TITLE PAGE

Protocol Title: A qualitative hybrid III implementation study to identify and evaluate strategies for successful implementation of the cabotegravir + rilpivirine long-acting injectable regimen in the US

Protocol Number	209493/ Amendment 03
Compound Number	GSK1265744
Study Phase	Phase 3
Approval Date	16-NOV-2020

Short Title: Study to Identify and Determine Best Implementation Practices for Injectable CAB + RPV in the US

This study is sponsored by ViiV Healthcare. GlaxoSmithKline is implementing and managing all aspects of this study on behalf of ViiV Healthcare.

Author (s): PPD

US IND Sponsor Legal Registered Address:

ViiV Healthcare
Five Moore Drive
P.O. 13398
Research Triangle Park, NC 27709-3398, USA
Telephone: PPD

Sponsor Legal Registered Address (excluding US):

ViiV Healthcare
980 Great West Road
Brentford
Middlesex, TW8 9GS
UK

In some countries, local law requires that the Clinical Trial sponsor is a local company legal entity. In these instances, the appropriate company to be identified as Sponsor must be agreed with the global ViiV Healthcare clinical team and signed off by the Vice President, Global Research and Medical Strategy.

This study is sponsored by ViiV Healthcare. GlaxoSmithKline is supporting ViiV Healthcare in the conduct of this study

Medical Monitor Name and Contact Information can be found in the Study Reference Manual

MEDICAL MONITOR/SPONSOR INFORMATION PAGE

Primary Medical Monitor/SAE Contact Information:

PPD
ViiV Healthcare
Research Triangle Park
Five Moore Drive, Research Triangle Park, NC 27709 (USA)
Mobile: PPD
Office Telephone: +same as mobile
e-mail: PPD

Secondary Medical Monitor:

PPD, DO, MSc
ViiV Healthcare
Research Triangle Park
Five Moore Drive, Research Triangle Park, NC 27709 (USA)
Mobile: PPD
Office Telephone: PPD
Fax: PPD
e-mail: PPD

Sponsor Serious Adverse Events (SAE) Contact Information:

PPD
ViiV Healthcare
Research Triangle Park
Five Moore Drive, Research Triangle Park, NC 27709 (USA)
Mobile: PPD
Office Telephone: +same as mobile
e-mail: PPD

Regulatory Agency Identifying Number(s):

IND: 109,678

SPONSOR SIGNATORY:

Sherene Shakib Min, MD, MPH
VP, Head of Clinical Development
ViiV Healthcare

Date

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**DNG Number**
Amendment No. 3	16-Nov-2020	2018N382441_03
Amendment No. 2	15-May-2020	2018N382441_02
Amendment No. 1	02-Apr-2019	2018N382441_01
Original	02-Jan-2019	2018N382441_00

Amendment 3: 16-NOV-2020

Overall Rationale for the Amendment: The primary purpose of this amendment is to allow participants who become pregnant while in the study to remain in the study and not be withdrawn as a result of the pregnancy. Allowing pregnant participants to continue in the study will negate any subsequent fetal exposures to new antiretrovirals agents that would occur if the pregnant participant was withdrawn from study and placed on an oral SOC regimen. An Appendix, "Information and Guidance for Managing Pregnant Participants" was inserted as Appendix 8 and all subsequent appendices were renumbered accordingly.

Minor additional edits were made which were previously addressed with a note to file (NTF), for clarity and/or correction.

Section # and Name	**Description of Change**	**Brief Rationale**
Medical Monitor/ Sponsor Information Page	Updated name and contact information for primary and secondary medical monitors, Sponsor Serious Adverse Events (SAE) Contact Information, and sponsor signatory details	Change in study medical monitor
General Change throughout the document	Women of Childbearing Potential (WCBP) has been changed to Females of Reproductive Potential Where appropriate, women has been change to females	Changed for consistency in terminology throughout
Section 1.2: Outcomes/Endpoints Table	Verbiage modified for clarity (previously addressed in NTF)	To address inconsistency in wording regarding the collection time for Month 12 subject interviews
Section 1.5: Schedule	Additional PK assessment	Reminder for additional

Section # and Name	Description of Change	Brief Rationale
of Activities Table 3 (CAB LA + RPV LA Monthly Administration)	instructions added before the table title	assessments for pregnant participants remaining in the study and directing to Appendix 8.
	Footnote “b” added for requirement for specific pregnancy ICF addendum; subsequent footnotes renumbered	Pregnant participants who remain in the study will need to sign a specific pregnancy ICF addendum
	Footnote “h” edited	Pregnant participants who remain in the study have additional assessments required, and do not need pregnancy testing performed for the duration of their pregnancy
	Footnote “j” added for additional PK sample collection; subsequent footnotes renumbered	Pregnant participants who remain in the study will have additional PK samples collected
	Footnote “k” (now footnote “m”) verbiage modified for clarity (previously addressed in NTF)	To address inconsistency in wording regarding the collection time for Month 12 subject interviews
Section 1.5: Schedule of Activities Table 5 (Long Term Follow-Up)	Footnote “c” added for for additional PK sample collection; subsequent footnotes renumbered Footnote “d” edited to reflect pregnancy testing is not needed during the study for pregnant participants.	Pregnant participants who remain in the study will have additional PK samples collected, and do not need pregnancy testing performed for the duration of their pregnancy
Section 2.3.1 Risk Assessment Oral CAB and CAB LA (GSK1265744/GSK1265744 LA) Risk Assessment Table:	Summary of Data/Rationale for Risk Effects in pregnancy seen in non-clinical studies Mitigation Strategy Late stage removed, as	Verbiage changed to indicate pregnant females are not enrolled in the study, but may participate, if they become pregnant during the course of the study. Additional language added to include the requirement for an additional

Section # and Name	Description of Change	Brief Rationale
	additional non-clinical data was added to describe effects of cabotegravir in animals	pregnancy specific ICF addendum, and directing the reader to Appendix 8 for management of pregnant participants. Language added to clarify that pregnant participants who remain in the study do not need pregnancy testing for the duration of the pregnancy
	Potential effects in females exposed to dolutegravir during conception and early pregnancy	Updated to reflect most recent DTG data regarding NTDs in pregnancy. Verbiage changed to indicate pregnant females are not enrolled in the study, but may participate, if they become pregnant during the course of the study. Additional language added to include the requirement for an additional pregnancy specific ICF addendum, and directing the reader to Appendix 8 for management of pregnant participants. Language added to clarify that pregnant participants who remain in the study do not need pregnancy testing for the duration of the pregnancy
Section 6.5.2 Prohibited Medications and Non-Drug Therapies	Wording changed to clarify permitted Hepatitis C therapy vs what is prohibited	Existing language interpreted as contradictory
Section 7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal	Deleted bullet: Pregnancy (intrauterine), regardless of termination status of pregnancy.	Participants may remain in the study, if they become pregnant during the course of the study, and are not required to be withdrawn
Section 8.4.1 Clinical	Bullets discussing pregnancy testing updated	Participants may remain in the study, if they become pregnant

Section # and Name	Description of Change	Brief Rationale
Evaluations	to include language regarding pregnant participants being permitted to remain in the study Language added to clarify that pregnant participants who remain in the study do not need pregnancy testing for the duration of the pregnancy	during the course of the study. Additional language was needed to include the requirement for an additional pregnancy specific ICF addendum, and directing the reader to Appendix 8 for management of pregnant participants. Pregnant participants who remain in the study do not need pregnancy testing during the study
Section 8.4.5 Clinical Safety Assessments	Bullet "f" added to the table footnote	Inadvertently omitted in the previous protocol version
Section 8.5.5 Pregnancy (including subsections 8.5.5.1, 8.5.5.2, 8.5.5.3)	Entire section edited. Directs the reader throughout to reference the Pregnancy appendix 8.5.5 - Added general instructions for first steps in the event that a participant in the study gets pregnant. Language regarding withdrawal in the event of pregnancy was removed. Language added to clarify that pregnant participants who remain in the study do not need pregnancy testing for the duration of the pregnancy 8.5.5.1 - New section added, providing general risk/benefit information regarding continued use in pregnancy 8.5.5.2 – Instructions	Pregnant participants are no longer required to be withdrawn from the study and may remain the study. The addition and updating of information/instructions was also necessary. Some repetitive information or information that was not/no longer relevant for this section was removed. Pregnant participants who remain in the study do not need pregnancy testing during the study

Section # and Name	Description of Change	Brief Rationale
	updated to include information for pregnant participants remaining in the study. Language around continued use of contraception removed. 8.5.5.3 - Instructions updated to include information for any participant who becomes pregnant while in the study, including those participants who chose to withdraw (and enter LTFU), or those who chose to remain in the study. Instructions removed regarding cord blood and/or breast milk collection.	
Section 8.6 Pharmacokinetics	Language added for PK collection of pregnant participants	Pregnant participants remaining in the study will have additional PK samples drawn at regularly scheduled visits, throughout the course of the pregnancy
Section 10.1.3 Informed Consent Process	Language added for pregnancy specific ICF addendum	Participants who become pregnant while in the study and who elect to continue to receive CAB + RPV LA injections must sign the pregnancy specific ICF addendum.
Section 10.7 Appendix 7, Table 15	Table 15: Removed footnote “b” that was inadvertently added and was not required.	Both long-acting reversible contraception (LARC) and progestogen only injectable contraception (POIC) are considered highly effective forms of contraception and are allowed as single agents Therefore, the footnote in the table requiring a second form of contraception was not accurate.

Section # and Name	Description of Change	Brief Rationale
	Pregnancy Testing – Added bullet to refer to Appendix 8 Collection of Pregnancy Information – Updated with general information; details deleted and moved to Appendix 8. Removed statements regarding withdrawal of participants who become pregnant while in the study and pregnancy testing for pregnant participants	Participants may remain in the study, if they become pregnant during the course of the study, provided that the pregnancy specific ICF addendum is signed. Reader is directed to Appendix 8 for details regarding management of pregnant participants. Language added to clarify that pregnant participants who remain in the study do not need pregnancy testing for the duration of the pregnancy
Section 10.8 – Appendix 8: Information and Guidance for Managing Pregnant Participants	New Appendix added; all subsequent sections renumbered.	Participants may remain in the study, if they become pregnant during the course of the study. Because the number of participants who become pregnant in the study is expected to be very small, and the information doesn't pertain to most of the study population, the decision was made to include this information in an Appendix, rather than in the full protocol. For managing participants who become pregnant while in the study, the Reader is directed to Appendix 8, where all details are available.
Section 10.8 Appendix 8: Abbreviations and Trademarks	Now Section 10.9 Appendix 9: Abbreviations and Trademarks Abbreviations APR, MTCT, NTF added. Trademark CABENUVA added	New Appendix 8 added; all subsequent sections renumbered New information included the use of new terms, and the mention of CABENUVA

Section # and Name	Description of Change	Brief Rationale
Section 10.9 Appendix 9: Patient Study Participant Surveys Section 10.10 Appendix 10: Staff Study Participant Survey Section 10.11 Appendix 11: COVID-19 Pandemic and Clinical Trial Continuity	 Now Section 10.10 Appendix 10: Patient Study Participant Surveys Now Section 10.11 Appendix 11: Staff Study Participant Survey Now Section 10.12 Appendix 12: COVID-19 Pandemic and Clinical Trial Continuity	New Appendix 8 added; all subsequent sections renumbered.
Section 10.12 Appendix 12: Protocol Amendment History	Now Section 10.13 Appendix 13: Protocol Amendment History. Amendment 2 information added to Appendix	

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A qualitative hybrid III implementation study to identify and evaluate strategies for successful implementation of the cabotegravir + rilpivirine long-acting injectable regimen in the US

Short Title: Study to Identify and Determine Best Implementation Practices for Injectable CAB + RPV in the US

Rationale:

CAB + RPV LA is an investigational HIV treatment regimen of long-acting cabotegravir plus long-acting rilpivirine administered as two individual intramuscular injections every month (CAB + RPV LA following an oral lead-in [OLI] period). This new HIV treatment will require changes to the current standard of prescribing oral antiretroviral therapies, including the logistics of delivering a complete antiretroviral treatment regimen as long acting (LA) injectable therapy. This new treatment option will require patients to receive injections from a provider every month and will require greater staff and logistical resources to administer the injections. As this is a promising new treatment modality for people living with HIV (PLHIV), it is important to understand how to optimize the delivery of CAB + RPV LA injectable from a PLHIV, HCP and healthcare system perspective in order to fully realize this benefit. In preparation for national implementation following regulatory approval, there is a need to understand what level of clinic training and staff support that will be needed to effectively deliver this regimen to patients. Therefore, the current study aims to identify and evaluate strategies for successful implementation of this injectable regimen. In this study, investigational sites will have access to a suite of training and implementation tools as well as short-term intensive facilitation calls; the study will evaluate both qualitative and quantitative measures across a range of clinic types to determine the most effective strategies and to identify barriers and facilitators (including solutions) for successful implementation of the CAB + RPV long-acting injectable regimen.

1.2. Objectives and Endpoints:

Objectives	Endpoints
Primary	
To evaluate acceptability, appropriateness, and feasibility of delivering CAB+RPV LA	Acceptability of Intervention Measure (AIM), Intervention Appropriateness Measure (IAM), and Feasibility of Intervention Measure (FIM). Assessed quantitatively by staff study participants at baseline- prior to any Month 1 visits, after at least 4 monthly facilitation calls and upon completion of all Month 12 visits at that site. Acceptability of Intervention Measure (AIM) and Intervention Appropriateness Measure (IAM). Assessed quantitatively by patient study participants at Month 1 prior to first injection, Month 4 and Month 12
Secondary	
To evaluate organizational facilitators and barriers	Facilitators/Barriers: Semi-Structured Interview (SSI) conducted with staff study participants at baseline- prior to any Month 1 visits, after at least 4 monthly facilitation calls and upon completion of at least 50% of Month 12 visits at that site. Barriers, facilitators and best practice sharing amongst clinics assessed by short-term facilitation (coaching calls) for at least 6 months. These will be a combination of structured questions and open-ended questions. Use of support materials/toolkit assessed via Survey responses of staff study participants prior to any Month 1 visits, after at least 4 monthly facilitation calls and upon completion of all Month 12 visits at a site. Use of support materials/toolkit assessed via Survey responses of patient study participants via Survey responses at Month 1 and Month 4 and Month 12, as well as SSI responses prior to Month 1 and at Month 12.

Objectives	Endpoints
Patient Facilitators and Barriers	Facilitators/Barriers: Semi-structured interviews conducted with patient study participants prior to month 1 and within 4 weeks of their Month 12 study visit
Implementation Fidelity	Injections occurring within target window from the expected injection date Use of support materials/toolkit assessed through SSI of staff study participants at Day 1, after at least 4 monthly facilitation calls and upon completion of at least 50% of Month 12 visits at that site.
Implementation Sustainability	Program Sustainability Assessment Tool (PSAT) assessed by staff study participants at Month 12.
To measure patient satisfaction with process (timeliness of visits, length of visit, patient education)	Patient Survey responses at Month 1, Month 4 and Month 12. Patient SSI responses prior to Month 1 and at Month 12 Length of patient visit from arrival until departure from clinic at Month 1, Month 5 and Month 11
Evaluate safety and efficacy measures of CAB+RPV LA	Proportion of participants with plasma HIV-1 RNA <50 c/mL over time Proportion of participants with confirmed virologic failure (CVF) over time Incidence of treatment emergent genotypic and phenotypic resistance to CAB and RPV in patients with CVF Incidence and severity of AEs and laboratory abnormalities over time Proportion of participants who discontinue treatment due to AEs over time Reported injection site reactions over time Absolute values and changes in laboratory

Objectives	Endpoints
	parameters over time

1.3. Overall Design:

This study is an evaluation of implementation strategies on the degree of acceptability, appropriateness, feasibility, fidelity, and sustainability of clinic practices to deliver the CAB+RPV LA regimen to appropriate HIV-infected patients. The study will use an implementation science approach to understand the barriers and facilitators for both patients and providers, including best practices for delivering CAB + RPV LA within an interventional clinical trial where the CAB + RPV LA regimen is delivered to HIV-infected, virologically-suppressed patients.

Staff Study Participants & Patient Study Participants:

Staff study participants will include lead HIV care providers (HCPs), Nurses/staff performing CAB + RPV LA injections, and administrators/clinic managers. Patient Study Participants are HIV-infected patients recruited at each study site. Patient study participants will receive CAB LA + RPV LA and clinical assessments throughout the study per the Schedule of Activities (SoA), Section 1.5. Additionally, data will be collected from staff study participants and patient study participants per Table 1.

Table 1 Implementation Science Data Collection Plans

Patient Schedule	HIV-infected participants	Staff Study Participant Schedule	Lead HIV provider	Nurse or person giving injection (Injector)	Administrators / Clinic Manager (Admin)
Month 1, prior to receiving injection After Baseline, Prior to First Injection	Survey (100% of patient study participants) Semi-structured Interviews (up to 4 patient study participants per site)	Baseline: (prior to first subject Month 1 visit at the site)	Survey of lead HIV provider Semi-structured Interviews of lead HIV provider Short-term facilitation*	Survey of nurse/person delivering CAB + RPV LA injections Semi-structured Interviews of nurse/person delivering CAB + RPV LA injections Short-term facilitation*	Survey of clinic administrator/ manager Semi-structured Interviews of clinic administrator/ manager Short-term facilitation*
Month 4	Survey (100% of patient study participants)	After 4th Monthly Facilitation Call	Survey of lead HIV provider	Survey of nurse/person delivering CAB + RPV LA	Survey of clinic administrator/ manager

Patient Schedule	HIV-infected participants	Staff Study Participant Schedule	Lead HIV provider	Nurse or person giving injection (Injector)	Administrators / Clinic Manager (Admin)
			Semi-structured Interview of lead HIV provider Short-term facilitation[a]	injections Semi-structured Interview of nurse/person delivering CAB + RPV LA injections Short-term facilitation*	Semi-structured Interview of clinic administrator/ manager Short-term facilitation*
Month 12/End of Study	Survey (100% of patient study participants) Semi-structured Interview (up to 4 patient study participants per site)[b]	End of Study[c]	Survey of lead HIV provider Semi-structured Interview of lead HIV provider	Survey of nurse/person delivering CAB + RPV LA injections Semi-structured Interview of nurse/person delivering CAB + RPV LA injections	Survey of clinic administrator/ manager Semi-structured Interview of clinic administrator/ manager

a) Short-term facilitation calls with the staff study participants (Investigator, nurse and clinic manager are expected to attend each call, but at least one person from each site must be present) will occur monthly for at least 6 months. Facilitation calls will begin after sites begin enrolling patient study participants. Facilitation calls will continue during the enrollment period until the last enrolled subject achieves their Month 6 study visit.

b) Semi-structured interviews for patient study participants should be conducted within approximately 4 weeks of their Month 12 study visit.

c) Surveys should occur within approximately 4 weeks of the last patient study participant visit at each site and interviews of staff study participants should occur after at least 50% of Month 12 patient study participant visits at each site.

All patient study participants enrolled in this study will switch from their pre-entry oral HAART regimen to the CAB + RPV LA regimen (single arm switch study) for at least 12 months, including a one-month safety lead-in period with oral cabotegravir and oral rilpivirine (Edurant) dosed once-daily. Patients who successfully complete the Month 12 visit and assessments will have completed the study and will need to obtain ongoing HIV treatment outside of the study. Patients who discontinue the CAB + RPV LA regimen after receiving ≥1 injection of cabotegravir and/or rilpivirine will enter a long-term

follow-up period with safety and efficacy/virology evaluated on a quarterly basis for 1 year.

Site/Clinic Selection: Investigational sites that have not previously delivered the CAB + RPV LA regimen will be targeted for inclusion in the study and screened based upon objective criteria of their ability to perform the assessments required in the study within GCP requirements. Sites will be identified as either university/hospital, private or public health clinic based upon their own determination (Principal Investigator determination). Clinics that include participants from multiple categories (public/private) will be categorized based on the principal investigator's determination of the majority of their patient base. In order to create a representative sample, sites will be chosen not only to represent all three categories of clinic type, but also based upon geographic and demographic representation (rural, suburban, urban), as much as possible within practical limitations.

Enrollment of Staff Study Participants: Investigational sites will be selected and staff study participants (lead HIV care providers (HCPs), Nurses/staff performing CAB + RPV LA injections, and administrators/clinic managers) will be identified prior to study commencement. Upon study initiation, clinical sites will have up to 2 months to engage and enrol up to 15 patient study participants into this study. Key objectives of this study relate to the delivery of the CAB + RPV LA regimen at a clinic, including the learning process clinic staff will undergo for this paradigm-changing regimen. One of the goals is to facilitate shared learnings across clinics in order to drive successful implementation, and this will be conducted through the short-term facilitation calls with study personnel. Thus, it is necessary for participating sites to initiate and complete enrolment concurrently within a short time frame. A limited enrolment period of up to 2 months is proposed with a goal to have approximately 80% of participating clinics fully prepared to enrol at the time of study commencement. Adjustments to this time frame will be considered by the sponsor study team based upon study progress and may include an extension of the enrolment period for up to a maximum of 4 months; if the enrolment period is extended beyond 2 months, enrolment caps at individual sites may be raised beyond 15, up to the study maximum of 135 patient study participants.

All lead investigators, nurses/injectors, and/or administrators responsible for implementation will attend an in-person investigator meeting prior to study start. The purpose of this meeting is to educate healthcare staff on the CAB + RPV LA regimen, including the proper administration of the regimen, protocol requirements for all study participants, data collection methods and an overview of available support tools (toolkit). Additionally, an overview of the key protocol objectives and relevant implementation science elements will be reviewed.

Upon study initiation, investigational sites will begin enrolment of eligible patient study participants into the study. Patient study participant enrolment is expected to continue for approximately 2 months. During the period after enrolment commences, patients will be screened and sites will begin to deliver the CAB + RPV LA regimen. Continuing through the last enrolled patient study participant achieving their Month 6 visit in the study CAB + RPV LA, staff study participants will receive short-term facilitation calls in addition to the available support tools (toolkit). The core component of the facilitation includes

structured monthly group coaching calls (inclusive of all participating clinics) facilitated through the study team/ CRO partners. The purpose of the monthly group facilitation/coaching calls is to share best practices, discuss alternative work flows, discuss support tools, and help identify barriers and facilitators to the successful delivery of the CAB + RPV LA regimen. After the last enrolled patient study participant achieves the Month 6 visit, the short-term facilitation calls will be discontinued. Following an additional 6 months during which no external facilitation occurs (Month 6 to Month 12), sustainment of implementation strategies will be assessed via surveys and semi-structured interviews of staff study participants as well as patient study participants. During the course of the study, staff study participants will be asked about their utilization of each element of the toolkit. For example, if they found the injection training video useful, which tools they used, for how long, and if they used any clinic-developed implementation strategies (not part of the study "toolkit") to facilitate successful utilization and sustainment of CAB + RPV LA. This data will be captured in the surveys and semi-structured interviews.

While a "toolkit" of supporting elements will be provided in this study, clinical sites will be allowed to choose how they will implement CAB + RPV LA delivery in their clinical setting (i.e. nurse visit during clinic hours, pre-post clinic hours, weekend hours, Tues/Thursday clinics, etc.) as well as to create and use their own clinic-developed resources. The delivery models chosen will be tracked by study staff and captured in the surveys and semi-structured interviews. Modifications made to the implementation process or approach during the study i.e. who administers the injection, timing of delivery of the injection, use of support materials, etc are permissible and encouraged in order to facilitate successful delivery of the CAB + RPV LA regimen. Investigators will inform the study team of their change and document the reasons why (step change).

