study. If you say no, all extra samples will be destroyed.

Who to contact

If you have questions about use of your extra samples:
[*insert name and telephone number of investigator or other study staff*].

If you change your mind about use of your extra samples:
[*insert name and telephone number of investigator or other study staff*].

If you have questions about your rights or how you are treated in the study:
[insert name and telephone number of IRB/EC contact person or other appropriate person/organization]

Signatures

Before deciding whether to allow your extra samples to be used for research, 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 your choices and the possible risks and benefits before making your decision.

You do not give up any rights by signing this form.

[Insert initial and signature blocks as required by site IRB/EC policies. Separate consent decisions must be documented for genetic testing].

Please write your initials or make your mark next to your choices:

_____ I allow my extra samples to be used for research on HIV, the immune system, and other diseases.

_____ I allow my extra samples to be used for tests of my genes.

_____ I do <u>not</u> allow my extra samples to be used for any research.

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 IV: Parent/Caregiver Participation in Qualitative Phone Interviews (U.S. Sites Only)

Appendix IV-A: Parent/Caregiver Qualitative Phone Interviews

Parents or caregivers of adolescent participants enrolled at U.S. study sites will be selected by the protocol interview team for enrollment into the study to conduct a single in-depth qualitative phone interview, with the purpose of evaluating their perceptions of adolescent acceptability and tolerability of CAB LA and/or RPV LA. The phone interviews with parents/caregivers will be conducted separately and apart from any phone interviews conducted with adolescent participants.

The protocol interview team will notify sites to initiate recruitment of the selected parent/caregiver. After obtaining consent, sites will confirm eligibility for the parent/caregiver to take part in the interview. Parents/caregivers meeting eligibility criteria will be enrolled as study participants, and site staff will work with the protocol interview team and the enrolled parent/caregiver to schedule and conduct the phone interview. Further details relating to these processes and procedures are provided below.

Protocol Section 11 provides information and details regarding the qualitative phone interviews with the adolescent participants.

1 Sample Size, and Selection Process

Enrolled adolescent participants at U.S. study sites will be selected by the protocol interview team for their parent/caregiver to be recruited by site staff to take part in a single in-depth qualitative interview for a maximum of 60 completed phone interviews: 30 phone interviews completed by parents/caregivers of Cohort 1 adolescent participants, and 30 phone interviews completed by parents/caregivers of Cohort 2 adolescent participants. The sample size is based on the likely number of interviews needed to achieve thematic saturation. Parent/caregiver selection for the interviews will continue until there is either saturation of themes among the parent/caregiver interview data, or the parent/caregiver maximum sample size is reached. See Protocol Section 11.6 regarding thematic saturation and qualitative interview data analyses.

Parent/caregiver selection is based on the adolescent participant's reported demographics from the adolescent's Screening and Entry visits, with the goal of balancing interviewed parents/caregivers across participants assigned female/male at birth and older/younger adolescent participants. Additionally, parents/caregivers of participants who permanently discontinue injectable study product will be purposefully selected. This will ensure that perspectives from parents/caregivers across the range of enrolled participants are reflected in the final analysis. Parents/caregivers will be selected across multiple sites, but restricted to those willing and able to conduct the interview in English.

When possible, parents/caregivers of adolescents also participating in interviews will be selected to allow for dyadic comparisons between the parents'/caregivers' and adolescents' perspectives. However, a parent/caregiver of an adolescent participant may be selected to take part in the qualitative phone interview even if their adolescent participant is not selected or does not complete a (separate) qualitative phone interview.

The interviews must be completed within the applicable specified interview window (see Appendix IV-A Section 2 below). Parents/caregivers will be selected on an on-going basis, and as their adolescent participant approaches the parent/caregiver interview procedural window. Parents/caregivers of

adolescent participants enrolling to the study early will be selected for interviews first, as their adolescent participant will be the first to receive the injectable study products. The selection process will continue until thematic saturation or the sample size is reached for each Cohort; therefore, some parents/caregivers may be selected after entering the interview procedure window. Parents/caregivers who complete an interview for Cohort 1 will not be eligible to complete an interview for Cohort 2.