Key informant interviews: Key informant interviews will be conducted with staff study participants and a subset (up to 4 patients per site) of patient study participants to assess whether acceptability, appropriateness, fidelity, and sustainability are achievable in the clinic settings. Interviews will also probe for multilevel barriers to, and facilitators of CAB + RPV LA implementation and sustainability. Key stakeholder interviews are an ideal method for the proposed research as they elicit in-depth, detailed information from a relatively small number of individuals with first-hand knowledge of the factors influencing local CAB + RPV LA implementation programs as well as contextual factors that impact implementation and sustainment. The interviews will be guided by a semi-structured interview guide with open-ended questions and prompts to elicit organic feedback. The interview guides will be included in the Study Reference Manual. Interview questions are based on the CFIR framework (described in Table 2), with a focus on characteristics of the patient needs and resources, readiness for implementation, available resources, champions, reflection and evaluation. The interview will elicit the characteristics that may enable or inhibit implementation and sustainability in order to inform future implementation efforts. Interviews will be conducted with 3 key stakeholders of various disciplines in each clinic relevant to the implementation of CAB + RPV LA (HIV care provider, nurse/person administering the injections, and clinic administrator/ manager). These interviews will be conducted at three time-points: at the start of the study (following the Investigator Meeting but prior to the first patient at each site receiving their first injection), after the 4th facilitation call, and after at least 50% of

patient study participants have completed Month 12. Because this study will employ qualitative methodology as a primary objective, there is no equivalent to power calculations to determine the number of interviews needed to address research questions. Rather, the objective is to conduct enough interviews to reach thematic "saturation" (i.e., no more themes emerge from the data). Interviews will be audio recorded, transcribed verbatim and coded.

Study "Toolkit"

A suite of educational items, training aids, treatment and planning tools, electronic reminders and patient-directed support items/ options will be made available as part of this study. These items and tools will be directed both towards HCPs (staff study participants, SSP) as well as patients (patient study participants, PSP) and will comprise the study "toolkit." Toolkit items are noted in the table below and are optional for use by both SSPs and PSPs. However, items in the toolkit will be offered to SSPs and PSPs throughout the study and, at a minimum, at the timepoints outlined in the table. Use of toolkit items will be evaluated in the study through survey and qualitative interviews and will consist of (i) Educational Materials; (ii) Operationalization Tools and (iii) Appointment Reminders.

Table 2 Study Toolkit Items

Material	Objective	Offered to	Timepoints when offered
CAB + RPV LA Factsheet	Overview of CAB + RPV LA regimen expectations and administration	SSP	Investigator Meeting, Site Initiation and per site preference
CAB + RPV LA Injection Video	Educational video of how to prepare and administer CAB + RPV LA	SSP	Investigator Meeting, Site Initiation and per site preference
Web-based Treatment Planner	Electronic tool to assist staff in managing patient work flow	SSP	Investigator Meeting, Site Initiation and per site preference
Patient Reminder System	App that can be used as a reminder service for future appointments (text, email, SMS)	SSP, PSP	Investigator Meeting, Site Initiation, Day 1, Month 1 and per site preference
Hot and cold packs	To be used to alleviate pain and potential ISR due to the CAB + RPV LA injection	PSP	At each study visit where a CAB + RPV LA injection occurs.
Injection flash card	Educational card about "What to expect" with CAB + RPV LA regimen	PSP	Screening, Day 1, Month 1 and per site preference
FAQ	Educational Question and Answer about the CAB +	PSP	Screening, Day 1, Month 1 and per site

Material	**Objective**	**Offered to**	**Timepoints when offered**
	RPV LA regimen		preference
"What to expect" video	Educational video about the CAB + RPV LA regimen	PSP	Screening, Day 1, Month 1 and per site preference

Unintended Consequences

Unintended consequences refer to outcomes that are not anticipated and intended at the time of intervention implementation; they can be both positive (e.g. improved job satisfaction) and negative (e.g. increased workload for healthcare professional). During the semi-structured stakeholder interviews, we will ask if there were any unintended consequences that were not anticipated (i.e. Yes or No), if they were positive or negative and specifically what were they.

Disclosure Statement: This is a single group, open-label, interventional treatment study to assess the implementation of a new therapeutic strategy for HIV infection.

Number of Participants:

Approximately 9 sites will be included in this study and will be allowed two months to enrol up to 15 patient study participants each. Additional time for recruitment of patient study participants (up to an additional two months) may be allowed depending upon the site activation and enrollment rate. Fifteen patient study participants per site is intended as a reasonable number to provide clinic staff adequate exposure to implement the CAB + RPV LA regimen so that they can describe the challenges and practical limitations experienced during initial implementation of CAB + RPV LA. Fifteen patient study participants per site may also yield enough recurring office visits at clinics to necessitate alternate approaches to successful injection implementation beyond typical clinic practice. Therefore, the maximum number of patients included in this study is anticipated to be approximately 135.

Staff study participants from each site (physician/ PCP, nurse/medication administration personnel, administrator/clinic manager) will also take part in this study, including participation in surveys, interviews and facilitation calls.

Intervention Groups and Duration:

Informed consent must be obtained prior to any study procedures, including any Day 1 assessment.

Patient study participants

All patient study participants will complete the screening phase of up to 21 days prior to Day 1 during which all clinical and laboratory assessments of eligibility must be performed and reviewed. Participants may be re-screened twice. Participants who are

enrolled into the trial and subsequently withdrawn from the study, for any reason, may not be re-screened. Participants may be enrolled as soon as all eligibility requirements have been confirmed at the site. Patient study participants with an undetectable HIV-1 RNA (<50 c/mL) at Screen are eligible to enter this study. A single repeat viral load to determine eligibility may be allowed ONLY after consultation with the medical monitor. Should a participant be allowed a repeat, results of this repeat must be available prior to Day 1 of this study, therefore the time needed for scheduling the Day 1 visit, lab draws and lab analysis should be considered.

HIV-infected participants who meet all eligibility criteria will be switched at Day 1 from their pre-baseline regimen to an oral regimen for one month (CAB 30 mg + RPV 25 mg). Participants will return to the clinic, and if laboratory and clinical evaluations continue to support progression into the LA portion of the study, will take the last dose of their oral regimen (CAB 30 mg + RPV 25 mg), and receive the first CAB LA (600 mg) + RPV LA (900 mg) injections (within 2 hours of the final oral dose of CAB + RPV). All subsequent injections (CAB LA 400 mg + RPV LA 600 mg) will occur every month thereafter. Note: Patient study participants with ≥ Grade 1 LFTs at screening and or day 1 must be discussed with the Medical Monitor prior to initiation of LA dosing; continuation in the study or progression onto LA dosing may require additional evaluations, including labs drawn after a period of oral dosing with CAB + RPV.

The dosing window for the second and third injection (Month 2 and Month 3) will be +0 / -7 days from the projected dosing visit; All subsequent injection windows (beginning at Month 4) will be +7/-7 days from the projected date of the visit. Doses outside of the window *may* be allowed with prior Medical Monitor approval.

Participants will continue CAB LA + RPV LA until:

- study intervention is locally approved and commercially available,
- the participant no longer derives clinical benefit,
- the participant meets a protocol-defined reason for discontinuation
- the development of either CAB LA or RPV LA is terminated
- participant withdraws consent
- investigator discretion
- participant or investigator non-compliance
- termination of the study by the Sponsor.

Safety and efficacy assessments will be conducted as per the Schedule of Assessments. Dosing will occur according to the selected regimen.

If the intramuscular (IM) dosing regimen is discontinued as a result of an independent data monitoring committee (IDMC) review from the ongoing Phase 3 studies, any subsequent analysis, or any other programmatic analysis, those participants who have not met any clinical management criteria for discontinuation will be discontinued permanently from the study and will enter into the LTFU Phase of the study.

LTFU Phase –Following the IM Regimen Only

Any participant who receives *at least one* dose of CAB LA and/or RPV LA and discontinues the CAB LA + RPV LA regimen for any reason must remain on suppressive HAART for at least 52 weeks after the last dose of CAB LA and/or RPV LA in order to prevent selective pressure on HIV during the period of declining drug exposures and the potential for selection of resistant mutants. **Investigators must discuss the choice of the follow-up HAART regimen with the Medical Monitor prior to initiating the new regimen with the participant. HAART therapy should be initiated within 4 weeks after the last monthly injection, however if withdrawn due to virologic failure, HAART should be initiated as soon as virologic failure is confirmed. Discuss with medical monitor.** The Long-Term Follow Up period (LTFU) will begin the day of the last CAB LA and/or RPV LA dose and continue for 52 weeks. These participants will not complete a Withdrawal visit, but will instead move directly into the LTFU as per the Schedule of Activities, Section 1.5. In addition, for participants who withdraw during the LTFU, the final visit will be considered the study withdrawal visit.

Participants will be assessed with clinic visits at months 3, 6, 9, and 12 during the LTFU Phase. Female participants of child bearing potential must continue to use adequate contraception methods for the entire year of follow up.

In order to assure that participants have access to HAART during the LTFU, ViiV Healthcare may supply HAART or reimbursement may be provided as needed during this phase. The LTFU Phase may be shortened or terminated at any time during the study for various reasons, e.g., better understanding of risks of development of resistance as CAB and RPV exposures decline, end of study timings, etc.

Staff study participants

Staff study participants will include HIV care providers (HCPs), nurses/ staff performing CAB + RPV LA injections, and administrators/clinic managers at each investigational site. Staff study participants will provide input through the use of surveys, semi-structured interviews (SSI) and via the monthly facilitation calls, per the Schedule of Assessments Table.

Should there be turnover in staff study participants over the course of the study, the replacement staff member will undergo study training per site standard practice, and provide input through surveys, SSI and monthly facilitation calls as per the Schedule of Activities Table, Section 1.5.

Dose Modifications

No dose reductions, modifications, or changes in the frequency of any components of each regimen will be allowed during the study beyond what is allowed within the protocol or directly approved by the study Medical Monitor. Protocol waivers or exemptions are not allowed. Therefore, adherence to the study design requirements is essential and required for study conduct.

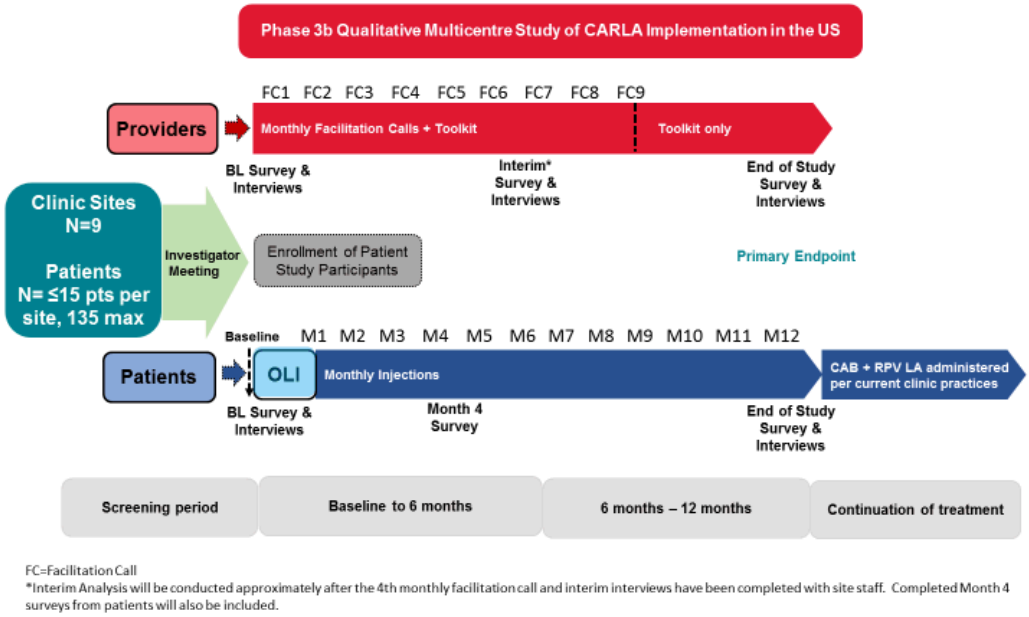
In exceptional circumstances, and in consultation with the Medical Monitor, investigators may provide oral CAB and/or RPV as a short-term "bridging" strategy for participants who have begun CAB LA + RPV LA. Should a participant need "oral bridging", sites must contact the Medical Monitor for guidance on treatment strategies prior to a missed CAB LA + RPV LA dose. Should a participant not notify the site in advance, the Medical Monitor must be contacted for further treatment guidance.

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying Study Procedures Manual (SPM). The SPM will provide the site personnel with administrative and detailed technical information.

Data Monitoring Committee:

A Data Monitoring Committee will not be used in this study.

1.4. Schema



FC=Facilitation Call
*Interim Analysis will be conducted approximately after the 4th monthly facilitation call and interim interviews have been completed with site staff. Completed Month 4 surveys from patients will also be included.

1.5. Schedule of Activities (SoA)

There are additional PK assessments for any pregnant participants who are remaining in the study. See Appendix 8

Table 3 Schedule of Activities for Patient Study Participants (CAB LA + RPV LA Monthly Administration)

Procedures	Screening[a]	Intervention Period													WD[o]
		Day 1	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10[c]	Month 11[c]	Month 12[c]	
Written Informed Consent [b]	X														
Demography	X														
Eligibility Verification	X														
Physical Exam	X														
Medical History	X														
Center for Disease Control and Prevention (CDC) Classification	X														
Randomization for interviews		X													
Rapid Plasma Reagin (RPR)	X														

Procedures	Screening[a]	Intervention Period												WD[o]
		Day 1	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10[c]	Month 11[c]	Month 12[c]	
Symptom Directed Physical Exam and Medical Assessment[d]	X	X	X	X		X		X		X		X		X	X
Injection site reaction (ISR) assessment			X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs (temperature, blood pressure [BP], heart rate [HR])[e]	X	X	X	X		X		X			X			X	X
Weight, Height & body mass index (BMI)[f]	X	X	X					X						X	X
HIV Associated Conditions, AE and serious adverse event (SAE) Assessments& Con Meds	X	X	X	X		X		X		X		X		X	X
12-Lead ECG[g]	X														X

Procedures	**Screening[a]**	**Intervention Period**												**WD[o]**
		Day 1	**Month 1**	**Month 2**	**Month 3**	**Month 4**	**Month 5**	**Month 6**	**Month 7**	**Month 8**	**Month 9**	**Month 10[c]**	**Month 11[c]**	**Month 12[c]**	
Clinical and Hematology			X	X		X		X			X			X	X
Pregnancy Testing (U)rine or (S)erum[h]	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U
HIV-1 RNA	X	X	X	X		X		X		X		X		X	X
Plasma sample for storage[i,j]		X	X	X		X		X		X		X		X	X
CD4+cell counts	X	X	X	X		X		X			X			X	X
Urinalysis	X														X
Glucose	X														
Prothrombin time (PT)/ partial thromboplastin time (PTT)/ international normalized ratio (INR)	X														X
Oral study product dispensation		X													

Procedures	Screening[a]	Intervention Period												WD[o]
		Day 1	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10[c]	Month 11[c]	Month 12[c]	
LA study product administration[k]			X[n]	X	X	X	X	X	X	X	X	X	X	X	
Participant Visit Reminder Contact	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Participant Contact Detail Confirmation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Record study visit length[l]			X				X						X		
Patient Questionnaire			X			X								X	
Selected Patient Interviews (SSI)[m]		X												X	

See footnote "c" for continuation of visit schedule after Month 12, if required. Subjects will continue on study until the CAB + RPV LA regimen is either locally approved and commercially available, the participant no longer derives clinical benefit or meets a protocol-defined reason for discontinuation or until development is terminated.

a. A screening visit will be conducted within 21 days of Day 1. However, it is preferred for Day 1 to be conducted as soon as practical after all screening results are available.
b. After discussion of risk:benefit, a pregnancy specific ICF addendum must be signed by pregnant participants who wish to remain in the study
c. Continue this pattern for visits for the remainder of the study if needed, until commercial CAB + RPV LA is available. For example, Month 13 will be conducted as per Month 10, Month 14 will be conducted as per Month 11, Month 15 will be conducted as per Month 12, Month 16 will be conducted as per Month 10, and so on. The exception to this pattern is that no questionnaires, study visit length collection, or patient interviews will be conducted after the Month 12 visit.
d. Physical exams should be conducted as part of normal routine clinical care but data will not be collected in the electronic case report form (eCRF). Medical assessments include any decisions the study staff must make for participant management.
e. Measure vital signs after about 5 minutes of rest in a semi-supine position.

f. Height collected at Day 1 only.
g. At Screening, ECGs should be performed in triplicate at least 5 minutes apart and following 5 minutes of rest in a semi-supine position. ECG evaluations performed at subsequent visits should be obtained after dosing, preferably 2-4 hours post dosing. ECG at Withdrawal should be performed following 5 minutes of rest in a semi-supine position.
h. A (-) urine pregnancy test is required prior to any injection and as required by medical monitor after a treatment interruption. A (+) urine test should be confirmed with a stat serum test. A Serum pregnancy test should be performed at any time pregnancy is suspected by the Investigator and may be used in place of a urine test at the discretion of the investigator. Pregnant participants who remain in the study do not need pregnancy testing during the study, for the duration of their pregnancy. Pregnant participants remaining in the study have additional assessments required, as described in Appendix 8
i. Plasma for storage samples are collected for possible future analyses, back-up in cases of loss/damage in transit, geno/pheno analyses for virologic failures or PK in the event of maladministration or virologic failure.
j. Participants who get pregnant while in study will have additional PK samples for CAB and RPV obtained. See Appendix 8
k. Monthly injections are 1 x CAB LA 600 mg IM + 1 x RPV LA 900 mg IM at Month 1. Subsequent injections beginning at Month 2 are 1 x CAB LA 400 mg IM + 1 x RPV LA 600 mg IM. If possible, injections should be spaced approximately 2 cm from one another and from the site of any previous injection and/or any injection site reaction. Bring RPV LA to approximately room temperature prior to injecting. Time and location of injection (right or left) as well as needle length used will be collected in the eCRF. **IM dosing is expected to occur during the month in which the participant's projected visit falls (as according to the Day 1 visit). A dosing window of +0 / -7 days from date of projected visit is stipulated for IM dosing at Month 2 and Month 3. A (+ or -) 7 day window from date of projected visit is stipulated for IM dosing beginning at Month 4. All decisions regarding dose interruption/ resumption must be discussed with the medical monitor in advance.**
l. Length of study visit from arrival until departure from clinic will be evaluated. Time of arrival, time of appointment, and departure times will be recorded in the eCRF.
m. The first semi-structured interview will be scheduled between Day 1 and prior to Month 1 visit. The end of study SSI will be scheduled within approximately within approximately 4 weeks of their Month 12 study visit.
n. **Note:** Patient study participants with ≥ Grade 1 LFTs at screening and or day 1 must be discussed with the Medical Monitor prior to initiation of LA dosing; continuation in the study or progression onto LA dosing may require additional evaluations, including labs drawn after a period of oral dosing with CAB + RPV.
o. Follow Up Visit - Conduct ~4 weeks after the last dose of investigational product (IP) if not entering Long-Term Follow Up and only if the participant has ongoing AEs or lab abnormalities at the last on-study visit. May be conducted by telephone.

Table 4 Schedule of Assessments Table for Staff Study Participants

Procedures	Prior to Enrollment	Intervention Period (Month)										
		Day 1	1	2	3	4	5	6	7	8	9	12
Staff Study Participant Questionnaire		X[a]				X[b]						X[b]
Staff Study Participant Interviews (SSI)		X[a]				X[b]						X[b]
Staff Study Participant Monthly Facilitation Calls[c]		X	X	X	X	X	X	X	X	X	X	

a. Questionnaire and interview should be conducted prior to the first patient receiving their first CAB + RPV LA injection at that site.

b. Questionnaire and interview should be conducted within approximately 4 weeks of the targeted subject visit at each site for Month 4 and after at least 50% of patient study participant visits at Month 12.

c. Facilitation calls will continue during the enrollment period until the last enrolled subject achieves their Month 6 study visit.

Table 5 Schedule of Activities Table for Patient Study Participants (Long Term Follow Up)[a]

Procedures for Long-Term Follow Up[a]	Month 3	Month 6	Month 9	Month 12	WD	Notes
HIV Associated Conditions, AE and SAE Assessments, Con Meds	X	X	X	X	X	Every effort should be made to enter participants into the Long-Term Follow Up if they withdraw from or discontinue the study after receiving at least one dose of CAB LA and / or RPV LA. a. The start of the 52-week follow-up period begins the day of the last CAB LA and/or RPV LA dose. b. A PK sample for storage should be collected in the event of virologic failure during the LTFU phase c. Participants who get pregnant while in study will have additional PK samples for CAB and RPV obtained, see Appendix 8 d. FRP only. U=urine; pregnant participants who remain in the study do not need pregnancy testing during the study, for the duration of their pregnancy e. FRP should continue to receive counselling on the need to use adequate contraception for the entirety of the Long-Term Follow-Up Period. f. Investigators must discuss choice of HAART regimen and timing of initiation with the medical monitor before initiating
HIV-1 RNA	X	X	X	X	X	
CD4+ cell counts	X	X	X	X	X	
Plasma for Storage	X	X	X	X	X	
PK Sample for Storage[b,c]						
Clinical Chemistry and Hematology	X	X	X	X	X	
Pregnancy Testing[d]	U	U	U	U	U	
Urinalysis				X	X	
PT/PTT/INR				X	X	
Contraception Counselling[e]	X	X	X	X	X	
HAART Dispensation[f]	X	X	X	X	X	

2. INTRODUCTION

While advances in the development of new anti-retroviral therapies (ART) provide extensive insights into the management of human immunodeficiency virus (HIV)-infected individuals, chronic HIV infection in adults continues to be characterized by increased development of resistant virus, increasing transmission of resistant virus and issues associated with the long-term toxicity of ART. The current paradigm in the treatment of HIV involves life-long therapy with multiple antiretrovirals. There is an enduring need to develop new agents and combinations with improved dosing schedules, and robust efficacy, safety and resistance profiles for both antiretroviral treatment-naive and treatment-experienced participants.

2.1. Study Rationale

CAB + RPV LA is an investigational HIV treatment regimen of long-acting cabotegravir plus long-acting rilpivirine administered as two concurrent intramuscular injections every month. This new HIV regimen will require changes to the current standard of care, which involves the prescription of oral antiretroviral therapies. Such changes will include managing the logistics of delivering a complete antiretroviral treatment regimen as long acting (LA) injectable therapy. This new treatment option will require patients to receive injections from a provider every month and require staffing resources and logistical arrangements for administration of the injections. It is therefore important to understand how to optimize the delivery of CAB + RPV LA from a PLHIV, HCP and healthcare system perspective in order to ensure equal and easy access for patients. In preparation for national implementation following regulatory approval, there is a need to understand what level of clinic training and support will be needed to effectively deliver this regimen. In this study, investigational sites will have access to a suite of training and implementation tools as well as short-term intensive counseling. The study will evaluate both qualitative and quantitative measures across a range of clinic types to determine the most effective strategies, identify barriers and facilitators for successful implementation of the CAB + RPV LA regimen.

The CAB + RPV LA regimen is also being studied for use once every two months in the ATLAS-2M study. If successful, a two-monthly regimen may become available after initial approval; while two-monthly dosing would reduce the frequency of injection visits for patients, it would require similar strategies for successful implementation, thus the learnings from this study are expected to be applicable to a two-monthly dosing regimen as well.

2.2. Background

The treatment of HIV-1 infection has advanced since the first oral antiretroviral agent (AZT) was approved for the treatment of HIV-1 infected individuals in 1987. Newer antiretrovirals are more potent, better tolerated and have enabled the formulation of multiple regimens that can provide viral suppression with a single tablet once daily. Moreover, clinic visits for laboratory monitoring have become less frequent; current standard of care for virally suppressed patients is a clinic visit with laboratory every 3-6 months. While there have been major advances in the field of HIV therapeutics,

tolerability, long term safety concerns and adherence remain significant limitations to treatment success. Consistent lifetime daily adherence is difficult for many patients, reducing effectiveness of these treatments [DHHS, 2018]. Moreover, intermittent compliance can result in HIV drug resistance, with subsequent regimens being more complicated to construct.

Long acting injectable versions of drugs are being developed to enable therapy with infrequent dosing injection. These therapeutic options hold great promise for future treatment and represent an emerging paradigm for the treatment of HIV infection. Cabotegravir (CAB) is a potent integrase inhibitor that possesses attributes that allow formulation and delivery as a long-acting (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. A two-drug regimen with CAB LA plus RPV LA (CAB + RPV LA) offers many potential advantages over daily oral regimens including infrequent dosing that decreases the daily reminder to patients of their HIV status, better tolerability, less likely to develop viral resistance due to intermittent compliance with oral agents that can lead to sub-therapeutic concentration of antiretroviral medication and emergence of resistance, and improved adherence and overall treatment satisfaction in virologically suppressed patients. Results to date have demonstrated the efficacy of a two-drug regimen of CAB + RPV LA as maintenance therapy with several on-going Phase 2 and 3 studies including LATTE-2, ATLAS, FLAIR, and ATLAS 2M currently underway. [Margolis, 2017]

This new treatment paradigm will require changes to the current standard of care of prescribing oral antiretroviral therapies including the logistics of delivering a complete antiretroviral treatment regimen as LA injectable therapy. This new treatment paradigm will require more frequent visits by patients to see a provider and receive injections, as well as potentially require greater resources in the clinical setting to administer the injection. As this is a promising new treatment modality for people living with HIV (PLHIV), it is important to understand how to optimize the delivery of CAB + RPV LA from a PLHIV, HCP and healthcare system perspective. Previous focus groups convened in the United States have provided some insights into the mixed reactions of how CAB + RPV LA will be implemented in the clinical setting. Concerns raised about chronic dosing injections include overburdening the health care system, CAB + RPV LA more frequent patient encounters and concerns that patients will not want, or not remember to come to clinic for scheduled monthly injections, with the potential to lead to inadequate ART coverage and the development of viral resistance.

The need for pragmatic data and experience is essential to fully understand the barriers and enablers for delivery of this evidence-based treatment. As this is a new and novel treatment in the field of HIV therapeutics, it is critical to understand “how” to effectively implement this treatment paradigm to ensure optimal impacts on healthcare service system- and patient-level outcomes. In preparation for national implementation following FDA approval, it is important to understand what level of support and preparation will be needed to ensure that clinics are well prepared for administering and incorporating this new and more frequent directly observed injectable therapy in the clinic setting. This study will explore a suite of training and implementation tools as well as short-term

intensive facilitation, to determine what will be effective in preparing clinics to deliver CAB + RPV LA across diverse clinical settings. Therefore, this study will aim to collect insights regarding clinical settings, context, barriers and facilitators from a patient, healthcare provider and healthcare system perspective in order to effectively implement the CAB + RPV LA regimen at the time of FDA approval.

Implementation Rationale/Theory of Change:

Lippitt, Watson, and Westley created a seven-step theory that focuses more on the role and responsibility of the change agent than on the evolution of the innovation itself. Information is continuously exchanged throughout the process. Infectious Disease/HIV providers were queried on their plan and ability to implement CAB + RPV LA effectively into their clinical settings. Mixed responses suggested that some sites might require more support and some sites many require less support to implement this new intervention well. Based on Powell's list of most effective intervention strategies, ViiV Healthcare is proposing to test a complex implementation strategy with external facilitation as a core component of this study [Powell, 2015] to help elucidate the level of support, best practices, and required tools needed to implement this novel evidenced-based intervention into a variety of clinical settings.

The seven steps of this theory are: 1. Understand the new change or innovation. 2. Assess the motivation and capacity for change. 3. Assess the resources and motivation to support the innovation. 4. Choose progressive change strategies. 5. Implement a clear intervention. 6. Maintain the change. 7. Gradually terminate from the helping relationship. The change agent should gradually withdraw from their role over time. This will occur when the change becomes part of the organizational culture (Lippitt, Watson and Westley).

The implementation strategy for this study was constructed based on Lippitt, Watson and Westley's theory of change but also took into consideration feedback from numerous focus groups and advisory boards conducted by ViiV Healthcare.

Implementation Questions:

How prepared are healthcare settings to incorporate a high volume of patients receiving the CAB + RPV LA regimen into their clinical flow across three different clinical settings in the US while also identifying multi-level barriers to and facilitators for successful implementation? In order to answer this fundamental question, the study will focus on the following four aims.

Study Aims:

Aim 1: Evaluate the degree of acceptability, appropriateness, feasibility, fidelity, and sustainability achieved for CAB + RPV LA;

Aim 2: Identify multi-level barriers and facilitators to implement and sustain the intervention (CAB + RPV LA);

Aim 3: To identify the optimized complex implementation strategy required for successful implementation of CAB + RPV LA in various clinical settings and contexts;

Aim 4: To measure patient satisfaction with the process (timeliness of visits, length of visit, and patient education).

Implementation Stage of Research Project:

Initial implementation stage: the first use of an evidence-based intervention (i.e., CAB + RPV LA) by healthcare professionals and patients/service users in pragmatic clinical care settings and learning how to support successful implementation into routine care.

The LATTE and LATTE-2 studies have demonstrated the efficacy of maintaining viral load suppression in participants who initiated a three drug ARV regimen prior to switching to the two-drug CAB + RPV regimen. Specifically, phase 2b studies including LATTE and LATTE-2 provided a proof of concept for a two-drug regimen in patients initially suppressed on three drugs. The LATTE study provided valuable information on both the optimal dose of oral CAB and the importance of an induction/maintenance approach to HIV therapy. The LATTE-2 study demonstrated the ability of a 2-drug maintenance therapy of LA CAB and LA RPV to maintain virologic suppression in patients who initiated on a triple antiretroviral oral based regimen

Several larger, phase 3 studies are currently underway (ATLAS, ATLAS-2M, and FLAIR) that will test the effectiveness of CAB + RPV LA in maintaining viral load suppression in patients initially suppressed on a three-drug regimen.

Design of Implementation Research:

Hybrid III: The primary focus of this study is implementation of mostly provider-focused implementation strategies (suite of training and implementation tools as well as short-term intensive facilitation); The secondary focus is on the clinical efficacy of this novel approach to antiretroviral therapy for the treatment of HIV infection (CAB + RPV LA). Implementation research outcomes are different than clinical outcomes more commonly incorporated into clinical trial research and design. In Implementation Science, research outcomes are typically provider and/or system behaviours rather than patient clinical outcomes. For example, outcomes can include levels and rates of acceptability, adoption, and fidelity to the clinical intervention [Proctor, 2011].

In addition, implementation research focuses on addressing the question ‘what works where and why.’ In other words, implementation research focuses on identifying factors/processes that negatively and positively impact implementation outcomes so that these issues can be effectively addressed in subsequent implementation efforts. The proposed research will allow us to tailor implementation strategies and clinical support materials to match the specific needs of different clinical settings. This proposal is thus guided by frameworks that are appropriate to the proposed stage of implementation research, including a determinants framework and an outcomes taxonomy, that is highly sensitive to features of the context in which the implementation efforts are to occur when CAB + RPV LA goes to scale. Additionally, this study will clinically monitor all patients enrolled and will collect routine HIV laboratory testing including basic safety analysis,

HIV RNA and CD4 measurements and physical assessments that will be obtained throughout the study to ensure clinical safety, tolerability and efficacy (Section 1.5).

Frameworks:

In this study, a combination of two complementary frameworks will guide the implementation evaluation. [Proctor, 2011] put forth a taxonomy of 8 distinct implementation outcomes that are key indicators of implementation success as well as proximal indicators of implementation processes. As this is a Phase III study with an investigational drug that is not registered or available commercially, the focus for initial implementation evaluation is on 5 key implementation outcomes: (1) acceptability, (2) appropriateness, (3) feasibility, (4) fidelity, and (5) sustainability (see Table 6 below for definitions). According to [Proctor, 2011], these represent key intermediate outcomes in relation to service system outcomes or clinical outcomes in treatment effectiveness and quality of care research. [Proctor, 2011]

Table 6 Primary Implementation Outcomes

Acceptability: Perception amongst implementation stakeholders (providers, administrators, and patients) that the new intervention is agreeable, palatable and satisfactory
Appropriateness: The perceived fit, relevance, or compatibility of the innovation or evidence-based practice for a given practice setting, provider, or consumer; and/or perceived fit of the innovation to address a particular issue or problem.
Feasibility: Extent to which an intervention can be successfully used or carried out in a given setting
Fidelity: Extent to which an intervention gets applied as originally designed/intended. Will the new intervention be administered as intended.
Sustainability: Extent to which the intervention becomes routinely available/maintained post introduction

For the purposes of this study we will quantitively assess (1) Acceptability (2) Appropriateness, (3) Feasibility, and (4) Sustainability. These will be conducted in short validated off the shelf surveys which take approximately 15 minutes per survey. By measuring acceptability, appropriateness and feasibility, these can act as surrogate markers for adoption (and can be extrapolated to real-world adoption outside of a clinical trial environment). (See Section 10.10 , Section 10.11, for a summary of elements to be evaluated in the surveys)

As the effectiveness of CAB + RPV LA has been documented in several Phase IIb studies with several larger Phase III studies (ATLAS, ATLAS-2M and FLAIR) nearing completion, it is therefore assumed that successful implementation of CAB + RPV LA will have a positive impact on patient-level outcomes.

In addition, this study requires rigorous application of a determinants implementation framework to identify and assess the factors—across multiple system levels and at the clinic and individual provider levels—that explain ***why*** the implementation of CAB + RPV LA is or is not successful across contexts and clinical settings. We know there are many different perceptions of the additional burden that regular injections may place on the healthcare system. However, because of the lack of real-world experience, we will be

exploring within this study what the pragmatic facilitators and barriers may be at clinic types where this study will be implemented.

Many implementation frameworks exist; each has advantages and disadvantages, with relative advantage conferred on those that are (a) highly specified operationally and (b) widely used in implementation evaluations. The Consolidated Framework for Implementation Research (CFIR) framework [Andrade, 2009; CDC, 2014; Damschroder, 2009] meets each of these criteria while emphasizing the central role of context and identification of multi-level barriers. The application of the CFIR framework will enable us to fully characterize and explain the ways in which implementation strategies and service system processes have and have not been successful across contexts and settings (Aims 1 and 2). These findings will inform the tailoring of implementation strategies to enhance the implementation effectiveness of CAB + RPV LA once approved and ready to be taken to scale in the US. We therefore propose to use the Consolidated Framework for Implementation Research (CFIR), a well-established, comprehensive, and widely used framework that is used to assess existing and potential barriers and facilitators to successful implementation and sustainment. CFIR is comprised of 39 constructs organized into five domains. It is not practical or necessary to assess all 39 constructs and therefore the focus will be on a subset of 14 key CFIR constructs that are most relevant to the implementation of CAB + RPV LA (Table 7).

Table 7 CFIR Constructs Guiding the Evaluation of Multi-Level Barriers to and Facilitators of CAB + RPV LA Implementation and Sustainment

CFIR Framework - CONSTRUCTS	SHORT DESCRIPTION
II. Outer Setting	
Patient needs and resources	The extent to which patient needs, as well as barriers and facilitators to meet those needs, are accurately known and prioritized by the organization
III. Inner Setting	
Readiness for Implementation – Leadership Engagement	Tangible and immediate indicators of organizational commitment to implement an intervention
Readiness for Implementation - Available resources	The level of resources dedicated for implementation and on-going operations, including money, training, education, physical space, and time
Readiness for Implementation – Access to Knowledge and Information	Ease of access to digestible information and knowledge about the intervention and how to incorporate it into work tasks.
Structural Characteristics	The social architecture, age, maturity, and size of an organization
Networks & Communications	The nature and quality of webs of social networks and the nature and quality of formal and informal communications within an organization
Implementation Climate	The absorptive capacity for change, shared receptivity of involved individuals to an intervention, and the extent to which use of that intervention will be rewarded, supported and expected within the organization

CFIR Framework - CONSTRUCTS	**SHORT DESCRIPTION**
Tension for Change	The degree to which stakeholders perceive the current situation as intolerable or needing to change
Compatibility	The degree of tangible fit between meaning and values attached to the intervention by involved individuals, how those align with individuals' own norms, values and perceived risks and needs, and how the intervention fits with existing workflows and systems
Learning Climate	A climate which a) leaders express their own fallibility and need for team members' assistance and input; b) team members feel that they are essential, valued, and knowledgeable partners in the change process; c) individuals feel psychologically safe to try new methods; d) there is sufficient time and space for reflective thinking and evaluation
IV. Characteristics of Individuals (e.g. Patients, Providers, Injectors, Administrators etc)	
Individual Stage of Change	Characterization of the phase an individual is in, as he or she progresses toward skilled, enthusiastic, and sustained use of the intervention
IV. Process	
Planning	The degree to which a scheme or method of behaviour and tasks for implementing an intervention re developed in advance, and the quality of those schemes or methods
Engaging Champions	Individuals who dedicate themselves to supporting, marketing, and 'driving through' an implementation, overcoming indifference or resistance that the intervention may provoke in an organization
Key Stakeholder	Individuals who are affiliated with an outside entity who formally influence or facilitate intervention decisions in a desirable direction
Executing	Carrying out or accomplishing the implementation according to plan

2.3. Benefit/Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with oral and CAB LA or RPV LA can be found in the Investigator's Brochures (2017 CAB IB: GlaxoSmithKline Document Number RH2009/00003/07; Rilpivirine Clinical Investigator Brochure, 2018).

Oral RPV is an approved medicinal product and detailed information on its benefit/risk profile together with any risk mitigation measures are described in product labelling. (Edurant Prescribing Information, 2018)

2.3.1. Risk Assessment

Oral CAB and CAB LA (GSK1265744/GSK1265744 LA)

Since CAB is in clinical development and exposure in humans with or without HIV infection is limited, the clinical safety profile in humans has yet to be fully elucidated. The following risks have primarily been identified during routine preclinical testing and/or from the clinical trial experience to date and are considered of potential relevance to clinical usage in the context of this protocol. Additional information about the clinical experience to date and possible risks associated with treatment using CAB can be found in the Summary of Data and Guidance for the Investigator section of the investigator's brochure (IB).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Drug Induced Liver Injury (DILI)	A small proportion of participants in the CAB program to date (total exposure >3100 participants) have developed transaminitis (elevated liver transaminases characterised by predominant alanine aminotransferase (ALT) elevation). In most participants, transient transaminitis was explained by acute hepatitis C infection (majority) and other systemic infections. In a small number of participants, there was not an alternative explanation, suggesting a mild form of drug induced liver injury (DILI) without hepatic dysfunction, which resolved upon withdrawal of treatment with CAB. All participants with suspected DILI identified to date were receiving oral CAB.	• Exclusion criteria as described in Section 5.2 will prohibit participation of PLWHIV who have significant liver impairment based on screening liver chemistry including transaminases (ALT and Aspartate aminotransferase [AST]) as well on prior medical history. Participants with a history of chronic liver disease with ongoing inflammation and/or fibrosis will have additional confirmatory assessments to confirm suitability for entry into the study. • Liver transaminases (ALT and AST) will be monitored throughout this study (refer to Schedule of Activities Table, Section 1.5) and the liver chemistry stopping criteria will be adopted as described in Section 10.6.2 of this protocol. Participants will be withdrawn from CAB treatment where no compelling alternative cause is identified, and DILI is suspected. • Participants who develop ALT ≥3 times the upper limit of normal (ULN) while on study must consult with Medical Monitor prior to initiation or continuation of CAB LA + RPV LA.
Injection Site Reactions (ISRs)	Clinical, experience to date has demonstrated ISRs occur in the majority of exposed participants treated with CAB LA but are generally mild (Grade 1) or moderate (Grade 2) and include events of pain, tenderness, erythema, or nodule formation of several days duration (median duration for individual events <1 week). ISRs may occur more than once in an individual participant receiving multiple injections. Although some Grade 3 ISRs have been reported, overall ISRs appear tolerable and have not to date been associated with an excess of participants' withdrawal.	• Administration advice will be given to minimize risk of poor administration technique giving rise to injection site reactions. Advice on care, monitoring, natural course, and treatment of ISRs is given in study documentation. • Advice will be given to participants on care of injection site on day/days immediately post administration, use of analgesia, compresses where appropriate. • Participants will be closely monitored for ISRs particularly for signs of pain, tenderness, infections, erythema, swelling, induration, or nodules (granulomas or cysts) throughout the study. • Complications of ISRs such as infections (abscess, cellulitis) and collections of fluid requiring drainage will be monitored,

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		• Significant ISRs may be photographed and referred to a dermatologist for specialist advice.
Hypersensitivity Reactions (HSR)	Hypersensitivity reactions have been reported as uncommon occurrences with integrase inhibitors (INI), including the closely related compound dolutegravir, and were characterized by rash, constitutional findings, and sometimes, organ dysfunction, including liver injury. While there have been no clinical cases of hypersensitivity to CAB to date, there is a theoretical risk of systemic or severe hypersensitivity reactions with or without hepatic symptoms associated with use of IM CAB. The long exposures anticipated after IM CAB injection may complicate the management of a drug hypersensitivity reaction, were it to occur.	• The risk of developing a hypersensitivity reaction post administration of IM CAB will be minimized by the use of a 4-week oral lead-in of oral CAB to determine individual safety and tolerability prior to the introduction of IM CAB. • Clinical assessments, laboratory tests (including liver transaminases) and vital signs will be performed throughout this study. Results from these assessments may aid early detection of HSR. • Oral CAB will be withdrawn immediately for cases with suspected HSR during the oral CAB lead-in phase and would not proceed to the injection phase. Participants receiving the injection who develop suspected HSR would not receive further injections. During oral (oral bridge) and IM CAB treatment, any HSR reactions that occur would be managed supportively.
Effects in pregnancy seen in non-clinical studies	In animal reproduction studies, CAB when administered to rats at > 30 times the systemic exposure at the maximum recommended oral human dose (MRHD) of 30 mg during organogenesis through delivery, had adverse effects on labor and delivery that may be related to a delay in the onset of parturition, resulting in increased fetal mortality (stillbirths) and neonatal deaths immediately after birth. A delay in the onset of parturition and increased stillbirths and neonatal deaths were observed in a rat pre- and postnatal development study at greater than 28 times the exposure at the recommended human dose (RHD). No evidence of adverse developmental outcomes was observed with oral cabotegravir in rats or rabbits (greater than 28 times or similar to the exposure at the RHD, respectively) given during organogenesis. The clinical significance of these finding in humans is unknown. For pregnant participants remaining in the study, refer to Appendix 8 for	• Pregnant females are excluded from enrollment in this study and females of reproductive potential (FRP) are required to adopt highly reliable means of contraception during participation and throughout the long term follow up phase of this study following exposure to CAB LA. • FRP are also required to undergo regular pregnancy testing throughout study conduct. Pregnant participants who remain in the study do not need pregnancy testing for the duration of the pregnancy • Participants who become pregnant during the study may remain in the study provided all protocol defined pregnancy related assessments, procedures and documentation are completed, and a pregnancy specific ICF addendum is signed by the participant. Details regarding management of pregnant participants are found

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	additional data regarding CAB and pregnancy.	in Appendix 8
Potential effects in females exposed to dolutegravir during conception and early pregnancy	A preliminary analysis of an ongoing birth outcome surveillance study in Botswana involving women exposed to dolutegravir (DTG) a different molecule in the same integrase class of medications as CAB, identified four cases (as of May 2018) of neural tube defects in 426 infants born to mothers who were exposed to DTG-containing regimens from the time of conception. In the same study, no infant born to a woman who started DTG during pregnancy had a neural tube defect, out of 2,824 women. 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. Recently updated data (April 2020) for this birth outcome study showed that among women who were on DTG when they got pregnant, 7/3591 neural tube defects (NTD) occurred (0.19%). In comparison, NTDs were identified in 21/19,361 (.11%) women delivering on any non-DTG antiretrovirals. There was not a significant difference in the number of neural tube defects between births to women taking DTG and those taking other non-DTG antiretroviral treatments (0.09% difference). The clinical relevance of either of these findings in relation to CAB use is unknown	• Pregnant females are excluded from enrollment in clinical trials of CAB at this time and females of reproductive potential (FRP) are required to adopt highly reliable means of contraception during participation and throughout long term follow up phases of studies after exposure to CAB LA. • FRP potential also undergo regular pregnancy testing throughout study conduct. Pregnant participants who remain in the study do not need pregnancy testing for the duration of the pregnancy It should be noted that CAB concentration could remain for prolonged periods despite discontinuation of CAB LA • Participants who become pregnant during the study may remain in the study, provided all protocol defined pregnancy related assessments, procedures and documentation are completed and a pregnancy specific ICF addendum is signed by the participant. Details regarding management of pregnant participants is found in Appendix 8
Development of Resistance following discontinuation of CAB LA	Residual concentrations of CAB would remain in the systemic circulation of participants who stop CAB LA treatment for prolonged periods (more than 1 year, in some participants after last injection (e.g., for tolerability issues or treatment failure). Participants discontinuing CAB LA regimen may be at risk for developing HIV-1 resistance to CAB many weeks after discontinuing injectable therapy.	• After participants stop CAB LA, Oral highly active antiretroviral therapy (HAART) regimens will be prescribed within 4 weeks after the last monthly dose, and following consultation with the medical monitor. This would be anticipated to result in continued suppression or rapid re-suppression of HIV-1 RNA thus minimizing the risk of emergent resistance • The participants in this study who discontinue IM CAB for any reason will be monitored for a minimum of 52 weeks from the time of the last IM CAB injection.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Drug-Drug Interactions (DDIs)	For a complete listing of permitted and prohibited concurrent medications for CAB and CAB LA, refer to Section 6.5. CAB and CAB LA should not be co-administered with the following medicinal products, as significant decreases in CAB plasma concentrations may occur (due to UDP-glucuronosyltransferase (UGT) enzyme induction), which may result in loss of therapeutic effect of CAB. - the anticonvulsants carbamazepine, oxcarbazepine, phenobarbital, phenytoin - the antimycobacterials rifampicin, rifapentine, rifabutin - St John's wort (Hypericum perforatum) Oral CAB administration only: Antacid products containing divalent cations (e.g., aluminum, calcium, and magnesium) must be taken at least 2 hours before or at least 4 hours after CAB. Participants discontinuing a LA regimen may be at risk for developing drug-drug interactions (DDIs) many weeks after discontinuing injectable therapy.	• All participants will be informed of prohibited medications throughout the study and updates provided as needed via the informed consent.
Inadvertent Intravenous Injection (Accidental Maladministration)	As with any intramuscular injection, it is possible that CAB LA can be inadvertently administered intravenously instead of intramuscularly possibly resulting in higher than expected concentrations of CAB shortly after injection and lower concentrations thereafter. This could be due to administrator error, improper injection technique and / or improper needle length used based on body type. The clinical consequences of accidental intravenous administration of CAB LA are currently unknown. HIV-1 viral suppression may not be effective following accidental maladministration.	• Training will be provided to all sites on proper injection technique. • Should IM maladministration be suspected at any time (e.g. suspected under or overdose or inadvertent IV dosing), a post dose electrocardiogram (ECG), vital signs, or any other supportive testing may be obtained at the discretion of the investigator, and the medical monitor will be notified. • Laboratory samples for safety parameters and HIV-1 RNA will be closely monitored in all participants. Additionally, 2 hour post dose PK samples may be obtained at a few

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		early timepoints for determination of CAB concentration and possible pharmacokinetic correlation with safety parameters such as ECG changes and virologic response.