2 Phone Interview Procedural Windows

The qualitative phone interviews will be conducted with selected parents/caregivers of adolescent participants within the following timeframes:

- Parents/caregivers of Cohort 1 adolescent participants: Between the adolescent participant's Week 4b and Week 12 visits (inclusive), or during LSFU visits.

- Parents/caregivers of Cohort 2A adolescent participants: Between the adolescent participant's Week 24 and Week 96 visits (inclusive), or during LSFU visits.

- Parents/caregivers of Cohort 2B adolescent participants: Between the adolescent participant's Week 20 and Week 92 visits (inclusive), or during LSFU visits.

3 Recruitment Considerations

The protocol interview team will notify sites of an adolescent participant's PID to then initiate the recruitment of the adolescent participant's parent/caregiver. Recruitment of the parent/caregiver will generally rely on the enrolled adolescent participant identifying the potentially eligible parent/caregiver and referring him/her to site staff for the qualitative interview; site staff may also identify a potentially eligible parent/caregiver (of the selected adolescent participant) as they present to the study clinic.

Sites must source document notification by the protocol interview team of adolescent participant selection for parent/caregiver recruitment, all attempts to contact the adolescent participant for parent/caregiver recruitment. Sites must follow their IRB/EC approved recruitment methods for approaching a potential parent/caregiver participant. Further guidance on recruitment considerations and processes is provided in the IMPAACT 2017 MOP.

Eligibility criteria for parents/caregivers are provided in Protocol Section 4.5, and details regarding confirmation of eligibility criteria and the enrollment process are provided in Appendix IV-A Section 5 below.

4 Consenting Considerations

Parents/caregivers must provide consent prior to enrollment and conducting the phone interview. After recruitment of a selected and potentially eligible parent/caregiver, study staff will provide information, education, and counseling as part of the study informed consent process for the qualitative phone interview. The consent process will include information exchange, discussion, and assessment of understanding of all required elements of informed consent, including the potential risks, benefits, and alternatives to study participation. Study staff will also provide time to address any questions or concerns the parent/caregiver may have, and an assessment of understanding, before proceeding to a consenting decision.

Obtaining informed consent from the parent/caregiver for the phone interview is ideally conducted in person and in writing by the parent/caregiver signing the informed consent form. Appendix IV-B provides a sample written informed consent form for parent/caregiver study participation in the qualitative phone interview which sites may modify for use. If the parent/caregiver is unable to read, the process for consenting illiterate participants, as defined or approved by the local IRB/EC, should be followed.

Sites have the option of seeking a waiver from their IRB/EC of the requirement to obtain written documentation of the consent process for parent/caregiver participation in the qualitative phone interview. Consistent with DAIDS policies on the requirements for obtaining informed consent (https://ohsr.od.nih.gov/public/SOP_12_v5_5-22-2017.pdf), when the IRB/EC considers waiving the requirement to obtain written documentation of the consent process, the IRB/EC reviews a written description of the information that will be provided, either verbally or in writing, to the parents/caregivers. Appendix IV-C provides a sample of a script or statement which sites may modify for use, should an IRB/EC grant a waiver of written documentation.

Additionally, sites also have the option of seeking IRB/EC approval for obtaining parent/caregiver consent by telephone, rather than in person. In such instances, a witness to the consent process (e.g., another study or non-study staff member) must be present at the time of the study site staff obtaining consent from the parent/caregiver, and should ideally also listen in to the consenting discussion between the parent/caregiver and study staff member. Appendix IV-C may be modified for use as a verbal script to obtain consent by telephone. If telephone consent is used and the parent/caregiver is seen at the site prior to conducting the phone interview, it is recommended to re-confirm the parent/caregiver's understanding of the phone interview and willingness to participate through an additional, brief consent process, as required by the IRB.

Study sites are permitted to develop a separate parent/caregiver consent form and/or script for this study, if required by site or IRB/EC policies and procedures. Sites must establish and maintain an informed consent SOP with written procedures describing standards for obtaining informed consent, and roles and responsibilities of study staff involved in obtaining informed consent for all the consenting options being utilized for the parents/caregivers (i.e., written signed consent, waiver of written consent, and/or verbal consent by telephone), reflective of applicable IRB/EC guidance. For sites seeking IRB/EC approval for obtaining consent by telephone, the site's informed consent SOP should include procedures for subsequently obtaining a written signed consent form from the parent/caregiver (unless the IRB waives written consent), and how a copy of the consent form (or script) will be provided to the parent/caregiver.

Regardless of a waiver of written consent, all the informed consent processes will be fully source documented, consistent with the DAIDS policies referenced in Protocol Section 12.2.

5 Eligibility Confirmation and Enrollment Process

Eligibility criteria for parents/caregivers are provided in Protocol Section 4.5. Inclusion criteria include confirmation from both the parent/caregiver as well as the adolescent participant that the identified parent/caregiver has knowledge of how the adolescent participant tolerated the study product, and lives with or has regular supportive contact with the adolescent participant. As these inclusion criteria require reporting from separate individuals, parent/caregiver eligibility may be assessed at multiple timepoints after obtaining consent and prior to enrollment and may be assessed in-person at the study clinic or by telephone. It is generally expected that site staff will ascertain adolescent participant report of parent/caregiver eligibility during the adolescent's study visit. Eligibility criteria 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 (whether in-person or over the phone), where and when recruitment and confirmation of eligibility criteria will be performed; roles and responsibilities for assessing (whether in-person or over the phone) and confirming eligibility; and procedures for documenting the process.

The DMC system will not be used for tracking parent/caregiver screening process. However, sites will source document reasons for any consenting parent/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 Data Management Center (DMC) Subject Enrollment System (SES). Successful entry into the SES will generate a study identification number (SID).

The IMPAACT 2017 MOP provides further guidance on operational and logistical considerations of assessing and confirming eligibility, and enrolling the parent/caregiver to the study prior to the phone interview being conducted.

6 Scheduling and Conducting Phone Interviews

Site staff will work with the protocol interview team and the parent/caregiver to schedule the phone interview at a time that is convenient for the parent/caregiver and within the applicable interview procedural window. Scheduling of the interview may occur at any point with the intention to minimize the number of scheduled but uncompleted interviews. Parents/caregivers must be consented, confirmed as eligible, and enrolled prior to conducting the phone interview.

Once the phone interview is scheduled, site staff will provide the parent/caregiver with detailed instructions and guidance on accessing the phone interview platform. Phone interviews may be completed either in the study clinic during their adolescent participant's scheduled study visit, or from a phone outside the study clinic. All phone interviews will be conducted by a protocol interview team member external to participating clinical research sites, following an interview guide, and will be audio recorded and transcribed.

After obtaining consent, sites must source document all attempts to contact the parent/caregiver and interview scheduling attempts, and enter into eCRFs demographics and the date the phone interview occurred. Operational and logistical details regarding communication with the protocol interview team members and site staff are provided in the IMPAACT 2017 MOP.

7 Human Subjects Protections

Protocol Section 14.1 provides information regarding IRB/EC review and approval requirements in relation to the IMPAACT 2017 study. Informed consent considerations are provided in Appendix IV-A Section 4 above.

There may be no direct benefit to parents/caregivers who take part in the qualitative phone interviews. Information learned in this study may be of benefit to adolescent participants and others in the future, particularly information that may lead to more treatment options for HIV-infected children and adolescents. Parents/caregivers may also appreciate the opportunity for themselves to contribute to HIV-related research.

Despite all efforts to maintain confidentiality, involvement in the qualitative phone interview could become known to others, possibly leading to unfair treatment, discrimination, or other social impacts (e.g., because adolescent participants could become known as having HIV). For example, adolescent

participants could be treated unfairly or discriminated against or could have problems being accepted by their families and/or communities.

Pending IRB/EC approval, parents/caregivers may be reimbursed for their time and any costs associated with completing the qualitative phone interview. Reimbursement amounts will be specified in the site-specific consent, verbal script, or other materials if applicable per IRC/EC policies and procedures.