Oral RPV

For safety and risk mitigation for oral RPV refer to the RPV local prescribing information [Edurant Prescribing Information, 2018]

RPV LA

Information about the clinical experience to date and possible risks associated with treatment using RPV LA can be found in the Summary of Data and Guidance for the Investigator section of the IB. Beyond what has already been identified with oral RPV, no new systemic adverse reactions to RPV LA (same active moiety) have been observed. The following risks are considered to be of specific clinical relevance in the context of IM use.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Injection Site Reactions	Clinical, experience to date has demonstrated ISRs occur in the majority of exposed participants treated with RPV LA but are generally mild (Grade 1) or moderate (Grade 2) and include events of pain, tenderness, erythema, or nodule formation of several days duration (median duration for individual events <1 week). ISRs may occur more than once in an individual participant receiving multiple injections. Although some Grade 3 ISRs were reported, overall ISRs have been well tolerated and have not to date been associated with an excess of participants' withdrawal due to ISRs. None of the ISRs was serious and no clinical significant complications were reported	• Administration advice to minimize risk of poor administration technique giving rise to injection site reactions. Advice on care, monitoring, natural course, and treatment of ISRs given in study documentation • Advice to participants on care of injection site on day/days immediately post administration, use of analgesia, compresses where appropriate. • Participants will be closely monitored for ISRs particularly for signs of pain, tenderness, infections, erythema, swelling, induration, or nodules (granulomas or cysts) throughout the study. • Complications of ISRs such as infections (abscess, cellulitis) and collections of fluid requiring drainage will be monitored • Significant ISRs may be photographed and referred to a dermatologist for specialist advice.
Rash	Some observations of rash with oral RPV have been reported in clinical studies executed to date (the majority are mild). Severe skin and hypersensitivity reactions have been reported during the postmarketing experience, including cases of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), with oral RPV-containing regimens. While some skin reactions were accompanied by constitutional symptoms such as fever, other skin reactions were associated with organ dysfunctions, including elevations in hepatic serum biochemistries.	• Participants with a Grade 1 or 2 rash will be allowed to continue treatment or to be rechallenged, depending on the clinical judgment of the investigator. • All participants experiencing a Grade 3 or 4 rash should discontinue their antiretroviral (ARV) medication (study medication and background regimen) and be withdrawn from the study. • All rash events should be assessed with special attention to systemic symptoms, laboratory abnormalities, or mucosal involvement. Close clinical follow-up, including follow-up of laboratory abnormalities, and appropriate medical intervention, including referral to dermatologist as appropriate, should be instituted for these events; daily follow-up is recommended for 5 days from the onset of the event to monitor for progression of the event. See Section 10.6.6.10.1 for additional guidance on management of rash.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Development of Resistance	Residual concentrations of RPV LA can remain in the systemic circulation of participants who stopped treatment (e.g., for tolerability issues or treatment failure) for prolonged periods (months to more than a year, in some participants) Participants discontinuing a LA regimen may be at risk for developing resistance to RPV many weeks after discontinuing injectable therapy.	• After participants stop RPV LA, Oral HAART regimens will be prescribed within one month after the last monthly dose, and following consultation with the medical monitor. This would be anticipated to result in rapid re-suppression of HIV-1 RNA thus minimizing the risk of emergent resistance • The Sponsor will continue to monitor participants in this study who discontinue the LA regimen for any reason for a minimum of 52 weeks from the time of the last LA administration.
Drug-Drug Interactions (DDIs)	For a complete listing of permitted and prohibited concurrent medications for RPV and RPV LA, refer to Section 6.5. RPV LA should not be co-administered with the following medicinal products, as significant decreases in RPV plasma concentrations may occur (due to CYP3A enzyme induction), which may result in loss of therapeutic effect of RPV LA. - the anticonvulsants carbamazepine, oxcarbazepine, phenobarbital, phenytoin - the antimycobacterials rifampicin, rifapentine, rifabutin - the glucocorticoid systemic dexamethasone, except as a single dose treatment - St John's wort (Hypericum perforatum). Of note, evidence to date indicates that clinically relevant DDIs with RPV LA and other antiretrovirals are unlikely to occur. Oral RPV administration only: - Antacid products containing divalent cations (e.g., aluminum, calcium,	• All participants will be informed of prohibited medications throughout the study and updates provided as needed via informed consent.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	and magnesium) must be taken at least 2 hours before or at least 4 hours after RPV. - H2-antagonists must be taken at least 12 hours before or at least 4 hours after taking RPV. - RPV should not be co-administered with proton pump inhibitors, such as esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole; Participants discontinuing a LA regimen may be at risk for developing DDIs many weeks after discontinuing injectable therapy.	
Inadvertent Intravenous Injection (Accidental Maladministration)	As with any intramuscular injection, it is possible that RPV LA can be inadvertently administered intravenously instead of intramuscularly possibly resulting in higher than expected concentrations of RPV shortly after injection and lower concentrations thereafter. This could be due to administrator error, improper injection technique and / or improper needle length used based on body type. In addition, HIV-1 viral suppression may not be effective following accidental intravenous maladministration.	• Training will be provided to all sites on proper injection technique. • Should IM maladministration be suspected at any time (e.g., suspected under or overdose or inadvertent intravenous [IV] dosing), post dose ECG monitoring and vital signs or any other supportive testing may be obtained at the discretion of the investigator, and the medical monitor notified. • Laboratory samples for safety parameters and HIV-1 RNA will be closely monitored in all participants. Additionally, 2-hour post dose PK samples will be obtained at a few early timepoints for determination of RPV concentration and possible pharmacokinetic correlation with safety parameters such as ECG changes and virologic response.
Overall Study Related Risks		
Venipuncture	Participants will be required to have blood samples taken. Risk of bruising, and rarely, infection	• Trained personnel will perform venipuncture
Risks of ECG pad removal	Some discomfort and rash may occur where the ECG pads are removed.	• ECGs will be conducted by appropriately trained personnel and effort made to minimize contact time for application of

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		the pads.
Risk of Treatment Failure	This study employs a novel 2 drug LA ART maintenance regimen for the treatment of HIV-1 infection that remains experimental. Both IM CAB and RPV have demonstrated antiviral activity in large clinical studies and the two-drug combination has demonstrated sustained antiviral activity in studies, LAI116482 and 200056. Doses of the CAB LA and RPV LA have been selected to achieve exposures that are expected to maintain virologic efficacy on the basis of available data with the oral and LA formulations. Due to administration error, it is possible that a participant could receive an inadequate dose of CAB LA or RPV LA. Sub-therapeutic concentrations of either CAB LA or RPV LA could lead to virologic failure and possibly the development of viral resistance.	• Viral loads and CD4+ cell counts will be closely monitored throughout the study (maintenance and extension phases), allowing for early detection of failing treatment. Where confirmed virological failure occurs, participants would be discontinued from study drugs and transferred to an oral HAART regimen. • Plasma samples will be collected as needed during the injection Phase for determination of CAB and RPV concentration and possible pharmacokinetic correlation with virologic response.

2.3.1.1. Other Clinically Relevant Information

Additional details concerning safety observations from clinical studies and for which a causal association has not been established or which are of minimal clinical significance may be found in the Investigator's Brochures. Refer to 'Summary of data and guidance for the investigator'.

Seizure

Several cases of seizure have occurred during the cabotegravir program. These cases have had alternative explanations for their occurrence. Overall, there is not convincing evidence that cabotegravir 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. However, seizure and seizure-like events are considered as AEs of special interest for CAB. Subjects with an unstable or poorly controlled seizure disorder will be excluded from study participation. Report any cases of seizure or seizure like events immediately.

2.3.2. Benefit Assessment

The antiviral activity against HIV-1 of CAB has been well established through in vitro and clinical studies. RPV is an established antiviral agent against HIV-1 in treatment naive participants, with long term durability (>96 weeks in Phase 3 and >240 weeks in Phase IIb).

2.3.3. Overall Benefit: Risk Conclusion

Participants receiving CAB LA + RPV LA are anticipated to benefit from maintenance of virological suppression using LA agents. Participants who receive CAB LA+ RPV LA as monthly dosing will not need to take concomitant daily oral antiretroviral therapy. Adherence in these participants is expected to be improved and will be directly observed during IM injections. Efficacy of this two-drug regimen, as IM agents, has been demonstrated through Week 96 of the ongoing 200056 study (Margolis, 2018).

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with the CAB LA and RPV LA regimen and the study as a whole are justified by the anticipated benefits that may be afforded to virologically suppressed, treatment-experienced participants with HIV-1 infection.

The questionnaires and interviews to be administered to clinical staff and study participants are not associated with additional risk.

3. OBJECTIVES AND ENDPOINTS

Objective	Endpoint
Primary	
To evaluate acceptability, appropriateness, and feasibility of delivering CAB+RPV LA	Acceptability of Intervention Measure (AIM), Intervention Appropriateness Measure (IAM), and Feasibility of Intervention Measure (FIM). Assessed quantitatively by staff study participants at baseline- prior to any Month 1 visits, after at least 4 monthly facilitation calls and upon completion of all Month 12 visits at that site. Acceptability of Intervention Measure (AIM) and Intervention Appropriateness Measure (IAM). Assessed quantitatively by patient study participants at Month 1 prior to first injection, Month 4 and Month 12
Secondary	
To evaluate organizational facilitators and barriers	Facilitators/Barriers: Semi-Structured Interview (SSI) conducted with staff study participants at baseline- prior to any Month 1 visits, after at least 4 monthly facilitation calls and upon completion of at least 50% of Month 12 visits at that site. Barriers, facilitators and best practice sharing amongst clinics assessed by short-term facilitation (coaching calls) for at least 6 months. These will be a combination of structured questions and open-ended questions. Use of support materials/toolkit assessed via Survey responses of staff study participants prior to any Month 1 visits, after at least 4 monthly facilitation calls and upon completion of all Month 12 visits at a site. Use of support materials/toolkit assessed via Survey responses of patient study participants via Survey responses at Month 1 and Month 4 and Month 12, as well as SSI responses prior to Month 1 and at Month 12.

Objective	Endpoint
Patient Facilitators and Barriers	Facilitators/Barriers: Semi-Structured Interviews (SSI) conducted with patient study participants prior to Month 1 and at Month 12
Implementation Fidelity	Injections occurring within target window from the expected injection date Use of support materials/toolkit assessed through SSI of staff study participants at Day 1, after at least 4 monthly facilitation calls and upon completion of at least 50% of Month 12 visits at that site.
Implementation Sustainability	Program Sustainability Assessment Tool (PSAT) assessed by staff study participants at Month 12.
To measure patient satisfaction with process (timeliness of visits, length of visit, patient education)	Patient Survey responses at Month 1, Month 4 and Month 12. Patient SSI responses prior to Month 1 and at Month 12 Length of patient visit from arrival until departure from clinic at Month 1, Month 5 and Month 11
Evaluate safety and efficacy measures of CAB+RPV LA	Proportion of participants with plasma HIV-1 RNA <50 c/mL over time Proportion of participants with confirmed virologic failure (CVF) over time Incidence of treatment emergent genotypic and phenotypic resistance to CAB and RPV in patients with CVF Incidence and severity of AEs and laboratory abnormalities over time Proportion of participants who discontinue treatment due to AEs over time Reported injection site reactions over time Absolute values and changes in laboratory parameters over time

4. STUDY DESIGN

4.1. Overall Design

This study is a single-arm, multicenter, one-year evaluation of the effect of an implementation strategy on the degree of acceptability, appropriateness, feasibility, fidelity, and sustainability of clinic practices to deliver the CAB + RPV LA regimen to appropriate HIV-infected patients. The study will use an implementation study approach at various clinic types (university/hospital, private clinic or public health) to develop a site-specific framework for delivering the CAB + RPV LA regimen which could be adapted for broad utilization upon commercial availability of this regimen.

4.2. Scientific Rationale for Study Design

This time-sensitive proposal will evaluate the implementation of CAB + RPV LA for HIV treatment into University/Hospital, public health clinics, and private practices clinic settings through an implementation Hybrid Type III evaluation. This will be a phase IIIb, qualitative, multicentre study design to evaluate intervention strategies (suite of training and implementation tools as well as short-term facilitation). The clinical effectiveness of CAB + RPV LA will be also captured as a secondary endpoint. A mixed methods approach is proposed where quantitative (surveys) and qualitative (key informant interviews) implementation outcomes are collected, as well as quantitative data to assess clinical effectiveness outcomes. Summative implementation outcome data will be analysed using the Proctor framework and survey questionnaires. The barriers, facilitators, sustainment, fidelity, use of implementation tools, training and patient satisfaction will be analysed using semi-structured interviews from the validated CFIR framework. Sharing best practices and key learnings will be analysed by short-term facilitation calls.

4.3. Justification for Dose

4.3.1. Oral Lead-In Phase

Participants in 209493 will enter the study virologically-suppressed on an oral SOC regimen and will receive oral CAB 30 mg + RPV 25 mg once daily during the oral lead-in phase to confirm tolerability prior to receiving CAB LA + RPV LA injectable treatment.

Oral CAB has been co-administered with oral RPV in several studies. No clinically relevant drug-drug interaction following repeat oral administration of CAB with RPV was observed in healthy subjects in LAI116181 [GlaxoSmithKline Document Number 2011N130484_00]. Oral RPV 25 mg once daily, the approved oral dose of RPV, was administered in combination with oral CAB to HIV-infected participants in the dose-ranging Phase 2b study LAI116482 [(LATTE, (CAB 10, 30, or 60 mg once daily)); GlaxoSmithKline Document Number 2014N216014_00] and 200056 [LATTE-2] (GlaxoSmithKline Document Number 2013N168152_05) with CAB 30mg once daily during the ~4 week oral lead-in phase and in Phase 3 studies 201585 [ATLAS] and 201584 [FLAIR] which are evaluating Q4W dosing of CAB LA + RPV LA.

LAI116482 (LATTE), a Phase 2b, dose-ranging study (randomized 1:1:1: to CAB 10 mg, 30 mg, or 60 mg) evaluated the long-term efficacy and safety of a two-drug, two-class, once-daily combination of CAB + RPV in HIV-infected, treatment-naïve adult participants. Following a 24-week phase of induction of virologic suppression using CAB + 2 NRTIs, the regimen was simplified to a dual regimen, where subjects continued their randomized oral dose of CAB with RPV 25 mg once daily for an additional 72-weeks (total comparative study duration of 96 weeks; [Margolis, 2018], after which one oral CAB dose was selected for progression into the Extension Phase with RPV 25 mg once daily.

Across all dose arms, CAB achieved similar efficacy when co-administered with 2 NRTIs at Weeks 16 and 24, and on dual treatment with RPV at Weeks 48 and 96, respectively (Table 8). Rates of virologic suppression through Week 96 (Maintenance) were numerically higher than the EFV-based comparator regimen.

Table 8 Proportion (95% CI) of Participants with Plasma HIV-1 RNA <50 c/mL at Key Visits - Snapshot (MSDF) Analysis (ITT-E Population) in LATTE

Visit		CAB 10 mg N=60	CAB 30 mg N=60	CAB 60 mg N=61	CAB Subtotal N=181	EFV 600 mg N=47
Week 16 +2 NRTIs	n (%)	54 (90)	50 (83)	53 (87)	157 (87)	46 (74)
	95%CI Proportion	(82, 98)	(74, 93)	(78, 95)	(82, 92)	(63, 85)
Week 24 + 2 NRTIs	n (%)	52 (87)	51 (85)	53 (87)	156 (86)	46 (74)
	95%CI Proportion	(78, 95)	(76, 94)	(78, 95)	(81, 91)	(63, 85)
Week 48 + RPV	n (%)	48 (80)	48 (80)	53 (87)	149 (82)	44 (71)
	95%CI Proportion	(70, 90)	(70, 90)	(78, 95)	(77, 88)	(60, 82)
Week 96 + RPV	n (%)	41 (68)	45 (75)	51 (84)	137 (76)	39 (63)
	95%CI Proportion	(57,80)	(64,86)	(74, 93)	(69, 82)	(51, 75)

CAB was administered with 2 NRTIs through Week 24 (Induction Phase) of LATTE.
95% CIs are normal approximation confidence intervals.

Overall, the efficacy and safety data from the LATTE study, CAB exposure following LA administration, and limited drug-drug interaction potential, supported selection of the CAB 30 mg dose for once daily administration with the approved dose of RPV 25 mg once daily during the oral lead-in phase of studies with CAB LA and RPV LA. Select

plasma CAB PK parameters observed following oral administration with oral RPV, including following the oral lead-in for LATTE-2, are summarized in Table 9.

Table 9 Summary of CAB Pharmacokinetic Parameters Following Repeat Oral Administration in HIV-Infected Subjects

Study	Once Daily Dose	Phase	Plasma CAB PK Parameter (Geometric mean [95%CI] (CVb%)			
			AUC(0-τ) (μg.h/mL) Cmax (μg/mL)	Cτ or C0 (μg/mL)	Tmax[a] (h)	AUC(0-τ) (μg.h/mL)
LAI116482 (LATTE)	10 mg tab (n=14)	Induction Phase +2 NRTIs	45.7 [38.2, 54.6] (32)	2.77 [2.3, 3.3] (33)	1.35[b] [1.2, 1.5] (45)	1.0 (0.9 – 8.0)
		Maintenance Phase +RPV 25 mg	---	---	1.34[c] [1.1, 1.6} (58)	---
	30 mg tab (n=12)	Induction Phase +2 NRTIs	134 [110, 163] (32)	7.49 [6.3, 8.9] (28)	4.20[d] [3.8, 4.7] (40)	2.0 (1.0 – 8.0)
		Maintenance Phase +RPV 25 mg	---	---	3.93[e] [3.5, 4.4] (44)	---
	60 mg tab (2x30 mg) (n=9)	Induction Phase +2 NRTIs	195 [138, 277] (48)	11.5 [8.8, 15.0] (36)	7.93[f] [7.2, 8.8] (39)	2.0 (1.0 – 8.0)
		Maintenance Phase +RPV 25 mg	---	---	8.22[g] [7.4, 9.1] (37)	---
200056 LATTE-2 Day 1, predose	30 mg tab (n=246)	Induction Phase +2NRTIs	---	---	4.22 [4.0, 4.4} (43)]	---

median (range)
n=57
n=50
n=53
n=51
n=55
n=49

4.3.2. Long Acting Injectable Phase

Study 200056 (LATTE-2) is an ongoing, Phase 2b dose-ranging study evaluating the long-term efficacy and safety of a two-drug, two-class combination of CAB LA + RPV LA given every 4 weeks (Q4W) or every 8 weeks (Q8W), as compared to an oral three-drug regimen, for maintenance of virologic suppression in HIV-infected, treatment-naive adults. The first phase of the LATTE-2 study was a 20-week Oral Phase (16 weeks of oral CAB + 2 NRTIs, 4 weeks of CAB + 2 NRTIs + oral RPV) to induce suppression of HIV and assess for tolerability to CAB and RPV prior to receiving LA injections. Participants who were eligible to continue into the Injection Phase were then randomized (2:2:1) to receive IM CAB LA every 4 weeks (800 mg Day 1 then 400 mg Q4W) or every 8 weeks (800 mg Day 1, 600 mg Week 4, 600 mg Week 8, then 600 mg Q8W) in combination with IM RPV LA every 4 weeks (600 mg Day 1 then 600 mg Q4W) or every 8 weeks (900 mg Day 1, 900 mg Week 8, then 900 mg Q8W), respectively, or to continue on their oral triple ART regimen.

Both Q4W and Q8W regimens were continued throughout the Injection Phase as planned, and Week 96 results (Table 10) were supportive of further evaluation both the Q4W regimen in ATLAS and FLAIR as well as the Q8W regimen in the ATLAS-2M study. Subjects completing the 96-week Injection Phase remained on their randomized LA regimen (either Q4W or Q8W) during the Extension Phase (post Week 96), and those subjects randomized to the oral comparator arm were allowed transition to either LA regimen at Week 96. Forty-four subjects were transitioned from the oral comparator arm to LA treatments in the Extension Phase; 34 (77%) opted for the Q8W regimen and 10 (23%) for the Q4W regimen. Initial LA injections were administered at Week 100 following a 4-week oral lead-in where 2 NRTIs were discontinued and RPV 25 mg once daily was added to CAB 30 mg once daily.

At week 160, 90% of patients receiving intramuscular CAB + RPV every eight weeks and 83% of patients receiving the same regimen every four weeks remained virally suppressed. Of the patients that switched from the comparator regimen of oral CAB + abacavir(ABC)/lamivudine(3TC) to the intramuscular regimen following week 96, 98% remained suppressed through to week 160. (Margolis, 2018)

Approximately 86% of patients reported an injection site reaction (ISR), of which 85% were mild and 14% were moderate. 87% of ISRs resolved within 7 days. Excluding site ISRs, the most common adverse events (AEs) were nasopharyngitis (38%), diarrhea (22%), and headache (22%). 21% and 25% of patients dosed every 8 or 4 weeks, respectively, reported AEs grade 3 or above, of which 2% and 5% reported grade 3 drug-related AEs. 3% and 5% of patients had AEs leading to withdrawal or permeant discontinuation of the intramuscular CAB + RPV regimen. 15% and 18% of patients reported serious adverse events, and 1 patient had a serious adverse event that was reported as drug related.

Only two patients originally randomised to the LA dosing regimens had ISRs leading to discontinuation and none after week 24. Of the patients who switched to IM therapy following Week 96, 1/44 patients had an ISR leading to discontinuation. The overall ISR discontinuation rate was very low 3/274 (1%), and suggests good tolerability to CAB +

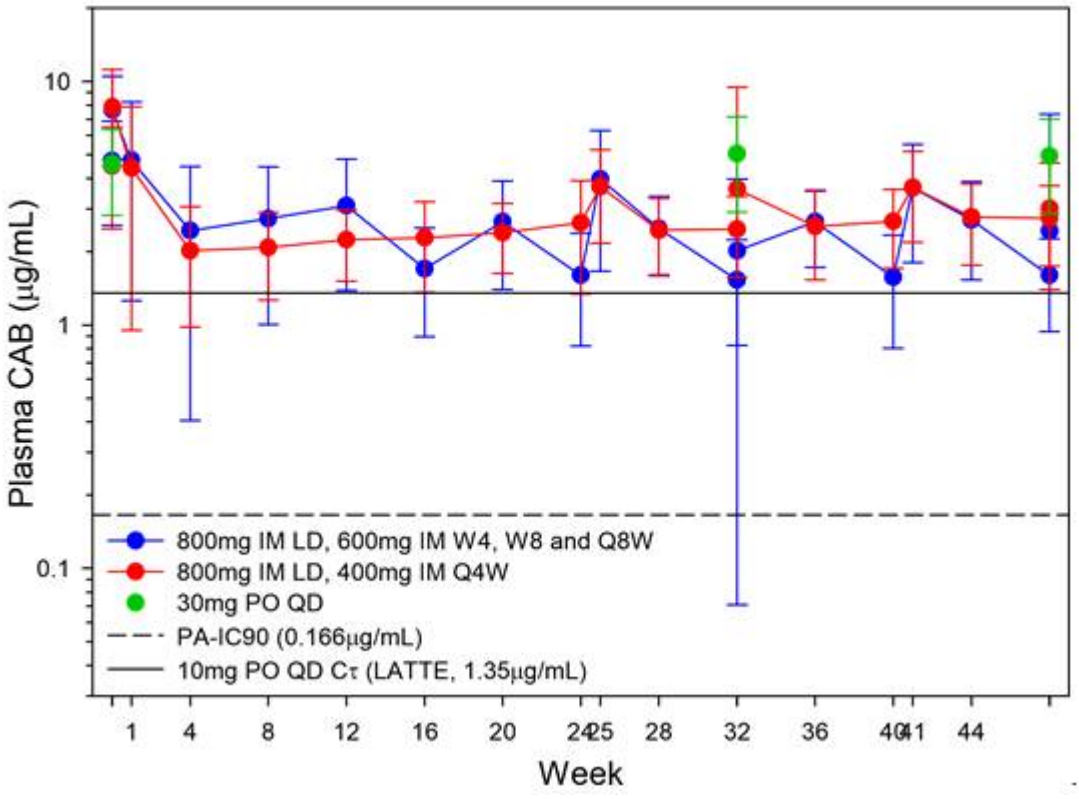
RPV injections for up to 3 years. No serious ISRs were reported and the majority were mild/moderate pain and discomfort with <1% of ISRs classified as severe (grade 3).

Table 10 Summary of Study Outcomes (<50 copies/mL) at Weeks 48 and 96 – Snapshot (MSDF) Analysis (ITT-ME Population) in LATTE-2

Endpoint (Week)	Outcome	Q8W IM N=115 n (%)	Q4W IM N=115 n (%)	CAB 30 mg+ ABC/3TC N=56 n (%)	Subtotal IM N=230 n (%)
W48	Virologic Success, n (%)	106 (92)	105 (91)	50 (89)	211 (92)
	Virologic Failure, n (%)	8 (7)	1 (<1)	1 (2)	9 (4)
W96	Virologic Success, n (%)	108 (94)	100 (87)	47 (84)	208 (90)
	Virologic Failure, n (%)	5 (4)	0	1 (2)	5 (2)

Observed pharmacokinetic data for both CAB LA regimens in LATTE-2 are presented in Figure 1 and summarized in Table 11.

Figure 1 Observed Mean (SD) Concentration-Time Data following CAB LA Q8W and Q4W and Cτ following 30 mg PO QD through Week 48 (200056, LATTE-2)



Both predose and 2h post injection concentrations are shown at Time Zero, Week 32, and Week 48.