All study procedures will be conducted in private and every effort will be made to protect parent/caregiver privacy and confidentiality to the extent possible. Parent/caregiver information will not be released without written permission to do so except as necessary for review, monitoring, and/or auditing as described in Protocol Section 13. Refer to Protocol Section 14.7 for further information on privacy and confidentiality.

8 Disclosure of Harm

As described above, the purpose of conducting in-depth qualitative phone interviews with parents/caregivers is to evaluate their perceptions of adolescent acceptability and tolerability of CAB LA and/or RPV LA. Conducting the interviews is not expected to increase the likelihood or risk of self-harm or harm to others.

During the consent process, parents/caregivers will be informed that the information they provide in the interview will be kept confidential, with the exception of disclosures of significant risk for harm, including suicidality, or at risk of committing harm toward others, including abuse, violence or homicidality.

If at any time during a qualitative phone interview, a parent/caregiver divulges that s/he is at significant risk for harm or at significant risk of committing harm toward the adolescent participant, or if harm is suspected or likely, or if the parent/caregiver states s/he is suicidal or homicidal, the following will occur:

- The protocol interview team member conducting the interview will immediately contact the site IoR or designee and share any time-sensitive, potentially life-threatening information received from the parent/caregiver as part of the phone interview discussions.
- The IoR or designee contacted with this information will follow local policies for management of such situations including engaging immediate/first responders as applicable.
- The IoR or designee will also follow local reporting policies and legal statutes, including reporting to child protection or other appropriate agencies, as well as arranging referrals to appropriate support, counseling or treatment resources.

For disclosure of safety concerns to the parent/caregiver, the IoR or designee will notify the CMC after completing the steps above. No further safety reporting of the parents/caregivers is required, and Protocol Section 7 Safety Assessment, Monitoring, and Reporting does not apply for the parents/caregivers.

For disclosure by the parent/caregiver of safety concerns to the adolescent participant, the IoR or designee will notify the CMC after completing the steps above, and document and report the event as applicable per Protocol Section 7.

To facilitate rapid communications, the IoR or designee is expected to provide up-to-date contact information to the protocol interview team while phone interviews are being scheduled and conducted with participants from the site.

9 Data Management, Clinical Site Monitoring, and Administrative Procedures

Protocol Section 11.6 provides details on the qualitative phone interview data analyses, and Protocol Section 12 provides details on the management, handling, and record keeping of the qualitative phone interview data. Protocol Section 13 provides information on clinical site monitoring, and Protocol Section 15 provides information on overarching administrative procedures for the IMPAACT 2017 study.

Appendix IV-B: Parent/Caregiver Phone Interview Sample Informed Consent Form
for parents/caregivers of adolescents enrolled in:

IMPAACT 2017
Phase I/II Study of the Safety, Acceptability, Tolerability, and Pharmacokinetics of Oral and Long-Acting Injectable Cabotegravir and Long-Acting Injectable Rilpivirine in Virologically Suppressed HIV-Infected Children and Adolescents

Version 4.0, dated 27 May 2022

Introduction

You are being asked to take part in the research study named above.

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 your role in the study clearly.

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. Your choice will have no effect on your child's medical care at this clinic or your child participating in the study. Access to services and the benefits and rights you and your child normally have will not be affected.

Your role in the study

If you agree, you may be asked to complete one phone interview about how you felt and how you think your child felt about the shots they receive in this study. Not all parents/caregivers of adolescents who receive shots will be asked to complete a phone interview. Some, but not all adolescents who receive shots will also be asked to complete a phone interview.

If you are eligible and selected to complete an interview, we will help you to schedule the interview at a time that works for you. During the interview, you will be asked questions about how you felt about your child receiving shots of CAB or [and] RPV. The interview will be audio recorded. The words that you say will then be written down. This information will help us understand if CAB shots and RPV shots have any bad side effects for adolescents. It will also help us understand how adolescents and families feel about them receiving the shots.

The interview may take place at or in between your child's Week 4b through their Week 12 study visits in Cohort 1 [Week 24 through 96 visits in Cohort 2A; Week 20 through 92 visits in Cohort 2B] or during the long-term follow-up visits. The interview could also take place at or in between any of the long-term follow-up visits if your child enters into long-term follow-up. You will only complete one interview. Your part in the study should take about 1-2 hours.

There are no costs from being in the study.

There are no costs to you for this phone interview.

[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 the recording of the interview. The interview will only be labeled with a code number.

To help us protect your privacy, we have obtained a Certificate of Confidentiality that protects us from 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 US federal government or from the US Food and Drug Administration. Regardless of the certificate, you can release information about your participation in the study to others, if you wish.

Possible Benefits

By joining the study, you will be part of the search for ARVs that may be better for adolescents. 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 adolescents. Information learned from this study may help other adolescents 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:

- *[insert name of site IRB/EC]*
- *[insert name of site drug regulatory authority]*
- *[insert name of other site 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
- ViiV Healthcare (the company that makes CAB)
- Janssen Pharmaceuticals (the company that makes RPV)

The study staff and these groups are required 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 study will be available on ClinicalTrials.gov as required by U.S. law. This website will not include information that can identify your child. At most, the website will include a summary of the results. You can search this website at any time.

[Sites may modify this paragraph to reflect local reporting requirements and legal statues: Your child's study information may be disclosed to other authorities if required by law. Public health authorities are required by law to receive information for the prevention or control of disease, injury or disability. (We must comply with laws requiring the reporting of suspected child abuse and neglect).]

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.

[Insert signature blocks as required by site IRB/EC policies.]

Signature blocks for participants of legal age to provide independent informed consent

Participant's Name (print)	Participant's Signature and Date
Study Staff Conducting Consent Discussion (print)	Study Staff Signature and Date
Witness's Name (print) (As appropriate)	Witness's Signature and Date

Appendix IV-C: Parent/Caregiver Phone Interview Sample Informed Consent Verbal Script

for parents/caregivers of adolescents enrolled in:

IMPAACT 2017
Phase I/II Study of the Safety, Acceptability, Tolerability, and Pharmacokinetics of Oral and Long-Acting Injectable Cabotegravir and Long-Acting Injectable Rilpivirine in Virologically Suppressed HIV-Infected Children and Adolescents

Version 4.0, dated 27 May 2022

Introduction

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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 your role in the study clearly.

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. Your choice will have no effect on your child's medical care at this clinic or your child participating in the study. Access to services and the benefits and rights you and your child normally have will not be affected.

Your role in the study

If you agree, you may be asked to complete one phone interview about how you felt and how you think your child felt about the shots they receive in this study. Not all parents/caregivers of adolescents who receive shots will be asked to complete a phone interview. Some, but not all adolescents who receive shots will also be asked to complete a phone interview.

If you are eligible and selected to complete an interview, we will help you to schedule the interview at a time that works for you. During the interview, you will be asked questions about how you felt about your child receiving shots of CAB or [and] RPV. The interview will be audio recorded. The words that you say will then be written down. This information will help us understand if CAB shots and RPV shots have any bad side effects for adolescents. It will also help us understand how adolescents and families feel about them receiving the shots.

The interview may take place at or in between your child's Week through their Week 12 study visits in Cohort 1 [Week 24 through 96 visits in Cohort 2A; Week 20 through 92 visits in Cohort 2B], or during the long-term follow-up visits. The interview could also take place at or in between any of the long-term follow-up visits if your child enters into long-term follow-up. You will only complete one interview. Your part in the study should take about 1-2 hours.

There are no costs from being in the study.

There are no costs to you for this phone interview.

[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 the recording of the interview. The interview will only be labeled with a code number.

To help us protect your privacy, we have obtained a Certificate of Confidentiality that protects us from 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 US federal government or from the US Food and Drug Administration. Regardless of the certificate, you can release information about your participation in the study to others, if you wish.