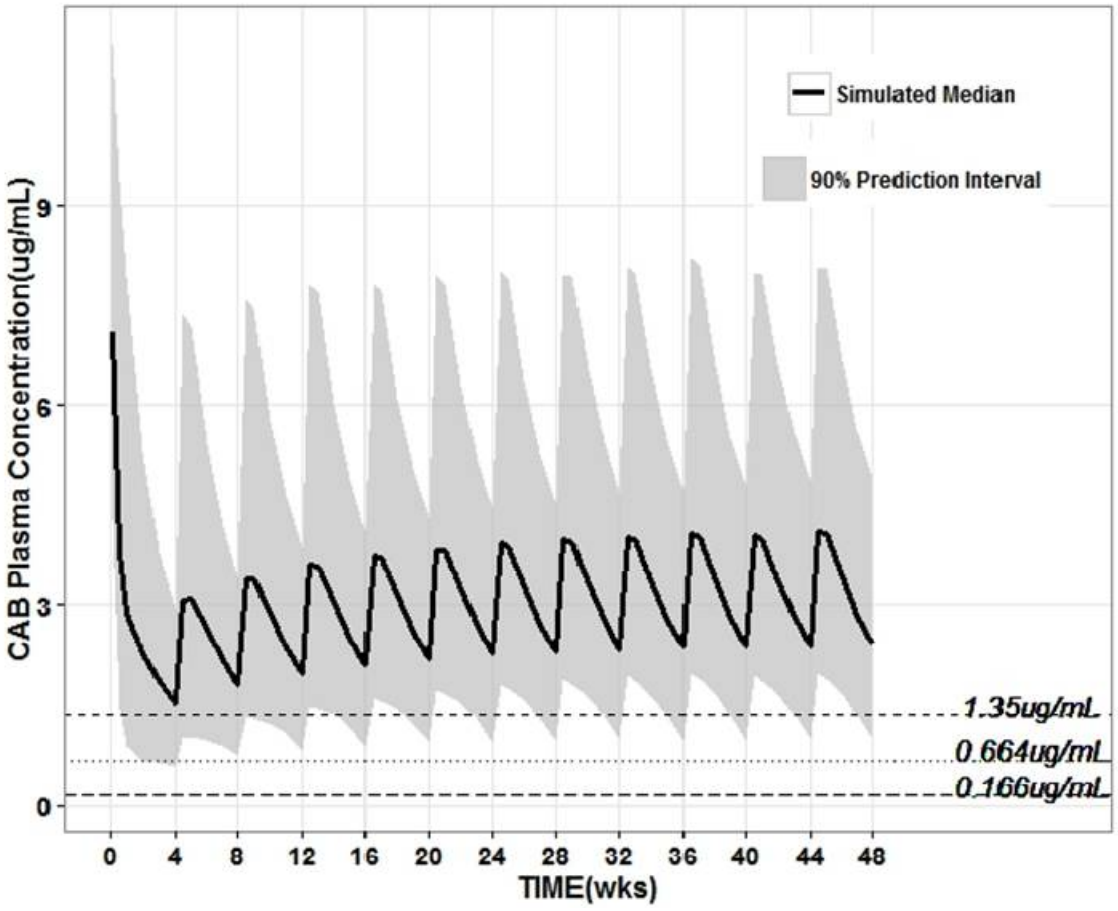
Table 11 Summary of CAB PK Parameters Following Repeat Dose Administration of CAB LA to Healthy and HIV-infected Subjects

Population	Study	CAB LA Regimen	Dosing Interval	Plasma CAB PK Parameter (Geometric mean [95%CI] (CVb%)			
				AUC(0- τ) (μg•h/mL)	Cmax (μg/mL)	Cτ (μg/mL)	Tmax[a] (day post last dose)
Healthy Subjects	LAI115428	800 mg IM/ 400 mg IM Q4W (n=10)	D1-W4	1252 [836, 1873] (61)	2.74 [1.72 4.35] (72)	1.78 [1.35, 2.36] (41)	6 (6 – 28)
			W4-W8	2010 [1619, 2494] (31)	3.79 [2.89, 4.99] (40)	2.60 [2.20, 3.07] (24)	6 (2 – 28)
			W8-W12	2182 [1798, 2647] (28)	4.03 [3.05, 5.30] (40)	2.69 [2.21, 3.27] (28)	6 (2 – 28)
			W12-W16	2473 [2063, 2965] (26)	4.41 [3.55, 5.48] (31)	3.27 [2.71, 3.94] (27)	6 (2 – 13)
HIV Infected Subjects	200056 LATTE2	800 mg IM/ 400 mg IM Q4W (n=115)	W24-W28 (n=97)	1858[b] [1719, 2007] (37)	3.50 [3.2, 3.8] (39)	2.35[c] [2.2, 2.5] (32)	6.9 (0 – 29)
			W40-W44 (n=95)	2017[d] [1847, 2203] (41)	3.50[e] [3.3, 3.8] (37)	2.56[f] [2.4, 2.7] (32)	6.9 (0 – 28)
		800 mg IM/ 600 mg IM Q8W (n=115)	W24-W32 (n=98)	3037[g] [2786, 3310] (42)	3.55 [3.2, 3.9] (56)	1.43[h] [1.3, 1.6] (54)	6.9 (0 – 59)
			W40-W48 (n=104)	3027[i] [2762, 3322] (47)	3.33 [3.1, 3.6] (47)	1.49 [1.4, 1.6] (42)	7.0 (0 – 57)

a. median (range)
b. n=84
c. n=108
d. n=80
e. n=98
f. n=86
g. n=100
h. n=93
i. n=112

The predicted CAB profile for the Q4W regimen based on population PK modelling is shown in Figure 2.

Figure 2 Simulated* Median (90% Prediction Interval [PI]) CAB Plasma Concentrations versus Time for the CAB LA Q4W Regimen (600 mg IM Day 1, then 400 mg IM Q4W thereafter)

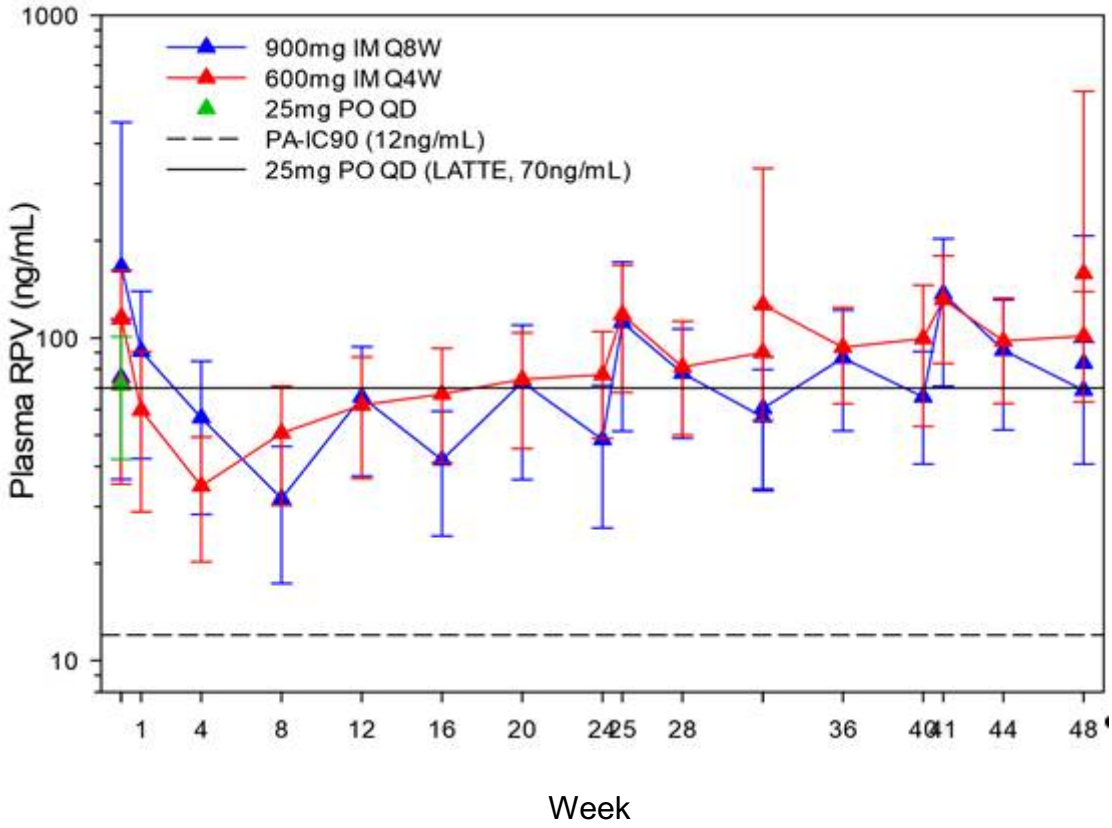


* Note: current simulations based on interim plasma concentration dataset
^Study schedule of activities include a 4 week oral lead in. Therefore, Day 1 = day of first injections (Week 4b study visit); Week 4 = second injections (Week 8 study visit)
Medium dashed line at 1.35 μg/mL corresponds to the geometric mean Ctrough concentration following oral CAB 10 mg once daily (LATTE) and is equivalent to 8x PA-IC90
Dotted line at 0.664 μg/mL corresponds to 4x PA-IC90

4.3.3. RPV LA Pharmacokinetics

Observed PK data for both RPV LA Q4W and Q8W regimens in LATTE-2 are presented in Figure 3 and Table 12. The RPV LA population PK model has been updated to include data from LATTE-2 and from Phase 1 studies in healthy volunteers.

Figure 3 Observed Mean (SD) Plasma Concentration-Time Data following RPV LA Q8W and Q4W through Week 48 and Day 1 Cτ following RPV 25 mg PO QD (LATTE-2)



Both predose and 2 hr post injection concentrations are shown at Time Zero, Week 32, and Week 48.

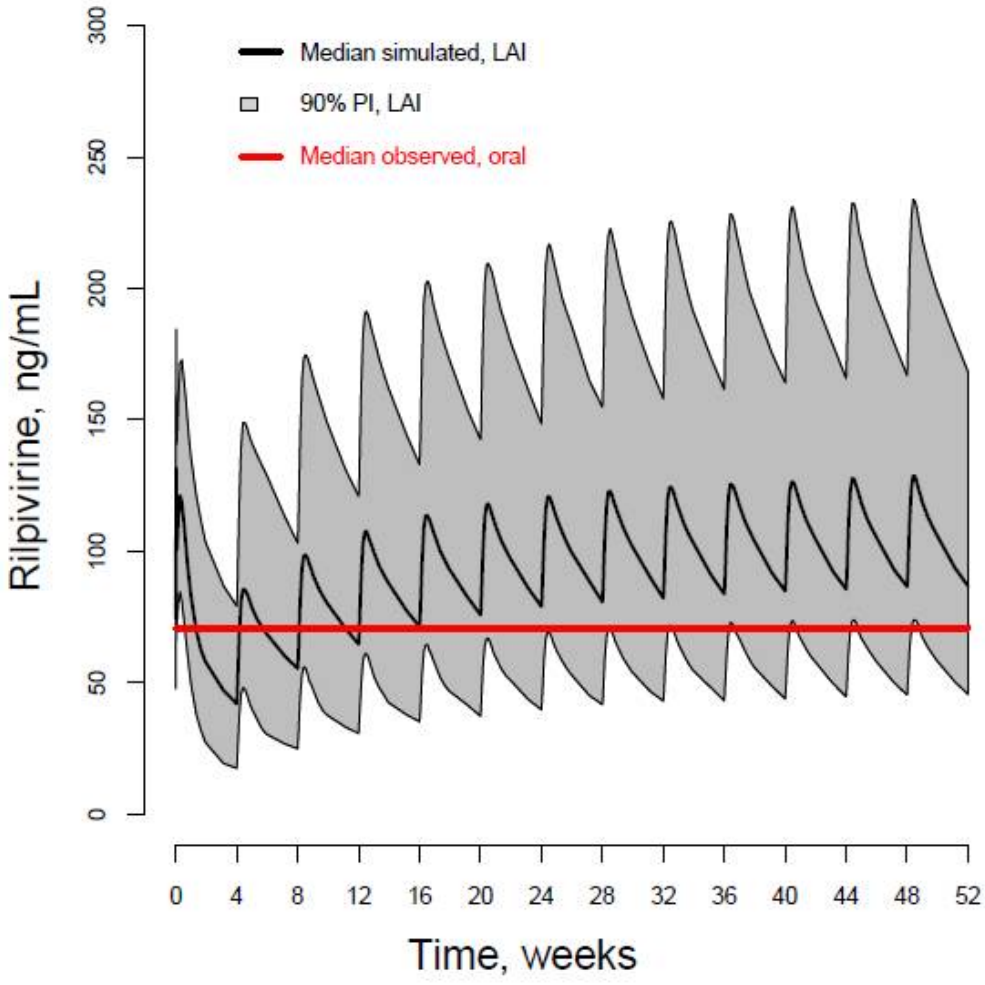
Table 12 Summary of RPV PK Parameters following Repeat Dose RPV LA Administration with CAB LA in Healthy and HIV-infected Subjects

Study/ Population	RPV LA Regimen	Dosing Interval (from 1st RPV IM dose)	Plasma RPV PK Parameter (Geometric mean [95%CI] (CVb%)				
			AUC(0-τ) (μg•h/mL)	Cmax (μg/mL)	Cτ (μg/mL)	Tmax[a] (day post last dose)	AUC(0-τ) (μg•h/mL)
LAI115428/ Healthy Subjects	1200 mg IM/ 900 mg IM (+ CAB LA 200 mg IM) (n=9)	D1-W4	52762 [36468, 76335] (51)		109 [74.2, 159] (53)	61.6 [39.3, 96.6] (64)	6 (1.8 – 20)
		W4-W8	74420 [57323, 96615] (35)		168 [128, 222] (37)	79.1 [57.2, 109] (44)	6 (2 – 13)
	1200 mg IM/ 600 mg IM (+ CAB LA 400 mg IM) (n=10)	D1-W4	52703 [42917, 64721] (29)		108 [87.6, 133] (30)	64.0 [50.6, 80.9] (34)	6 (2 – 28)
		W4-W8	63656 [50186, 80741] (34)		126 [101, 158] (32)	78.9 [60.3,103] (39)	9.5 (2 – 27)
200056 (LATTE2)/ HIV Infected Subjects	600 mg IM Q4W (n=115)	W24-W28 (n=96)	61309[b] [56724, 66264] (37)		111 [103, 120] (40)	77.2[c] [72, 83] (35)	6.0 (0 – 29)
		W40-W44 (n=94)	71106[d] [65354, 77366] (39)]		127 [118, 136] (36)	92.1[e] [87, 98] (32)	6.0 (0 – 28)
	900 mg IM Q8W (n=115)	W24-W32 (n=97)	96196[f] [87286, 106015] (48)		104 [95, 114] (47)	49.3[g] [46, 53] (41)	7.0 (0 – 57)
		W40-W48 (n=104)	116160[h] [108189, 124719] (35)		121 [111, 131] (42)	63.2[i] [59, 68] (35)	6.0 (0 – 59)

a. median (range)
b. n=84
c. n=104
d. n=80
e. n=102
f. n=86
g. n=101
h. n=92
i. n=100

The predicted RPV profile for the Q4W regimen based on population PK modelling is shown in Figure 4.

Figure 4 Simulated* Median (90% PI) RPV Plasma Concentrations versus Time Profile for the RPV LA Q4W regimen (900 mg IM Day 1, then 600 mg IM Q4W thereafter^)



* Note: current simulations based on interim plasma concentration dataset
^Study schedule of activities include a 4 week oral lead in. Therefore, Day 1 = day of first injections (Week 4b study visit); Week 4 = second injections (Week 8 study visit)
Horizontal line at 72 ng/mL corresponds to median $C\tau$ following oral RPV 25mg once daily in LATTE-2 (oral lead-in) and is similar to median RPV $C\tau$ in other studies in HIV-infected patients (LATTE, ECHO/THRIVE)

4.4. End of Study Definition

4.4.1. Study Completion

Patient Study Participants

The investigator is responsible for ensuring that consideration has been given to the post-study care of the patient study participant's medical condition.

Patient study participants are considered to have completed the study if they remain on therapy (i.e., have not permanently discontinued study intervention) and satisfy the following:

- Have completed all Month 12 evaluations
- remaining on study until commercial supplies of the CAB LA + RPV LA regimen becomes locally available, or initiates alternate antiretroviral therapy at the discretion of their HIV care provider, or
- development of CAB LA + RPV LA is terminated;

Upon completion of the above, patient study participants will exit the study and transition to commercial supplies of CAB LA + RPV LA, or alternate antiretroviral therapy at the discretion of their HIV HCP.

Until meeting the definition for study completion, participants will continue in the study until:

- the participant no longer derives clinical benefit,
- the participant meets a protocol-defined reason for discontinuation

Participants who withdraw from CAB LA + RPV LA and go into the LTFU Phase will be considered to have prematurely withdrawn from the study intervention.

Patient study participants will complete the 52-week Follow-Up phase required for participants who receive one or more injections with CAB LA or RPV LA. Assessments at the Follow-up visits should reflect any ongoing complaints (e.g., blood draws to follow a laboratory abnormality). Follow-Up visits are not required for successful completion of the study.

Study Staff Participants

Study Staff participants will have completed the study upon completion of all surveys and qualitative interviews after Month 12 evaluations have been completed at their site, per the Schedule of Activities (Section 1.5).

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the investigational regimen or other study intervention that may impact participant eligibility is provided in the current Investigator's Brochures (IB) for CAB (GlaxoSmithKline Document Number RH2009/00003/07 and Rilpivirine Clinical Investigator Brochure, 2018, and Edurant Prescribing Information, 2018.

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or participant safety. Therefore, adherence to the criteria as specified in the protocol is essential.

5.1. Inclusion Criteria

A participant will be eligible for inclusion in this study only if all of the following criteria apply:

- Be able to understand and comply with protocol requirements, instructions, and restrictions;
- Understand the long-term commitment to the study and be likely to complete the study as planned;
- Be considered appropriate candidates for participation in an investigative clinical trial with oral and intramuscularly injectable medications (e.g., no active substance use disorder, acute major organ disease, or planned long-term work assignments out of the country, etc.).

The following are study specific eligibility criteria unless stated otherwise. **In addition to these criteria, Investigators must exercise clinical discretion regarding selection of appropriate study participants, taking into consideration any local treatment practices or guidelines and good clinical practice (GCP). All participants must be considered appropriate candidates for antiretroviral therapy in accordance with local treatment guidelines**.

Laboratory results from the central laboratory services provided by this trial will be used to assess eligibility. In exceptional circumstances only, if a repeat lab is required because a central lab result cannot be generated, local lab results can be reviewed and approved by the Medical Monitor for consideration of participant eligibility. A repeat sample to the central lab will be submitted concurrently or at the next planned visit.

Source documentation to verify entry criteria must be reviewed by the Principal Investigator or designee prior to enrolment. Source documents from other medical facilities must be located/received during the 21-day screening phase and under no circumstances may the participant be enrolled in the absence of source documentation.

All Participants eligible for enrolment in the study must meet all of the following criteria:

AGE

1. Aged 18 years or older at the time of signing the informed consent.

TYPE OF PARTICIPANT AND DIAGNOSIS INCLUDING DISEASE SEVERITY

2. HIV-1 infected and must be on an active HAART (2 or 3 drug) regimen for at least 6 months prior to Screening. Any prior switch, defined as a change of a single drug or multiple drugs simultaneously, must have occurred due to tolerability/safety, access to medications, or convenience/simplification, and must NOT have been done for treatment failure (HIV-1 RNA ≥200 c/mL).

   Acceptable stable ARV regimens prior to Screening include 2 NRTIs plus:

- INI (either the initial or second cART regimen)
- NNRTI (either the initial or second cART regimen)
- Boosted PI (or atazanavir [ATV] unboosted) (must be either the initial cART regimen or one historical within class switch is permitted due to safety/tolerability)
- Any suppressed participants on a triple ART regimen for at least 6 months who had their regimen switched to a 2DR of DTG/RPV

3. Documented evidence of at least two plasma HIV-1 RNA measurements <50 c/mL in the 12 months prior to Screening: at least one within 6 months prior to Screening;
4. Plasma HIV-1 RNA <50 c/mL at Screening;

SEX

5. A female participant is eligible to participate if she is not pregnant (as confirmed by a negative urine human chorionic gonadotrophin (hCG) test at screen and at Day 1), not lactating, and at least one of the following conditions applies:

a. Non-reproductive potential defined as:

- Pre-menopausal females with one of the following:
  - Documented tubal ligation
  - Documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion
  - Hysterectomy

• Documented Bilateral Oophorectomy • Postmenopausal defined as 12 months of spontaneous amenorrhea [in questionable cases a blood sample with simultaneous follicle stimulating hormone (FSH) and estradiol levels consistent with menopause (refer to laboratory reference ranges for confirmatory levels)]. Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrolment. b. Reproductive potential and agrees to follow one of the options listed in the Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) (Section 10.7, Appendix 7) from 30 days prior to the first dose of study medication, throughout the study, and for at least 30 days after discontinuation of all oral study medications and for at least 52 weeks after discontinuation of CAB LA and RPV LA. The investigator is responsible for ensuring that participants understand how to properly use these methods of contraception.
INFORMED CONSENT
Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the consent form and in this protocol. Eligible participants or their legal guardians (and next of kin when locally required), must sign a written Informed Consent Form before any protocol-specified assessments are conducted. Enrolment of participants who are unable to provide direct informed consent is optional and will be based on local legal/regulatory requirements and site feasibility to conduct protocol procedures.

ALL participants in the study should be counseled on safer sexual practices including the use and benefit/risk of effective barrier methods (e.g., male condom) and on the risk of HIV transmission to an uninfected partner.

5.2. Exclusion Criteria

Deviations from exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, or participant safety. Therefore, adherence to the criteria as specified in the protocol is essential.

A participant will not be eligible for inclusion in this study if any of the following criteria apply:

HIV-1 RNA

1. Within 6 months prior to Screening, plasma HIV-1 RNA measurement ≥50 c/mL;
2. During the previous 12 months, any confirmed HIV-1 RNA measurement ≥200 c/mL

Exclusionary medical conditions

3. Women who are pregnant, breastfeeding, or plan to become pregnant or breastfeed during the study.
4. Any evidence of a current Center for Disease Control and Prevention (CDC) Stage 3 disease [CDC, 2014], except cutaneous Kaposi's sarcoma not requiring systemic therapy, and CD4+ counts <200 cells/μL are not exclusionary..
5. Any pre-existing physical or mental condition (including substance use disorder) which, in the opinion of the Investigator, may interfere with the participant's ability to comply with the dosing schedule and/or protocol evaluations or which may compromise the safety of the participant.
6. Participants determined by the Investigator to have a high risk of seizures, including participants with an unstable or poorly controlled seizure disorder. A participant with a prior history of seizure may be considered for enrolment if the Investigator believes the risk of seizure recurrence is low.
7. Participants who, in the investigator's judgment, pose a significant suicide risk. Participant's recent history of suicidal behavior and/or suicidal ideation should be considered when evaluating for suicide risk
8. The participant has a tattoo or other dermatological condition overlying the gluteus region which may interfere with interpretation of injection site reactions
9. Evidence of Hepatitis B virus (HBV) infection based on the results of testing for Hepatitis B surface antigen (HBsAg), Hepatitis B core antibody (anti-HBc), Hepatitis B surface antibody (anti-HBs) and HBV DNA as follows:
    a. •Participants positive for HBsAg are excluded;
    b. •Participants negative for anti-HBs but positive for anti-HBc (negative HBsAg status) and positive for HBV DNA are excluded

Note: Participants positive for anti-HBc (negative HBsAg status) and positive for anti-HBs (past and/or current evidence) are immune to HBV and are not excluded.