Possible Benefits

By joining the study, you will be part of the search for ARVs that may be better for adolescents. 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 adolescents. Information learned from this study may help other adolescents 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:

- *[insert name of site IRB/EC]*
- *[insert name of site drug regulatory authority]*
- *[insert name of other site 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
- ViiV Healthcare (the company that makes CAB)
- Janssen Pharmaceuticals (the company that makes RPV)

The study staff and these groups are required 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 study will be available on ClinicalTrials.gov as required by U.S. law. This website will not include information that can identify your child. At most, the website will include a summary of the results. You can search this website at any time.

[Sites may modify this paragraph to reflect local reporting requirements and legal statues: Your child's study information may be disclosed to other authorities if required by law. Public health authorities are required by law to receive information for the prevention or control of disease, injury or disability. (We must comply with laws requiring the reporting of suspected child abuse and neglect).]

Agreement to participate

Before deciding whether to participate in this study, please ask me any questions that you have. 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 agreeing to participate.

[Insert signature blocks as required by site IRB/EC policies.]

Signature blocks for witnesses to verbal consent of parents/guardians of legal age to provide independent informed consent

Participant's Name (print)	Participant's Signature and Date
Study Staff Conducting Consent Discussion (print)	Study Staff Signature and Date
Witness's Name (print) (As appropriate)	Witness's Signature and Date

Appendix V: Injectable Study Product Preparation

This appendix provides requirements for injectable study product preparation for both CAB LA and RPV LA. The study product regimen, administration, formulation, storage requirements, supply and other relevant information is described in protocol Section 5 Study Product. The IMPAACT 2017 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 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:
  - 21G x 1.5" SurGuard Safety Hypodermic Needle CE MARKED Mfg Catalog Number: SG3-2138 (Central Supply as applicable per country)
  - 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 and/or needles with different gauge (1.5 inch, 2 inch; CAB LA: 21 to 25 gauge; RPV LA: 21 to 23 gauge) are permitted if needed to accommodate individual body types.
NOTE: 25G needle is not permitted for administration of RPV LA.

Appendix V-A: Preparation of CAB LA

1 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 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.

7. 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.

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.

2 Preparation of CAB LA 400mg/2mL (using one 400 mg/2 mL vial)

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 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. Removed 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 the entire contents (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 10).
   Record the time that the suspension is withdrawn into the syringe.
9. 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).
10. 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).
11. 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 V-B: Preparation of RPV LA

1 Preparation of RPV LA 900mg/3mL (using one 900mg/3 mL vial or two 600 mg/2 mL vials)

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 24 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 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.
7. 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.

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.

2 Preparation of RPV LA 600mg/2mL (using one 600mg/2 mL vial)

1. Remove one 2-mL RPV LA vial 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 24 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 the entire contents (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.

Appendix VI: 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 2017 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.

Study Products and Background cART Regimens

- For Cohort 1 participants and all LSFU participants: Sites should provide adherence counseling and support at each study visit regarding the importance of correctly and consistently taking background cART regimens.
- For Cohort 1 Step 1 and Cohort 2 Step 3 participants: Oral study product may be dispensed at the off-site Week 2 or Week 4a visits in accordance with protocol Section 6.1.3.
- For Cohort 1 Step 2, Cohort 2A Step 4, and Cohort 2B Step 5 participants: Injectable study products (CAB LA, RPV LA) must be administered on-site. Sites should carefully assess their ability to utilize alternative approaches (as provided below) for monitoring participant safety, in the event of disruptions or limitations to conducting on-site visits for non-injection follow-up visits. Sites should only consider administering injectable study products if there is adequate assurance that participant safety monitoring can be conducted through one of the alternative approaches provided below. In addition, injectable study products should only be administered if collection, processing, and storage of PK specimens, consistent with the Laboratory Processing Chart (LPC), remains possible for the injection visit and for the subsequent non-injection visits.
  - At sites where these conditions can be met, administration of injectable study products may continue; the procedures listed in protocol Section 6.9 must be performed before administration.
  - At sites where these conditions cannot be met, Cohort 1 Step 2 participants with study product injections remaining should be permanently discontinued from injectable study product and followed per the long-term safety and washout PK follow-up (LSFU) visit schedule. The IMPAACT 2017 CMC should be consulted for guidance on short-term oral bridging options for Cohort 2A Step 4 and Cohort 2B Step 5 participants.