10. Participants who are anticipated to require HCV treatment within 12 months must

be excluded. Asymptomatic individuals with chronic hepatitis C virus (HCV) infection will not be excluded; investigators must carefully assess if therapy specific for HCV infection is required. (HCV treatment on study may be permitted, following consultation and approval of the DAA based therapy being considered with the medical monitor)

11. Participants with HCV co-infection will be allowed entry into this study if:
    a. Liver enzymes meet entry criteria
    b. HCV Disease has undergone appropriate work-up, and is not advanced. Additional information (where available) on participants with HCV co-infection at screening should include results from any liver biopsy, Fibroscan, ultrasound, or other fibrosis evaluation, history of cirrhosis or other decompensated liver disease, prior treatment, and timing/plan for HCV treatment.
    c. In the event that recent biopsy or imaging data is not available or inconclusive, the Fib-4 score will be used to verify eligibility
        i. Fib-4 score >3.25 is exclusionary
        ii. Fib-4 scores 1.45 – 3.25 requires Medical Monitor consultation

        Fibrosis 4 Score Formula:

        (Age x AST) / (Platelets x (sqr [ALT])

12. Unstable liver disease (as defined by any of the following: presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, or persistent jaundice or cirrhosis), known biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones or otherwise stable chronic liver disease per investigator assessment)
13. History of liver cirrhosis with or without hepatitis viral co-infection.
14. Ongoing or clinically relevant pancreatitis
15. Clinically significant cardiovascular disease, as defined by history/evidence of congestive heart failure, symptomatic arrhythmia, angina/ischemia, coronary artery bypass grafting (CABG) surgery or percutaneous transluminal coronary angioplasty (PTCA) or any clinically significant cardiac disease
16. Ongoing malignancy other than cutaneous Kaposi's sarcoma, basal cell carcinoma, or resected, non-invasive cutaneous squamous cell carcinoma, or cervical intraepithelial neoplasia; other localized malignancies require agreement between the investigator and the Study medical monitor for inclusion of the participant prior to inclusion
17. Any condition which, in the opinion of the Investigator, may interfere with the absorption, distribution, metabolism or excretion of the study drugs or render the participant unable to receive study medication
18. History or presence of allergy or intolerance to the study drugs or their components or drugs of their class.

19. Current or anticipated need for chronic anti-coagulation with the exception of the use of low dose acetylsalicylic acid (≤325 mg per day) or hereditary coagulation and platelet disorders such as haemophilia or Von Willebrand Disease. 20. Corrected QT interval (QTc (Bazett)) >450 msec *or* QTc (Bazett) >480 msec for subjects with bundle branch block).
Exclusionary Laboratory Values or Clinical Assessments (a single repeat to determine eligibility is allowed)
21. Any evidence of primary resistance based on the presence of any major known INI or NNRTI resistance-associated mutation, except for K103N, (International AIDS Society [IAS]-USA) by any historical resistance test result (Wensing, 2017) 22. Alanine aminotransferase (ALT) ≥5 × ULN *or* ALT ≥3xULN and bilirubin ≥1.5xULN (with >35% direct bilirubin) over the last 6 months 23. Any verified Grade 4 laboratory abnormality. A single repeat test is allowed during the Screening phase to verify a result 24. Participant has estimated creatinine clearance <50 mL/min/1.73m^2 via the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Levey, 2009).
Concomitant Medications
25. Exposure to an experimental drug or experimental vaccine within either 28 days, 5 half-lives of the test agent, or twice the duration of the biological effect of the test agent, whichever is longer, prior to Day 1 of this study; 26. Treatment with any of the following agents within 28 days of Day 1: • radiation therapy; • cytotoxic chemotherapeutic agents; • tuberculosis therapy with the exception of isoniazid (isonicotinylhydrazid [INH]); • anti-coagulation agents; • Immunomodulators that alter immune responses such as chronic systemic corticosteroids, interleukins, or interferons. Note: Participants using short-term (e.g. ≤21 days) systemic corticosteroid treatment; topical, inhaled and intranasal corticosteroids are eligible for enrolment. 27. Treatment with an HIV-1 immunotherapeutic vaccine within 90 days of Screening. 28. Use of medications which are associated with Torsade de Pointes must be discussed with the Medical Monitor to determine eligibility. (See SPM for a list of relevant medications) 29. Participants receiving any prohibited medication and who are unwilling or unable to switch to an alternate medication. Note: Any prohibited medications that decrease CAB or RPV concentrations should be discontinued for a minimum of four weeks or a minimum of three half-lives (whichever is longer) prior to the

first dose and any other prohibited medications should be discontinued for a minimum of two weeks or a minimum of three half-lives (whichever is longer) prior to the first dose

5.2.1. Additional Eligibility Criteria

To assess any potential impact on participant eligibility with regard to safety, the investigator must refer to the IB and supplements, approved product labels, and/or local prescribing information for detailed information regarding warnings, precautions, contraindications, AEs, drug interactions, and other significant data pertaining to the study drugs.

Note: Patient study participants with ≥ Grade 1 LFTs at screening and or day 1 must be discussed with the Medical Monitor prior to initiation of LA dosing; continuation in the study or progression onto LA dosing may require additional evaluations, including labs drawn after a period of oral dosing with CAB + RPV.

5.3. Lifestyle Considerations

No restrictions are required.

5.4. Screen Failures

Screen failures are defined as patient study participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse events (SAEs).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened one time within 4 weeks of the original screening; informed consent will need to be reviewed and re-signed for each rescreen. Subjects will be issued a new subject number for every screening/re-screening event.

Staff study participants will not be captured for screen failure reporting.

6. STUDY INTERVENTION

6.1. Study Intervention(s) Administered

The term ‘study intervention’ is used throughout the protocol to describe any combination of products received by the participant as per the protocol design. **Study intervention is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol**. Study intervention may therefore refer to the individual study interventions or the combination of those study interventions.

Investigational product (IP) in this protocol refers to the investigational study drugs Oral Cabotegravir, Cabotegravir LA, Oral Rilpivirine and Rilpivirine LA. These will be supplied by GlaxoSmithKline/ViiV Healthcare and Janssen Pharmaceuticals, respectively.

Participants entering the Long-Term Follow-Up Phase will not have their selected HAART provided as clinical trial material. The selected HAART will be recorded on the Concomitant Antiretroviral Therapy (ConART) eCRF page.

Dosing and Administration

Day 1 to End of Study+	
CAB + RPV LA Oral Lead-In	
Day 1 to Month 1 (two once daily tablets taken with food)	• Take one tablet of CAB 30 mg + RPV 25 mg once daily
CAB + RPV LA	
First Injections (Loading Doses) – Month 1	
Month 1	• Receive last dose of oral CAB + RPV regimen • Receive CAB LA 600 mg given as 1 X **3 mL** IM injection • Receive RPV LA 900 mg given as 1 X **3 mL** IM injection
Maintenance Injections – every one month following Loading Dose at Month 1	
Month 2 to End of Study+ (two 2 mL injections every month)	• Receive CAB LA 400 mg given as 1 X **2** mL IM injection • Receive RPV LA 600 mg given as 1 X **2** mL IM injection
+Until locally approved and commercially available, the participant no longer derives clinical benefit, the participant meets a protocol-defined reason for discontinuation or until development of CAB LA or RPV LA is terminated	

6.1.1. Formulations of CAB + RPV

6.1.1.1. Cabotegravir Tablets (CAB)

CAB is manufactured by GlaxoSmithKline and is formulated as white to almost white oval shaped film coated 30 mg tablets for oral administration, packaged in high density polyethylene (HDPE) bottles with desiccant and child-resistant closure that include an induction seal. CAB tablets will be packaged in bottles of 30 tablets. Participants must keep all IP in its original pack container. GSK will notify sites if and when data are

available to support the use of pill boxes. The recommended storage conditions, and expiry date where required, are stated on the product label.

CAB Tablet is composed of cabotegravir sodium, lactose monohydrate, microcrystalline cellulose, hypromellose, sodium starch glycolate, magnesium stearate, and white film-coating. The white film-coating contains hypromellose, titanium dioxide and polyethylene glycol.

6.1.1.2. Rilpivirine Tablets (RPV)

RPV is provided by Janssen Research & Development, LLC, a division of Janssen Pharmaceuticals, as 25 mg tablets that are off-white, round, biconvex, film-coated and debossed on one side with “TMC” and the other side with “25”. RPV is manufactured by Janssen-Cilag S.p.A, Latina, Italy. RPV will be provided as a globally marketed product which includes approvals in the US and the European Union. RPV will be overlabeled and packaged in bottles of 30 tablets. The recommended storage conditions, and expiry date where required, are stated on the product label.

Each tablet contains 27.5 mg of rilpivirine hydrochloride, which is equivalent to 25 mg of RPV. Each tablet also contains the inactive ingredients croscarmellose sodium, lactose monohydrate, magnesium stearate, polysorbate 20, povidone K30 and silicified microcrystalline cellulose. The tablet coating contains hypromellose 2910 6 mPa.s, lactose monohydrate, PEG 3000, titanium dioxide and triacetin.

6.1.1.3. Cabotegravir Injectable Suspension (CAB LA)

CAB LA (GSK1265744 LA) is manufactured by GlaxoSmithKline and is a sterile white to slightly pink suspension containing 200 mg/mL of GSK1265744 as free acid for administration by intramuscular (IM) injection. The product is packaged in a glass vial with a 13 mm stopper and aluminum seal. Each vial is for single-dose use containing a withdrawable volume of 2.0 mL (400 mg) or 3.0 mL (600 mg) and does not require dilution prior to administration. The recommended storage conditions, and expiry date where required, are stated on the product label.

CAB LA is composed of cabotegravir free acid, polysorbate 20, polyethylene glycol 3350, mannitol, and water for injection.

6.1.1.4. Rilpivirine Injectable Suspension (RPV LA)

RPV LA (also named JNJ-16150108-AAA), 300 mg/mL Extended Release Suspension for Injection (G001), is provided by Janssen Research & Development, LLC, a division of Janssen Pharmaceuticals, as a sterile white suspension containing 300 mg/mL of RPV as the free base. The route of administration is by intramuscular (IM) injection. RPV LA is packaged in a single use 4 mL glass vial with a 13 mm stopper and aluminum seal. Each vial contains a nominal fill of 2.0 mL (600 mg) or 3.0 mL (900 mg), and does not require dilution prior to administration. The recommended storage conditions, and expiry date where required, are stated on the product label.

RPV LA is composed of RPV free base, poloxamer 338, sodium dihydrogen phosphate monohydrate, citric acid monohydrate, glucose monohydrate, sodium hydroxide, water for injection.

6.1.1.5. CAB + RPV LA Packs

CAB + RPV LA will be packaged in a pharmacy pack. In addition to the CAB + RPV LA vials, the pharmacy pack will contain:

- Vial adapters, used to draw IP out of the vials into the injection syringes
- Syringes
- Needles (23ga, 1.5 inch)
- Printed instructions for use

The CAB + RPV LA packs will be available with both vials including a 3mL fill of CAB LA and RPV LA (for Loading dose use) and vials including a 2mL fill, for use during Maintenance dosing.

6.2. Preparation/Handling/Storage/Accountability

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
- Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
- In accordance with local regulatory requirements, the investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation and final disposition records). The amount of IP dispensed and/or administered to study participants, the amount returned by study participants, and the amount received from and returned to GSK must be documented.
- Further guidance and information for the final disposition of unused study intervention are provided in the Study Reference Manual.
- Under normal conditions of handling and administration, study intervention is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.
- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

- Product accountability records must be maintained throughout the course of the study.

IP accountability will be evaluated using pill counts of unused IP for participants receiving oral treatment (oral CAB and oral RPV). This assessment will be conducted each time the participant receives a new (refill) supply of IP through the withdrawal or study completion.

IP accountability for participants receiving CAB LA + RPV LA will be performed at the 'vial' level (e.g., correct number of vials were used for each injection). There may be a small amount of solution remaining in the vial which does not require quantification. Used vials may be discarded at the site once accountability is complete.

Please refer to Section 10.12, Appendix 12 in for study management information during the COVID-19 pandemic.

6.2.1. Dosing Considerations for CAB LA + RPV LA

Vials of CAB LA and RPV LA are each supplied as a suspension and need no further dilution or reconstitution. Since RPV LA requires refrigeration, sites should allow the vial(s) to come to approximately room temperature prior to injecting. The vials should be gently inverted a few times to re-suspend sediments and allow bubbles to subside, and then use a syringe or provided vial adapter to withdraw the required volume of suspension for IM injection.

All injections must be given intramuscularly in the gluteus medius. Sites may use their discretion as to where in the gluteus muscle each injection is given according to individual participant circumstance. If possible, injections should be spaced approximately 2 cm from one another, from the site of any previous injection or any injection site reaction. The time and location of injection will be captured in the eCRF.

Intermuscular injections should be administered at a 90-degree angle into the gluteus medius muscle using a needle of appropriate gauge and length (In most participants, a 1.5" 23 gauge needle for CAB LA and a 1.5" 23 gauge needle for RPV LA is recommended). The needle should be long enough to reach the muscle mass and prevent study drug from seeping into subcutaneous tissue, but not so long as to involve underlying nerves, blood vessels, or bone. Variable needle lengths and/or needles with different gauge (CAB LA: 21 to 25 gauge; RPV LA: 21 to 23 gauge) are permitted if needed to accommodate individual body types. Longer needle lengths may be required for participants with higher body mass indexes (BMIs, example > 30), to ensure that injections are administered intramuscularly as opposed to subcutaneously. BMI, needle gauge and length used will be collected in the eCRF. Additional details of the injection device used by sites for IM administration including, but not limited to functional performance, may also be collected within the eCRF.

At the Day 1 visit, participants transitioning from oral CAB + RPV should be dosed with the IM regimen within 2 hours of taking the last oral regimen dose where possible.

Should IM maladministration be suspected at any time (e.g., suspected under or overdose or inadvertent IV dosing), the investigator may consider requesting the participant stay

onsite for approximately 2-3 hours post dose for safety monitoring and notifying the Medical Monitor. An ECG or any other supportive testing may be obtained at the discretion of the investigator. Additionally, a PK sample may be drawn approximately 2 hours post dosing for future evaluation of CAB and RPV plasma concentrations.

Additional dosing instructions and considerations can be found in the SPM.

6.3. Measures to Minimize Bias: Randomization and Blinding

This will be an open-label, single-arm study and therefore no blinding will be performed.

6.4. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the participant's eCRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

When participants self-administer oral study interventions at home, compliance with CAB + RPV dosing will be assessed through querying the participant during the site visits and documented in the source documents and CRF. IP accountability will be evaluated using pill counts of unused IP (CAB + RPV tablets). This assessment will be conducted each time the participant receives a new (refill) supply of oral study medication or any oral bridging phase. A record of the number of CAB + RPV tablets dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Treatment start and stop dates will also be recorded in the eCRF.

Due to the long acting nature of the CAB LA and RPV LA it will be imperative that the participant is compliant with dosing instructions. As part of the screening and participant selection process, it is imperative that Investigators discuss with potential participants the long-term commitments for the trial, and the importance of adhering to treatment regimens. Sites are to have plans in place for adherence counselling for both treatment arms of the study for the duration of the study including the LTFU Phase. In addition, Investigators must have plans in place to verify the participant's contact information at each visit. Investigators should contact participants directly in the event that a participant misses any scheduled visit.

6.5. Concomitant Therapy

Participants must be advised to notify their Investigator of any current or proposed concomitant medication, whether prescribed or over-the-counter, because of the potential for interactions between such treatments and the study medications. Concomitant medications (prescription and non-prescription) will be permitted during the course of the study at the investigator's discretion (except for prohibited medications described in Section 6.5.2 and should be administered only as medically necessary during the study. All concomitant medication, blood products, and vaccines taken during the study will be

recorded in the eCRF. The minimum requirement is that the drug name, route, and the dates of administration are to be recorded.

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- reason for use
- dates of administration including start and end dates
- dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1. Permitted Medications and Non-Drug Therapies

Chemoprophylaxis for HIV-associated conditions is encouraged, if appropriate, at the discretion of the participant and their physician. All concomitant medications, blood products, and vaccines taken during the study will be recorded in the eCRF with dates of administration.

Because non-HIV vaccines may cause a temporary increase in the level of plasma HIV-1 RNA, it is recommended that a vaccine, if necessary, be given during or immediately after a scheduled visit after all laboratory tests have been drawn. This approach will minimize the risk of non-specific increases in the level of plasma HIV-1 RNA at the next scheduled assessment.

Other IM injectables (with exceptions below) are permitted but must be administered away from the site of IP administration (should be spaced 2 cm or more away from site of IP injection).

Antacid and H2 Antagonist Use:

The most restrictive dosing requirements must be taken into consideration to account for the co-administration of oral CAB and RPV. The marketed approved recommendation for administration of antacids and H2 antagonists with the FDC of DTG + RPV incorporates the most restrictive dosing requirements and should be used when antacids and H2 antagonists are co-administered with oral CAB + RPV.

CAB oral administration only: Antacid products containing divalent cations (e.g., aluminium, calcium and magnesium) must be taken at least 2 hours before or at least 4 hours after CAB.

Concurrent administration of multivitamins is acceptable.

RPV oral administration only: Antacid products must be taken at least 2 hours before or at least 4 hours after RPV. H2-Receptor antagonists (e.g. cimetidine, famotidine, nizatidine, ranitidine) may cause significant decreases in RPV plasma concentrations. H2-receptor antagonists should only be administered at least 12 hours before or at least

4 hours after RPV. RPV should not be co-administered with proton pump inhibitors, such as esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole.

RPV: Administration of clarithromycin, erythromycin and telithromycin is not recommended with RPV due to possible increase in plasma concentration of RPV due to CYP3A enzyme inhibition. Where possible, alternatives such as azithromycin should be considered. Please refer to the local rilpivirine prescribing information for guidance regarding other drugs that are prohibited, should be used with caution, require dose adjustment, or increased clinical monitoring if taken with rilpivirine.

Drugs with a known risk of Torsade des Pointes (TdP) should be used with caution when on rilpivirine (see SPM for list of drugs associated with TdP).

6.5.2. Prohibited Medications and Non-Drug Therapies

The following concomitant medications or therapies are not permitted at any time during the study:

- HIV immunotherapeutic vaccines are not permitted at any time during the study.
- Other experimental agents, antiretroviral drugs not otherwise specified in the protocol, cytotoxic chemotherapy, or radiation therapy may not be administered (see Exclusion Criteria, Section 5.2).
- Systemically administered immunomodulators (such as interleukin and interferon agents) are prohibited (a list of examples is provided in the SPM). This includes topical agents with substantial systemic exposure and systemic effects. Use of topical imiquimod is permitted.
- Acetaminophen (paracetamol) cannot be used in participants with acute viral hepatitis (James, 2009).
- Chronic use of systemic (oral or parenteral) glucocorticoids must be avoided due to their immunosuppressive effect; however, short treatment courses with oral prednisone/ prednisolone/methylprednisolone (e.g. adjunctive treatment of Pneumocystis pneumonia with ≤ 21 days of tapering prednisone) are allowed. A single dose of systemic dexamethasone is permitted (more than a single dose in a treatment course may cause significant decrease in RPV plasma concentration and is prohibited). Topical, inhaled or intranasal use of glucocorticoids will be allowed.
- Direct acting antivirals (DAA) against Hepatitis C infection is allowed, provided there are no DDIs associated the DAA being considered for treatment.
- Interferon-based HCV therapy is prohibited throughout the entire study, partly because as an immunomodulator, Interferon is a prohibited medication.

For information on concurrent therapies and interactions suspected to be relevant to other antiretroviral therapy in the regimen, please consult the local prescribing information.

6.5.2.1. Concurrent with CAB and/or RPV

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

- Carbamazepine
- Oxcarbazepine
- Phenobarbital
- Phenytoin
- Rifabutin
- Rifampicin / Rifampin
- Rifapentine
- St. John's wort (*Hypericum perforatum*)

6.5.2.2. Concurrent with oral RPV

In addition to the medications listed in Section 6.5.2, participants must discontinue the following (or change to an allowable alternative) while receiving treatment with oral RPV:

- proton pump inhibitors, such as esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole;
- systemic dexamethasone (more than a single dose)

If the participant cannot discontinue use or change to an allowable alternative while receiving treatment with RPV, the participant should not be randomized into the study.

6.5.2.3. Concurrent with either CAB LA or RPV LA

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

Note: Any prohibited medications that decrease cabotegravir or rilpivirine concentrations should be discontinued for a minimum of four weeks or a minimum of three half-lives (whichever is longer) prior to the first dose and any other prohibited medications should be discontinued for a minimum of two weeks or a minimum of three half-lives (whichever is longer) prior to the first dose.

6.5.2.4. Prohibited Medications for Participants Receiving HAART during the Long-Term Follow-Up Phase

For participants taking HAART during the Long-Term Follow-Up Phase, refer to local prescribing information for details regarding concurrent therapies.

6.6. Dose Modification

No dose reductions, modifications, or changes in the frequency of any components of each regimen will be allowed during the study beyond what is allowed within the protocol or directly approved by the study Medical Monitor. Protocol waivers or exemptions are not allowed. Therefore, adherence to the study design requirements is essential and required for study conduct.

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying Study Procedures Manual (SPM). The SPM will provide the site personnel with administrative and detailed technical information.

6.6.1. Protocol Permitted Substitutions

6.6.1.1. Oral Bridging

In exceptional circumstances, to address pre-planned missed CAB LA + RPV LA dosing visits, in consultation with the medical monitor, Investigators may provide daily oral CAB 30 mg and RPV 25 mg as a short-term (≤3 months) "bridging" strategy for participants who have begun CAB LA + RPV LA. In certain circumstances (e.g., prior to steady state dosing and following a >8 weeks since last injection) repeating the loading doses of CAB IM and RPV IM may be required. Should a participant require "oral bridging", sites must contact the study Medical Monitor for guidance with treatment and dosing strategies prior to a missed CAB LA + RPV LA dose.

Please refer to Section 10.12, Appendix 12 in for study management information during the COVID-19 pandemic.

6.6.2. IM Dosing

Participants receiving CAB LA and/or RPV LA are anticipated to be at risk for development of virologic resistance if ART is interrupted. The time period during which participants are at risk for development of virologic resistance may be determined by the period between when drug levels fall below therapeutic values and when they fall below levels which exert selective pressure on HIV. This time period will vary by ART agent and is dependent upon effective concentration, inhibitory concentration, and half-life. Plasma concentrations of both LA drugs may be measurable for more than one year following IM injections. Any interruption in IM dosing should be discussed with the Medical Monitor. Investigators should ensure that the participant initiates alternative highly active ART to minimize the risk of developing resistance as concentrations of CAB and RPV decline over time.

IM dosing is expected to occur during the week in which the participant's projected visit falls (as according to the date of the first injection).

Since the first injection visit (Month 1) will determine the future injection visit schedule for participants, planning for the first injection visit date (within allowed visit windows) should take into consideration the availability of the participants to adhere to future visit windows (planned vacations, business trips, *etc*.).

CAB LA + RPV LA dosing for participants transitioning from oral CAB + RPV is as follows:

All injections should be planned as single injections per drug.

6.6.2.1. IM injections every 1 month:

On Day 1, participants will return to the clinic, take the last dose of their oral (CAB 30 mg + RPV 25 mg), and receive the first CAB LA (600 mg) + RPV LA (900 mg) injections (within 2 hours of the final oral dose of CAB + RPV).

The second injection will be administered at Month 2 (CAB LA 400 mg + RPV LA 600 mg, with all subsequent injections (CAB LA 400 mg + RPV LA 600 mg) occurring every 1 month thereafter. The dosing window for the second and third injections allow administration between -7 days of the proposed injection visit date but preferably not later than the target date (-7 days/ +0 days around the proposed visit date). Beginning on Month 4, a dosing window (±7 days) for injections is stipulated. The Medical Monitor must be contacted to discuss individual participant case management if a dose must be administered outside of the window.

6.6.3. Oral Dosing

Any interruption in therapy (scheduling conflicts, life circumstances, *etc*.) during any oral dosing period that is greater than 7 consecutive days must be discussed with the Medical Monitor prior to resumption of therapy. The Medical Monitor must be contacted upon site staff becoming aware of resumption in therapy, if therapy was resumed without prior approval.

Visits for participants in LTFU are expected to occur as projected according to the last injection.

6.7. Intervention after the End of the Study

The investigator is responsible for ensuring that consideration has been given to the post-study care of the participant's medical condition, whether or not GSK is providing specific post-study intervention. Participants who have successfully completed IM dosing for 12 months will continue to have access to both CAB LA and RPV LA until study intervention is either locally approved and commercially available, the participant no longer derives clinical benefit, the participant meets a protocol-defined reason for discontinuation or until development of either CAB LA or RPV LA is terminated.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Participants permanently discontinuing study treatments prior to the Month 12 visit are considered to be withdrawn from the study treatments. Participants permanently discontinuing study treatments prior to the commercial availability of CAB LA + RPV LA visit are not considered to be withdrawn from the study because they will enter the long-term Follow-up Phase.

A participant may withdraw consent and discontinue participation in this study at any time at his/her own request. The investigator may also, at his or her discretion, discontinue the participant from participating in this study at any time (e.g., safety, behavioral or administrative reasons). If a participant withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records. Withdrawn participants will not be replaced.

All participants who discontinue prematurely from the study will be asked for additional information to establish the reason for withdrawal.

Participants are not obligated to state the reason for withdrawal. However, the reasons for withdrawal, or failure to provide a reason, must be documented by the Investigator on the Completion/Withdrawal section of the electronic case report form (eCRF). Every effort should be made by the Investigator to follow-up participants who withdraw from the study.

Participants may have a temporary interruption to their study intervention for management of toxicities.

Participants <u>may</u> be prematurely discontinued from the study intervention for any of the following reasons:

- Adverse event / Serious adverse event
- Protocol deviation
- Intolerability of injections
- Participant lost to follow-up
- Participant or Investigator non-compliance;
- Termination of the study by the Sponsor
- At the request of the participant, Investigator, GSK or ViiV Healthcare;
- The participant requires concurrent prohibited medications during the course of the study. The participant may remain in the study if in the opinion of the Investigator and the medical monitor; such medication will not interfere with the conduct or interpretation of the study or compromise the safety of the participant.

Participants <u>must</u> be discontinued from study intervention for any of the following reasons:

- Virologic withdrawal criteria as specified in Section 7.1.3 are met;
- Participant requires substitution of ART;
- Participant requires substitution or dose reduction of CAB LA, RPV LA (oral bridging supply and potential for a second loading dose may be permissible following discussion with the Medical Monitor)
- Liver toxicity where stopping criteria are met and no compelling alternate cause is identified (see Section 10.6.2);

- Renal toxicity is met and no compelling alternate cause is identified;
- Corrected QT interval (QTc) >550 msec from three or more tracings separated by at least 5 minutes and considered causally related to IP. *Note: ECGs are not routinely conducted in this study*.
- Grade 4 clinical AE considered causally related to study drug;
- Participant has a Grade 3 or higher rash or Grade 2 rash with evidence of systemic involvement and no compelling alternative cause is identified.
- Participant withdrew consent

Safety data for all participants who receive any amount of study drug, including participants who withdraw from the study, will be included in evaluations of safety.

If a participant is prematurely or permanently withdrawn from the study, the procedures described in the Schedule of Activities Table, Section 1.5, for the in-clinic Withdrawal visit are to be performed. An in-clinic Follow-Up visit will be conducted 4 weeks after the last dose of study medication for participants with ongoing AEs, and serious adverse events (SAEs) related & not related to study drug and also any laboratory abnormalities that are considered to be AEs or potentially harmful to the participant, at the last on-study visit.

All data from the Withdrawal visit will be recorded, as they comprise an essential evaluation that should be done prior to discharging any participant from the study.

The following actions must be taken and documented in relation to a participant who fails to attend the clinic for a required study visit:

a. The site must attempt to contact the participant and re-schedule the missed visit as soon as possible.
b. The site must counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
c. In cases where the participant is deemed ‘lost to follow up’, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and if necessary a certified letter to the participant’s last known mailing address or local equivalent methods). These contact attempts should be documented in the participant’s medical record.
d. Should the participant continue to be unreachable, only then will he/she be considered to have withdrawn from the study with a primary reason of “Lost to Follow-up”.

A participant may withdraw from study intervention at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral or administrative reasons. If a participant withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records.

7.1. Discontinuation of Study Intervention

Participants unable to manage drug toxicity or tolerate investigational product (either formulations of CAB or RPV,) must have IP discontinued. Any participant receiving at least one dose of CAB LA and /or RPV LA who discontinue IP / Withdraw will initiate treatment with HAART enter the LTFU Phase for an additional 52 weeks of follow up.

7.1.1. QTc Stopping Criteria

A participant who has a QTc interval >550 msec considered causally related to IP will be withdrawn from the study. The QTc should be based on averaged QTc values of triplicate electrocardiograms obtained over a brief (e.g., 5 to 10 minute) recording period.

If an alternative cause of the QT prolongation is determined (e.g., participant receiving drug known to cause prolonged QT or TdP), the IP may be restarted (or continued) after consultation and agreement with the Medical Monitor. RPV and RPV LA should not be administered to participants who are receiving a drug known to be associated with TdP.

When performing ECGs, the *same* QT correction formula *must* be used for *each individual participant* to determine eligibility for, and discontinuation from, the study. 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, then QTcB must be used for discontinuation of this individual participant as well.

Once the QT correction formula has been chosen for a participant's eligibility, the *same formula* must continue to be used for that participant *for all QTc data being collected for data analysis*. Safety ECGs and other non-protocol specified ECGs are an exception.

7.1.2. Virologic Failure

Only plasma HIV-1 RNA values determined by the central laboratory will be used to assess virologic failure.

7.1.3. Definition of Protocol-Defined Confirmed Virologic Failure

For the purposes of clinical management in this study, CVF is defined as:

Rebound as indicated by two consecutive plasma HIV-1 RNA levels ≥200 c/mL.

7.1.4. Managing Virologic Failure

Following study entry, no changes, or intensification of ART will be permitted prior to protocol-defined virologic failure, outside of the planned protocol regimens. Only plasma HIV-1 RNA values determined by the central laboratory will be used to assess virologic failure. Baseline plasma HIV-1 RNA is the assessment completed on study Day 1. The definition of confirmed virologic failure does not apply to participants in the LTFU Phase. These participants will be followed for the emergence of viral resistance.

Inadequate adherence or maladministration may be a cause for virologic failure and should be explored as a first step in the management of study participants (e.g., at the first indication of inadequate virologic response or rebound). Upon notification that a participant's HIV-1 RNA plasma level qualifies him/her as a suspected virologic failure (SVF), the Investigator should query the participant regarding intercurrent illness, recent immunization, or interruption of oral therapy.

7.1.4.1. HIV-1 RNA Blips

HIV-1 RNA "blips" are not usually associated with subsequent virologic failure [DHHS, 2018]. Although the implications of persistent HIV-1 RNA levels between the lower level of detection and <200 c/mL are unclear, the risk of emerging resistance is believed to be relatively low.

Participants with transient increases in HIV-1 RNA ('blips' HIV-1 RNA <200 c/mL) are not considered suspected virologic failures and do not require a change in therapy.

Participants who have a HIV-1 RNA ≥50 c/mL at the key analysis timepoints (Month 12, End of Study visit) should return for a repeat HIV-1 RNA as soon as possible but no later than 4 weeks after the date of the Month 12 or End of study visit, respectively such that the result falls within the same analysis window.

In order to better characterize HIV-1 RNA 'blips,' if there is a known reason / explanation for the blip (e.g., immunization, allergies, etc), the study team should be notified of the reason and case context.

If the Investigator has concerns regarding persistent low-level viremia (HIV-1 RNA ≥50 c/mL and <200 c/mL), the Medical Monitor should be contacted to discuss participant management. Following discussion with the Medical Monitor, additional viral load testing may be performed between visits to determine the appropriate participant disposition for the next scheduled visit.

7.1.4.2. Suspected Virologic Failure

Upon notification that a participant's HIV-1 RNA plasma level meets the definition of virologic failure, the Investigator should confirm the definition is met by initiating a repeat of the HIV-1 RNA assessment.

The following guidelines should be followed for scheduling confirmatory HIV-1 RNA testing in an effort to avoid false-positive results:

- Confirmatory testing should be scheduled within 2 to 4 weeks following resolution of any intercurrent illness, during which time the participant should receive full dose of all IP.
- Confirmatory testing should be scheduled at least 4 weeks following any immunization, during which time the participant should receive full dose of all IP.

- If therapy is interrupted* due to toxicity management, non-compliance, or other reasons, confirmatory testing should be scheduled 2 to 4 weeks following resumption of full dose of all IP.
- The participant should have received full dose of IP for at least 2 weeks at the time confirmatory plasma HIV-1 RNA testing is done.

*Note: treatment interruption guidelines above may not apply for participants on CAB LA + RPV LA treatment. The study team should be contacted to discuss any treatment interruptions for participants meeting the definition of virologic failure.

In addition, the Investigator should query the participant regarding intercurrent illness, recent immunization, or interruption of therapy.

Sites should contact the Medical Monitor to discuss individual participants, whenever necessary.

7.1.4.3. Confirmed Virologic Failure

Participants with CVF must be discontinued from study treatment. However, participants who have received at least one dose of CAB LA or RPV LA prior to confirming virologic failure will remain in the study on oral HAART in the LTFU Phase.

A plasma sample from the suspected virologic failure visit as well as Day 1 (if baseline HIV-1 RNA level ≥200 c/mL) will be sent for genotypic and phenotypic resistance testing and the result made known to the Investigator when available. A plasma sample from the confirmation visit will be obtained for storage. This sample may be used for possible future analyses, e.g., for genotypic and phenotypic analyses of participants who experience virologic failure.

For all participants who meet CVF, baseline and suspected virologic failure plasma samples with HIV-1 RNA level ≥200 c/mL will be analyzed in an attempt to obtain genotype/phenotype data on as many samples as possible. Plasma samples for storage will also be obtained at unscheduled visits including confirmation of CVF. Participants may continue to receive study drug at the discretion of the investigator until results of resistance testing are available at which time the participant must be discontinued from the study. Even if genotype/phenotype data cannot be generated, participant must also be discontinued from the study intervention.

If a participant is prematurely discontinued from the study intervention, the investigator must make every effort to perform the Withdrawal Visit evaluations outlined in the Schedule of Activities Table, Section 1.5. These data will be recorded as they comprise essential evaluations needed to be done before discharging any participant from the study.

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety,

behavioral, compliance or administrative reasons. This is expected to be uncommon.

- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the Schedule of Activities, Section 1.5. See SoA, Section 1.5 for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Section 10.1.

8. STUDY ASSESSMENTS AND PROCEDURES

Protocol waivers or exemptions are not allowed with the exception of urgent actions to address immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Schedule of Activities Table, Section 1.5, are essential and required for study conduct.

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the Schedule of Activities, Section 1.5.

The following points must be noted:

If assessments are scheduled for the same nominal time, THEN the assessments should occur in the following order:

1. 12-lead ECG

2. vital signs

3. blood draws

•The IRB/independent ethics committee (IEC) will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the Informed Consent Form.

Please refer to Section 10.12, Appendix 12 in for study management information during the COVID-19 pandemic.

8.1. Screening Assessments

Eligibility criteria must be carefully assessed at the Screening visit. Physical examinations should be conducted as part of normal routine clinical care. Background information to be collected at Screening includes demography and prior ART history.

Eligible participants may be enrolled immediately as soon as all Screening assessments are complete and the results are available and documented. All participants will complete the screening period of approximately 21 days prior to Baseline (Day 1) during which all clinical and laboratory assessments of eligibility must be performed and reviewed. All Screening results **must** be available prior to enrollment.

All information about the participant's current regimen must be available for review by the Principal Investigator or designee prior to enrollment. Source documents from other medical facilities must be located/received during the 21 day screening period and under no circumstances may the participant be randomized in the absence of source documentation even if there are delays in receipt of this information.

Participants who meet all entry criteria and are enrolled will be assigned a randomization number. A single repeat of a procedure/lab parameter is allowed to determine eligibility (unless otherwise specified). Participants not meeting all inclusion and exclusion criteria at initial screen may be rescreened one time within 4 weeks and receive a new participant number. Participants who are enrolled into the trial and subsequently withdrawn from the study for any reason may not be rescreened.

8.2. Baseline Assessments

8.2.1. Patient Study Participants

At Day 1, any changes to the eligibility parameters must be assessed and any results required prior to enrollment (e.g., Day 1 urine pregnancy test for women of childbearing potential) must be available and reviewed. The following demographic parameters will be captured: year of birth, sex, race and ethnicity. Medical/medication/family history will be assessed as related to the inclusion/exclusion criteria listed in Section 5.1.

Baseline information to be collected at Day 1 includes general medical history and current medical conditions. Laboratory assessments will also be assessed. Questionnaire/surveys are recommended to be administered at the beginning of the visit before any other assessments are conducted, in the order specified.

In addition to a full routine medical history at Baseline, more detailed information will be collected for some disease processes such as:

- Cardiovascular medical history/risk factors (as detailed in the eCRF) will be assessed at Baseline and assessments will include height, weight, blood pressure, smoking status and history, pertinent medical conditions (e.g., hypertension, diabetes mellitus), and family history of premature cardiovascular disease. In addition, medical history/risk factors for renal disease such as nephropathy, renal failure, and nephrolithiasis will be assessed.

- history of illicit drug use [e.g., cocaine, heroin, and methamphetamine use]);

- intravenous drug use history;

- gastrointestinal disease (e.g., gastrointestinal [GI] bleeding, peptic ulcer disease [PUD], etc);

- metabolic (e.g., Type I or II diabetes mellitus);

- psychiatric (e.g., depression);

- renal (e.g., nephrolithiasis, nephropathy, renal failure); and,

- neurologic disorders

Procedures conducted as part of the participant's routine clinical management [e.g., laboratory assessments] and obtained prior to signing of informed consent may be

utilized for baseline purposes provided the procedure meets the protocol-defined criteria and has been performed in the timeframe of the study. Where possible local lab results should be confirmed by submission of samples to the central lab.

8.2.2. Staff Study Participants

Surveys and Questionnaires for staff study participants should be performed/ collected prior to the first Patient Study Participant CAB + RPV LA injection, but may be conducted after Patient Study Participant screening or Day 1 visits.

8.3. Efficacy Assessments- Patient Study Participants

8.3.1. Plasma HIV-1 RNA

Plasma for quantitative HIV-1 RNA will be collected according to the Schedule of Activities (Section 1.5). Methods to be used may include but are not limited to the Abbott RealTime HIV-1 Assay lower limit of detection (LLOD) 40 c/mL. In some cases, (e.g., where the HIV-1 RNA is below the lower limit of detection for a given assay) additional exploratory methods will be used to further characterize HIV-1 RNA levels.

8.3.2. Lymphocyte Subsets, CD4+ and CD8+

Lymphocyte subsets will be collected for assessment by flow cytometry (total lymphocyte counts, percentage and absolute CD4+ and CD8+ lymphocyte counts, ratios) according to the Schedule of Activities (Section 1.5).

8.3.3. HIV Associated Conditions

HIV-associated conditions will be recorded and will be assessed according to the 2014 CDC Revised Classification System for HIV Infection.

8.4. Safety Assessments- Patient Study Participants

8.4.1. Clinical Evaluations

The following clinical evaluations will be performed according to the schedule of activities:

- Monitoring and recording of all AEs and SAEs. Additional information on the Time Period and Frequency of Detecting AEs and SAEs is provided in Section 1.5.
- Physical exams should be conducted as part of normal routine clinical care. Abnormalities noted during any exam must be recorded in the eCRF (e.g., in the current medical conditions or AE logs).
- Height and weight will be measured and recorded. Height collected on the Day 1 (Baseline) only.
- Vital signs will include systolic and diastolic blood pressure and heart rate collected after resting for about 5 minutes. Temperature will also be collected.

- Past medical history, family history, social history, medication history. Targeted history on cardiovascular risk (smoking history, family and personal history).
- HIV-associated conditions will be recorded.
- Electrocardiogram: A 12-lead ECG will be performed in a semi-supine position after 5 minutes of rest. At Screening, ECGs should be performed in triplicate. An ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals is preferred, and these calculated numbers can be used for reporting purposes. Otherwise, an appropriately qualified ECG reader must interpret the results. The same interpreter should assess all ECGs for each participant for the site. Regardless, each ECG should be reviewed by a qualified ECG reader. The qualified ECG reader will make the non-calculated ECG interpretations. The same QT correction formula must be used for each individual participant to determine eligibility for and discontinuation from the study. This formula may not be changed or substituted once the participant has been enrolled.
- Regular monitoring of hematology, blood chemistry, glucose and lipids (parameters to be tested listed below).
- Pregnancy testing. A negative urine pregnancy test is required prior to initiation of IP, any dose of CAB LA or RPV LA or as required by the Medical Monitor following a treatment interruption(s). If serum testing is required locally, the results should be available prior to the visit where urine testing is indicated per the Schedule of Activities, Section 1.5.
    - Participants who are enrolled in the study and have a positive pregnancy test during the course of the study, will be allowed to remain in the study, provided a pregnancy specific ICF addendum is signed by the participant. No IP can be continued (oral or LA) in any pregnant participant until the benefit/risk assessment is discussed with the participant and the pregnancy specific ICF addendum has been signed. See details in Appendix 8.
    - Pregnant participants who remain in the study do not need pregnancy testing during the study, for the duration of their pregnancy.
- Evaluation and documentation of all concomitant medications and blood products.
- Injection Site Reactions (ISRs) will be assessed clinically during the study for the following:

  Pain, tenderness, pruritis, warmth, bruising, discoloration, infections, rash, erythema, swelling, induration, and nodules (granulomas or cysts).
- A clinical assessment (using Division of Acquired Immunodeficiency Syndrome [DAIDS] grading scale) should be performed both before and after an injection to identify resolving and new ISRs. All injection site reactions are considered adverse events. The clinical assessment and interpretation of any ISR, will be documented in the ISR AE eCRF.

Any appropriately qualified site personnel (e.g., Investigator, sub-Investigator, or study coordinator/nurse) can perform assessments.

8.4.2. Physical Examinations

Physical exams should be conducted as part of normal routine clinical care. Abnormalities noted during any exam must be recorded in the eCRF (e.g., in the current medical conditions or AE logs).

- A complete physical examination will include, at a minimum, assessment of the Cardiovascular, Respiratory, Gastrointestinal, and Neurological systems. Height and weight will also be measured and recorded as per the Schedule of Activities (Section 1.5).
- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- The site of IM injection administration should be assessed at every visit for signs of any possible reaction.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.4.3. Vital Signs

Vital signs will be measured in semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure and pulse rate. These will be recorded as per the Schedule of Activities (Section 1.5).

8.4.4. Electrocardiograms

A 12-lead ECG will be performed in a semi-supine position. ECGs should be performed in triplicate at Screening. Refer to Section 7.1.1 for [QTc] withdrawal criteria and additional [QTc] readings that may be necessary.

8.4.5. Clinical Safety Laboratory Assessments

Hematology			
Platelet count		Automated WBC differential:	
RBC count		Neutrophils	
WBC count (absolute)		Lymphocytes	
Hemoglobin		Monocytes	
Hematocrit		Eosinophils	
MCV		Basophils	
Clinical Chemistry			
BUN	Potassium	AST	Total bilirubin[a]
Creatinine	Chloride	ALT	Albumin
Glucose[c]	Total CO_2	Alkaline phosphatase	Creatine phosphokinase
Sodium	Lipase	Phosphate	Creatinine clearance[b]
Other Tests			
Plasma HIV-1 RNA[d]			
CD4+ and CD8+ cell counts [CD4/CD8 ratio][e]			
Peripheral Blood Mononuclear Cells (PBMCs): Day 1 and Withdrawal only			
Rapid Plasma Reagin (RPR)			
Prothrombin Time (PT)/International Normalized Ratio (INR)/ Partial Thromboplastin Time (PTT)			
Pregnancy test for FRP[f]			
Urinalysis, urine albumin/creatinine ratio, and urine protein/creatinine ratio, urine phosphate			
Follicle stimulating hormone (FSH) and estradiol (only for instances when postmenopausal status is questionable)			

MCV = mean corpuscular volume, RBC = red blood cells, WBC = white blood cells, BUN = Blood urea nitrogen, AST=aspartate aminotransferase, ALT = alanine aminotransferase, CO2 = carbon dioxide, HBsAg= hepatitis B virus surface antigen, PT/INR = prothrombin time/international normalized ratio.

a) Direct bilirubin will be reflexively performed for all total bilirubin values >1.5 × ULN.
b) Glomerular filtration rate (GFR) will be estimated by the central laboratory using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) [Levey, 2009].
c) Screening glucose test will be done in a non-fasting state.
d) For participants meeting virologic withdrawal criteria, plasma samples will be analyzed in attempt to obtain genotype/phenotype data.
e) CD8+ cells will only be reported at Baseline and end of the study.
f) Urine pregnancy test/ serum pregnancy test will be performed according to the Schedule of Activities (Section 1.5).

8.4.6. Suicidal Ideation and Behaviour Risk Monitoring

Participants with HIV infection may occasionally present with 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 participants being treated with INIs including DTG. Additionally, depression and anxiety has been reported in some participants being treated with RPV. Therefore, it is appropriate to monitor and closely observe participants prospectively before and during treatment for suicidal ideation and/or behavior, or any other unusual changes in behavior. It is recommended that the Investigator consider mental health consultation or referral for participants who experience signs of suicidal ideation or behavior.

Participants presenting with new onset/treatment emergent depression should be advised to contact the investigator immediately if symptoms of severe acute depression (including suicidal ideation/attempts) develop, because medical intervention and discontinuation of the study medication may be required.

The investigator will collect information using the Possible Suicidality-Related AE (PSRAE) eCRF form in addition to the Adverse Event (non-serious or Serious Adverse Events) eCRF form on any participant that experiences a possible suicidality-related adverse event while participating in this study. This may include, but is not limited to, an event that involves suicidal ideation, a preparatory act toward imminent suicidal behavior, a suicide attempt, or a completed suicide. The investigator will exercise his or her medical and scientific judgment in deciding whether an event is possibly suicide related. PSRAE forms should be completed and reported to ViiV/GSK within one week of the investigator diagnosing a possible suicidality-related adverse event. All sites should have a plan in place for managing possible risks for suicide related events.

8.5. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Section 10.5, Appendix 5.

The investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or the study, or that caused the participant to discontinue IP. (see Section 7).

Please refer to Section 10.12, Appendix 12 in for study management information during the COVID-19 pandemic.

8.5.1. Time Period and Frequency for Collecting AE and SAE Information

- All SAEs will be collected from the signing of the informed consent form until the follow-up visit at the time points specified in the SoA (Section 1.5).
- All AEs will be collected from Day 1 until the follow-up visit at the time points specified in the SoA (Section 1.5).
- Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF) not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.5.6. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek AEs or SAEs after the conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.5.2. Method of Detecting AEs and SAEs

- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.5.6.
- Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.5.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up. Further information on follow-up procedures is given in Section 10.5, Appendix 5.

8.5.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information e.g., summary or listing of SAE) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.5.5. Pregnancy

Women of childbearing potential must have a negative pregnancy test at Screening, and at Baseline (Day 1). Pregnancy testing will also be conducted as per the Schedule of Activities (Section 1.5) and at any time during the trial when pregnancy is suspected. Pregnant participants who remain in the study do not need pregnancy testing during the study, for the duration of their pregnancy.

- Additionally, the Medical Monitor may request that a urine pregnancy test be performed in the event of a treatment interruption greater than 7 days.

- Details of all pregnancies in female participants will be collected after the start of study intervention and until the last follow-up assessment. This includes the entirety of the long-term follow-up period.
- If a pregnancy is reported, the investigator should inform GSK within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 10.7, Appendix 7.
- If pregnancy is confirmed, a discussion with the pregnant study participant assessing the benefit/risk assessment of continuing in the study will be undertaken. If, after this discussion, the participant would like to continue in the study, this will be allowed, provided the pregnant participant signs the pregnancy specific ICF addendum. See Appendix 8 for details.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

8.5.5.1. Rationale for Continued Use in Pregnancy

Additional data regarding the use of CAB + RPV LA during pregnancy, and management of pregnant participants remaining in the study are found in Appendix 8

The use of CAB + RPV LA during pregnancy may offer unique benefits. It is well documented that treatment adherence challenges to oral therapy exists both in the peri-partum and post-partum periods with LA dosing offering a unique opportunity to overcome such adherence challenges. LA therapy may also help with nausea (50 % mild to moderate) or hyperemesis (2%) that is frequently seen, especially during the first trimester of gestation.