Prioritization of Study Visit Procedures

- Sites with limited capacity to conduct study visits in-person at the study clinic may conduct study visits — in full or in part — off-site or remotely (e.g., by telephone or other IRB-approved method) as follows:
  - Sites attempting to minimize in-person contact with potential study participants may obtain informed consent/assent remotely. Likewise, sites attempting to minimize in-person contact with enrolled participants may conduct split study visits with some visit procedures conducted remotely, as outlined below, and other visit procedures conducted in-person at the clinical research site (or off-site for non-injection follow-up study visits). As noted above, study product injections must be administered at the clinical research site and the procedures listed in protocol Section 6.9 must be performed before injectable study product administration.

  - The Entry and Week 4b visits (for both Cohort 1 and Cohort 2A) may not be split and must be conducted in-person at the clinical research site.
  - See protocol Section 6.1.3 for detailed guidance on conducting off-site (in-person) non-injection follow-up visits.
  - Prior to conducting remote study visits or study visit procedures (for a split visit), site staff should communicate with participants/parents/guardians as applicable to determine in advance how and when such visits will take place, with adequate protections for safety, privacy, and confidentiality. Remote visit procedures should be conducted by site staff who are adequately qualified and trained to conduct the procedures, as determined by the site Investigator of Record (IoR), with attention paid to data chain of custody. These staff should also be adequately qualified and trained to immediately assess and/or manage any adverse events or social impacts that may occur during the visits. If adverse events requiring further evaluation or management are identified during a remote visit, staff conducting the visit should arrange for appropriate clinical management, in consultation with the IoR or designee as needed.
- Sites with limited capacity to conduct study visits (whether on-site, off-site or remotely) should prioritize the following procedures:
  - Adherence counseling and support for the background cART regimen (for Cohort 1 and LSFU participants); this may be done remotely.
  - Clinical procedures; local institutional guidance may be followed for prioritization of clinical procedures, guided by participant safety. Medical and medication histories may be obtained remotely. Identify/review/update adverse events may also be performed remotely; clinical signs or symptoms determined to be Grade 2 or lower may continue to be assessed remotely and per protocol Section 8. Adherence assessments may also be performed remotely but only if observed by site staff; see the IMPAACT 2017 MOP for further guidance regarding remote observations of the adherence assessment.
  - Laboratory procedures (see protocol Section 6.16.1 for specimen prioritization).
  - Provision of study product (injections may only be administered on-site).
  - Contraceptive counseling; this may be done remotely.
  - Acceptability/tolerability questionnaires; these may be administered remotely or skipped/missed.
- For visits at which PK specimen collection is expected per protocol, before any PK specimen is collected, sites should verify that they are able to process and store PK samples, as described in the LPC. If this cannot be verified, the samples should not be collected. As noted above, sites that are not able to collect, process, and store PK specimens consistent with the LPC should not administer injectable study products.
  - For sites with limited capacity to ship PK or genotypic and phenotypic resistance samples to the designated testing laboratory, the ability to store the samples locally must be verified prior to sample collection.
- If laboratory tests (other than PK testing) cannot be performed consistent with a site's Protocol Analyte List (non-US sites) or at a CAP/CLIA-certified laboratory, the tests may be performed in alternate laboratories using alternate assays (alternate laboratories must adhere to local regulations for clinical laboratory testing), in consultation with the CMC.

Documentation

- Site-specific COVID-19 contingency plans, and the implementation thereof, should be documented in essential document files for IMPAACT 2017.
- Documentation should be entered in participant study charts in real-time (or close to real-time) should any of the following occur:
  - Missed visits
  - Off-site visits (document the location of the visit)
  - Incomplete or partial visits (document which procedures were performed, and which were not)

  - Remote contacts 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. Please contact the IMPAACT Operations Center Clinical Research Managers with any questions related to documentation and reporting requirements.