Participants on LA dosing who become pregnant will have exposures throughout pregnancy due to the long half-life and PK tail of CAB/RPV. Prior to this protocol amendment, pregnant participants would have been withdrawn from the study, and initiated on an alternative oral ART regimen. Alternative regimens consist of either 2 or 3 antiretrovirals to protect the life of the mother and for the prevention of MTCT. This regimen, combined with the long half-life and PK tail of CAB/RPV, would potentially expose the fetus to additional ARVs during gestation (in some cases upwards of 5 antiretrovirals).

Given the risk/benefit ratio for cabotegravir and rilpivirine LA dosing in FRP, coupled with concerns of increasing fetal exposure to several additional antiretrovirals upon participant withdrawal, this amendment to the protocol will allow pregnant participants to remain in the study after a pregnancy specific ICF addendum is signed by the participant.

8.5.5.2. Time Period for Collecting Pregnancy Information

Pregnancy information will be collected from Day 1 until the last follow-up assessment. This includes the entirety of the LTFU Phase.

Pregnant study participants who consent to remain in the study during pregnancy will continue to have all clinical assessments performed as per the SoA, Table 3, including the collection of additional PK samples for CAB and RPV. See Appendix 8 for details.

Pregnant participants who have received at least one dose of CAB LA or RPV LA and decide NOT to continue in the study during pregnancy will be transitioned to the LTFU phase of the study and will be monitored for 52 weeks after the last LA dose. Moreover, an alternative oral ARV regimen will be initiated, at the discretion of the PI and in discussion with the medical monitor.

8.5.5.3. Action to be Taken if Pregnancy Occurs

Any pregnancy that occurs during study participation must be reported using a clinical trial pregnancy form. The investigator should inform GSK within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 8.

Pregnant participants who elect to continue with CAB + RPV LA must sign a pregnancy specific ICF addendum. Cabotegravir and rilpivirine are detected in systemic circulation for up to 12 months or longer after discontinuing injections of CAB + RPV LA; therefore, consideration should be given to the potential for fetal exposure during pregnancy and should be discussed between the study participant and the study PI.

All participants who become pregnant and who received at least one dose of LA therapy during the study, whether they elect to continue with CAB + RPV LA injections or transition to LTFU, will have additional PK samples collected to monitor cabotegravir and rilpivirine exposure levels throughout the pregnancy (see Appendix 8).

The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child(ren). Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

Any SAE occurring in association with a pregnancy brought to the investigator's attention after the participant has completed the study and considered by the investigator as possibly related to the study intervention, must be promptly reported to ViiV/GSK.

GSK's central safety department will also forward this information to the Antiretroviral Pregnancy Registry. The international registry is jointly sponsored by manufacturers or licensees of ARV products. Additional information and a list of participating manufacturers/licensees are available from http://apregistry.com/index.htm.

8.5.6. Cardiovascular and Death Events

Investigators will be required to fill out the specific CV event page of the eCRF for the following AEs and SAEs:

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias and QT prolongation-related adverse events
- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack

- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularisation

For any cardiovascular events detailed above and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The CV CRFs are presented as queries in response to reporting of certain CV MedDRA terms. The CV information should be recorded in the specific cardiovascular section of the CRF within one week of receipt of a CV Event data query prompting its completion.

The Death CRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within one week of when the death is reported.

8.5.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

Disease related events (DREs) or outcomes listed in the CDC Classification System for HIV-1 Infections (Section 10.4, Appendix 4) can be serious/life threatening and will be recorded on the HIV-Associated Conditions eCRF page if they occur. However, these individual events or outcomes, as well as any sign, symptom, diagnosis, illness, and/or clinical laboratory abnormality that can be linked to any of these events or outcomes are not reported to GSK as AEs and SAEs even though such event or outcome may meet the definition of an AE or SAE. However, if either of the following conditions applies, then the event must be recorded and reported as an SAE (instead of a DRE):

- The investigator determines that the event or outcome qualifies as an SAE under part 'other situations' of the SAE definition (see Section 10.5.2), or
- The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant, or
- The investigator considers that there is a reasonable possibility that the event was related to treatment with the investigational product, or
- Death occurring for any reason during a study, including death due to a disease-related event, will always be reported promptly.
- Lymphomas and invasive cervical carcinomas are excluded from this exemption; they must be reported as SAEs even if they are considered to be HIV-related.

If any of the above conditions is met then record the DRE on the SAE page rather than the HIV Associated Conditions eCRF page and report promptly (i.e., expedited reporting, see Section 10.5.2) to GSK.

8.6. Pharmacokinetics

Pharmacokinetic samples will be collected in subjects who experience virologic failure in order to determine drug levels at the time of viral rebounds.

Pregnant participants will have additional PK samples collected during the duration of the pregnancy. See Appendix 8 for details.

8.7. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.8. Genetics

Genetics are not evaluated in this study.

8.9. Biomarkers

Biomarkers are not evaluated in this study.

8.10. Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

No formal hypothesis testing is planned.

9.2. Sample Size Determination

As described above, the study size is based on practical considerations in terms of feasibility of enrolling an adequate number of sites on each intervention balanced with the desire to have interventions tested across several types of investigative sites: University Setting, Private Practice and Ryan White Clinic.

The primary consideration for study sizing is to obtain in-depth qualitative site level feedback via interviews of site personnel (treating clinician, nurses, administrators).

Additionally, this study is a single arm, open label interventional study, whereby patients at each site will receive the same intervention of the CAB + RPV LA ARV regimen and additional site facilitation to support the implementation of this regimen in their practice setting.

The primary endpoint is change from baseline to the study Month 12 injection visit in site survey responses for acceptability, appropriateness and feasibility, as described above (cross-reference and provide published citation). This survey includes a likert scale of

response ranging from 1 to 5, with higher values representing better outcomes. Although adequate prior information on expected responses are unavailable, it is expected that the standard deviation of change from baseline is 0.50.

9 sites will allow for estimation of paired mean change from baseline of 0.55 (half-width of the 95% confidence interval) using a two-sided confidence interval based on the normal distribution and assumed standard deviation of 1.

For subject level outcomes, the primary outcome will also be survey responses as described above (reference surveys). 135 subject pairs (average of 15 per site) will allow for estimation of paired mean change from baseline of 0.17 (half-width of the 95% confidence interval) using a two-sided confidence interval based on the normal distribution and assumed standard deviation of 1.

9.3. Populations for Analyses

Analysis populations will be defined as follows:

Population	Definition/Criteria
Intent to Treat Site (ITTS)	All sites enrolled and who have administered at least one dose of CAB LA + RPV LA
Intent to Treat Patient (ITTP)	All patients enrolled and who have administered at least one dose of CAB LA + RPV LA
Safety Population	All patients enrolled and who received at least one dose of CAB LA + RPV LA

9.4. Statistical Analyses

As mentioned above, this study has both site- and subject-level outcomes and each outcome will be analyzed and summarized accordingly.

Survey Data:

Qualitative interview data will be summarized by Evidera and reported as part of the overall study results (CSR). Details of these analyses will be described in a separate analysis plan provided by Evidera or other CRO partner under GSK's oversight. Randomization will be used to assign patients from the PSP to qualitative interview group or to no interview group.

Quantitative data (site and subject level) will be summarized using descriptive statistics including 95% confidence intervals for primary and secondary endpoints, as appropriate. ata will be summarized by month of study/injection visit as actual values and change from baseline.

Responses will be summarized overall and by site type. Exploratory analyses will be undertaken to assess the variability of responses by factors including but not limited to site type, setting (urban, suburban, rural) and for subject level outcomes markers of demographic and baseline characteristics.

Clinical Safety and Efficacy data:

Given that this is an interventional clinical trial of an unapproved investigational product, standard analyses will be applied to summarize descriptively clinical adverse events, laboratory evaluations, virologic parameters and other outcomes.

All analyses performed will be described in the study Reporting and Analysis Plan which will be finalized and approved prior to database lock.

One interim analysis will be timed to provide preliminary data to inform the initial commercial availability of the CAB + RPV LA regimen. No formal criteria for stopping or amending the study based on the interim analysis are envisioned.

9.4.1. Health Outcomes Analyses (Effectiveness Analyses)

Endpoint	Statistical Analysis Methods
Primary	Change from baseline at Month 12 in Acceptability of Intervention Measure (AIM), Intervention Appropriateness Measure (IAM), and Feasibility of Intervention Measure (FIM).
Secondary	Change from baseline at Month 12 in Acceptability of Intervention Measure (AIM), Intervention Appropriateness Measure (IAM), and Feasibility of Intervention Measure (FIM) by visit.

9.4.2. Efficacy Analyses

Endpoint	Statistical Analysis Methods
Secondary	Proportion of participants with plasma HIV-1 RNA <50 c/mL over time
Secondary	Proportion of participants with confirmed virologic failure (CVF) over time
Secondary	Incidence of treatment emergent genotypic and phenotypic resistance to CAB and RPV in patients with CVF

9.4.3. Safety Analyses

All safety analyses will be performed on the Safety Population.

Endpoint	Statistical Analysis Methods
Secondary	Incidence and severity of Adverse Events
Secondary	Incidence and severity of laboratory abnormalities over time
Secondary	Proportion of participants who discontinue treatment due to AEs over time
Secondary	Absolute values and changes in laboratory parameters over time

9.4.4. Other Analyses

The impact of demographic parameters including, but not limited to, age, sex, race, as potential predictors of inter- and intra-participant variability for acceptability, adoption, appropriateness, and sustainability may be explored if sufficient data are available.

9.5. Interim Analyses

One interim analysis will be timed to provide preliminary data to inform planning for the initial commercial availability of the CAB + RPV LA regimen. No formal criteria for stopping or amending the study based on the interim analysis are envisioned. The Reporting and Analysis Plan will describe the planned interim analyses in greater detail.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

Prior to initiation of a site, ViiV/GSK will obtain favorable opinion/approval from the appropriate regulatory agency to conduct the study in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) and applicable country-specific regulatory requirements.

- This study will be conducted in accordance with the protocol and with:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
    - Applicable ICH Good Clinical Practice (GCP) Guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
    - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
    - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities.

Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- Participants who are rescreened are required to sign a new ICF.
- Participants who become pregnant while in the study and who elect to continue to receive CAB + RPV LA injections must sign the pregnancy specific ICF addendum.

10.1.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Quality Control (Study Monitoring)

- In accordance with applicable regulations including GCP, and GSK procedures, GSK monitors will contact the site prior to the start of the study to

review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements.

- When reviewing data collection procedures, the discussion will also include identification, agreement and documentation of data items for which the eCRF will serve as the source document.

GSK will monitor the study and site activity to verify that the:

- Data are authentic, accurate, and complete.
- Safety and rights of participants are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.1.6. Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually agreeable location.
- GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.
- The procedures and timing for public disclosure of the protocol and results summary and for development of a manuscript for publication for this study will be in accordance with GSK Policy.
- GSK intends to make anonymized patient-level data from this trial available to external researchers for scientific analyses or to conduct further research that

can help advance medical science or improve patient care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding

10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the study data monitoring plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.8. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator’s site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the

discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.9. Study and Site Closure

GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study treatment development
- If GSK determines such action is needed, GSK will discuss the reasons for taking such action with the investigator or the head of the medical institution (where applicable). When feasible, GSK will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action.
- Upon completion or premature discontinuation of the study, the GSK monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and GSK Standard Operating Procedures.
- If the study is suspended or prematurely discontinued for safety reasons, GSK will promptly inform all investigators, heads of the medical institutions (where applicable) and/or institution(s) conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action.
- If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.

10.2. Appendix 2: Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events Version 2.1, March 2017

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events ("DAIDS AE Grading Table") is a descriptive terminology which can be utilised for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

Estimating Severity Grade for Parameters Not Identified in the Grading Table

The functional table below should be used to grade the severity of an AE that is not specifically identified in the grading table. In addition, all deaths related to an AE are to be classified as grade 5.

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Clinical adverse event **NOT** identified elsewhere in the grading table	Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death

Major Clinical Conditions
Cardiovascular

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Arrhythmia (by ECG or physical examination) *Specify type, if applicable*	No symptoms AND No intervention indicated	No symptoms AND Non-urgent intervention indicated	Non-life-threatening symptoms AND Non-urgent intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Blood Pressure Abnormalities[1]				
Hypertension *(with the lowest reading taken after repeat testing during a visit)* *≥ 18 years of age*	140 to < 160 mmHg systolic OR 90 to < 100 mmHg diastolic	≥ 160 to < 180 mmHg systolic OR ≥ 100 to < 110 mmHg diastolic	≥ 180 mmHg systolic OR ≥ 110 mmHg diastolic	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) OR Hospitalization indicated
< 18 years of age	> 120/80 mmHg	≥ 95th to < 99th percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	≥ 99th percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) OR Hospitalization indicated
Hypotension	No symptoms	Symptoms corrected with oral fluid replacement	Symptoms AND IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Cardiac Ischemia or Infarction *Report only one*	NA	NA	New symptoms with ischemia (stable angina) OR New testing consistent with ischemia	Unstable angina OR Acute myocardial infarction
Heart Failure	No symptoms AND Laboratory or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Symptoms at rest or with minimal activity or exertion (e.g., hypoxemia) OR Intervention indicated (e.g., oxygen)	Life-threatening consequences OR Urgent intervention indicated (e.g., vasoactive medications, ventricular assist device, heart transplant)

[1] Blood pressure norms for children < 18 years of age can be found in: Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. *Pediatrics* 2011;128;S213; originally published online November 14, 2011; DOI: 10.1542/peds.2009-2107C.

Cardiovascular

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hemorrhage (with significant acute blood loss)	NA	Symptoms AND No transfusion indicated	Symptoms AND Transfusion of ≤ 2 units packed RBCs indicated	Life-threatening hypotension OR Transfusion of > 2 units packed RBCs (for children, packed RBCs > 10 cc/kg) indicated
Prolonged PR Interval or AV Block *Report only one* *> 16 years of age*	PR interval 0.21 to < 0.25 seconds	PR interval ≥ 0.25 seconds OR Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥ 3.0 seconds	Complete AV block
≤ 16 years of age	1st degree AV block (PR interval > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥ 3.0 seconds	Complete AV block
Prolonged QTc Interval[2]	0.45 to 0.47 seconds	> 0.47 to 0.50 seconds	> 0.50 seconds OR ≥ 0.06 seconds above baseline	Life-threatening consequences (e.g., Torsade de pointes, other associated serious ventricular dysrhythmia)
Thrombosis or Embolism *Report only one*	NA	Symptoms AND No intervention indicated	Symptoms AND Intervention indicated	Life-threatening embolic event (e.g., pulmonary embolism, thrombus)

[2] As per Bazett's formula.

Dermatologic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Alopecia (scalp only)	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	NA	NA
Bruising	Localized to one area	Localized to more than one area	Generalized	NA
Cellulitis	NA	Non-parenteral treatment indicated (e.g., oral antibiotics, antifungals, antivirals)	IV treatment indicated (e.g., IV antibiotics, antifungals, antivirals)	Life-threatening consequences (e.g., sepsis, tissue necrosis)
Hyperpigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Hypopigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Petechiae	Localized to one area	Localized to more than one area	Generalized	NA
Pruritus[3] (without skin lesions)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA
Rash *Specify type, if applicable*	Localized rash	Diffuse rash OR Target lesions	Diffuse rash AND Vesicles or limited number of bullae or superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Stevens-Johnson syndrome OR Toxic epidermal necrolysis

[3] For pruritus associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section

Endocrine and Metabolic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Diabetes Mellitus	Controlled without medication	Controlled with medication OR Modification of current medication regimen	Uncontrolled despite treatment modification OR Hospitalization for immediate glucose control indicated	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma, end organ failure)
Gynecomastia	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing pain with greater than minimal interference with usual social & functional activities	Disfiguring changes AND Symptoms requiring intervention or causing inability to perform usual social & functional activities	NA
Hyperthyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., thyroid storm)
Hypothyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., myxedema coma)
Lipoatrophy[4]	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA

[4] Definition: A disorder characterized by fat loss in the face, extremities, and buttocks.

Endocrine and Metabolic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Lipohypertrophy[5]	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA

[5] Definition: A disorder characterized by abnormal fat accumulation on the back of the neck, breasts, and abdomen.

Gastrointestinal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)
Ascites	No symptoms	Symptoms AND Intervention indicated (e.g., diuretics, therapeutic paracentesis)	Symptoms recur or persist despite intervention	Life-threatening consequences
Bloating or Distension *Report only one*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Cholecystitis	NA	Symptoms AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis, perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction)
Diarrhea *≥ 1 year of age*	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools OR Increase of 4 to 6 stools over baseline per 24-hour period	Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)
< 1 year of age	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR Mild dehydration	Liquid stools with moderate dehydration	Life-threatening consequences (e.g., liquid stools resulting in severe dehydration, hypotensive shock)
Dysphagia or Odynophagia *Report only one and specify location*	Symptoms but able to eat usual diet	Symptoms causing altered dietary intake with no intervention indicated	Symptoms causing severely altered dietary intake with intervention indicated	Life-threatening reduction in oral intake
Gastrointestinal Bleeding	Not requiring intervention other than iron supplement	Endoscopic intervention indicated	Transfusion indicated	Life-threatening consequences (e.g., hypotensive shock)

Gastrointestinal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Mucositis or Stomatitis *Report only one and specify location*	Mucosal erythema	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Life-threatening consequences (e.g., aspiration, choking) OR Tissue necrosis OR Diffuse spontaneous mucosal bleeding
Nausea	Transient (< 24 hours) or intermittent AND No or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 to 48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
Pancreatitis	NA	Symptoms with hospitalization not indicated	Symptoms with hospitalization indicated	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)
Perforation (colon or rectum)	NA	NA	Intervention indicated	Life-threatening consequences
Proctitis	Rectal discomfort with no intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social & functional activities OR Operative intervention indicated	Life-threatening consequences (e.g., perforation)
Rectal Discharge	Visible discharge	Discharge requiring the use of pads	NA	NA
Vomiting	Transient or intermittent AND No or minimal interference with oral intake	Frequent episodes with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)

Musculoskeletal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Arthralgia	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Myalgia (generalized)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions
Osteonecrosis	NA	No symptoms but with radiographic findings AND No operative intervention indicated	Bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions
Osteopenia[6] *≥ 30 years of age*	BMD t-score -2.5 to -1	NA	NA	NA
< 30 years of age	BMD z-score -2 to -1	NA	NA	NA
Osteoporosis[6] *≥ 30 years of age*	NA	BMD t-score < -2.5	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences
< 30 years of age	NA	BMD z-score < -2	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences

[6] BMD t and z scores can be found in: Kanis JA on behalf of the World Health Organization Scientific Group (2007). Assessment of osteoporosis at the primary health-care level. Technical Report. World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, UK. 2007: Printed by the University of Sheffield.

Neurologic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acute CNS Ischemia	NA	NA	Transient ischemic attack	Cerebral vascular accident (e.g., stroke with neurological deficit)
Altered Mental Status (for Dementia, see *Cognitive, Behavioral, or Attentional Disturbance* below)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR Obtundation OR Coma
Ataxia	Symptoms causing no or minimal interference with usual social & functional activities OR No symptoms with ataxia detected on examination	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Disabling symptoms causing inability to perform basic self-care functions
Cognitive, Behavioral, or Attentional Disturbance (includes dementia and attention deficit disorder) *Specify type, if applicable*	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated
Developmental Delay *< 18 years of age* *Specify type, if applicable*	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated OR Headache with significant impairment of alertness or other neurologic function

Neurologic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Neuromuscular Weakness (includes myopathy and neuropathy) *Specify type, if applicable*	Minimal muscle weakness causing no or minimal interference with usual social & functional activities OR No symptoms with decreased strength on examination	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation
Neurosensory Alteration (includes paresthesia and painful neuropathy) *Specify type, if applicable*	Minimal paresthesia causing no or minimal interference with usual social & functional activities OR No symptoms with sensory alteration on examination	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
Seizures ***New Onset Seizure*** *≥ 18 years of age*	NA	NA	1 to 3 seizures	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
< 18 years of age (includes new or pre-existing febrile seizures)	Seizure lasting < 5 minutes with < 24 hours postictal state	Seizure lasting 5 to < 20 minutes with < 24 hours postictal state	Seizure lasting ≥ 20 minutes OR > 24 hours postictal state	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
Pre-existing Seizure	NA	Increased frequency from previous level of control without change in seizure character	Change in seizure character either in duration or quality (e.g., severity or focality)	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
Syncope	Near syncope without loss of consciousness (e.g., pre-syncope)	Loss of consciousness with no intervention indicated	Loss of consciousness AND Hospitalization or intervention required	NA

Pregnancy, Puerperium, and Perinatal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Stillbirth (report using mother's participant ID) *Report only one*	NA	NA	Fetal death occurring at ≥ 20 weeks gestation	NA
Preterm Birth (report using mother's participant ID)	Live birth at 34 to < 37 weeks gestational age	Live birth at 28 to < 34 weeks gestational age	Live birth at 24 to < 28 weeks gestational age	Live birth at < 24 weeks gestational age
Spontaneous Abortion or Miscarriage[7] (report using mother's participant ID) *Report only one*	Chemical pregnancy	Uncomplicated spontaneous abortion or miscarriage	Complicated spontaneous abortion or miscarriage	NA

[7] Definition: A pregnancy loss occurring at < 20 weeks gestational age.

Psychiatric

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Insomnia	Mild difficulty falling asleep, staying asleep, or waking up early causing no or minimal interference with usual social & functional activities	Moderate difficulty falling asleep, staying asleep, or waking up early causing more than minimal interference with usual social & functional activities	Severe difficulty falling asleep, staying asleep, or waking up early causing inability to perform usual social & functional activities requiring intervention or hospitalization	NA
Psychiatric Disorders (includes anxiety, depression, mania, and psychosis) *Specify disorder*	Symptoms with intervention not indicated OR Behavior causing no or minimal interference with usual social & functional activities	Symptoms with intervention indicated OR Behavior causing greater than minimal interference with usual social & functional activities	Symptoms with hospitalization indicated OR Behavior causing inability to perform usual social & functional activities	Threatens harm to self or others OR Acute psychosis OR Behavior causing inability to perform basic self-care functions
Suicidal Ideation or Attempt *Report only one*	Preoccupied with thoughts of death AND No wish to kill oneself	Preoccupied with thoughts of death AND Wish to kill oneself with no specific plan or intent	Thoughts of killing oneself with partial or complete plans but no attempt to do so OR Hospitalization indicated	Suicide attempted

Respiratory

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acute Bronchospasm	Forced expiratory volume in 1 second or peak flow reduced to ≥ 70 to < 80% OR Mild symptoms with intervention not indicated	Forced expiratory volume in 1 second or peak flow 50 to < 70% OR Symptoms with intervention indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Forced expiratory volume in 1 second or peak flow 25 to < 50% OR Symptoms causing inability to perform usual social & functional activities	Forced expiratory volume in 1 second or peak flow < 25% OR Life-threatening respiratory or hemodynamic compromise OR Intubation
Dyspnea or Respiratory Distress *Report only one*	Dyspnea on exertion with no or minimal interference with usual social & functional activities OR Wheezing OR Minimal increase in respiratory rate for age	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities OR Nasal flaring OR Intercostal retractions OR Pulse oximetry 90 to < 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilator support indicated (e.g., CPAP, BPAP, intubation)

Sensory

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hearing Loss *≥ 12 years of age*	NA	Hearing aid or intervention not indicated	Hearing aid or intervention indicated	Profound bilateral hearing loss (> 80 dB at 2 kHz and above) OR Non-serviceable hearing (i.e., >50 dB audiogram and <50% speech discrimination)
< 12 years of age (based on a 1, 2, 3, 4, 6 and 8 kHz audiogram)	> 20 dB hearing loss at ≤ 4 kHz	> 20 dB hearing loss at > 4 kHz	> 20 dB hearing loss at ≥ 3 kHz in one ear with additional speech language related services indicated (where available) OR Hearing loss sufficient to indicate therapeutic intervention, including hearing aids	Audiologic indication for cochlear implant and additional speech-language related services indicated (where available)
Tinnitus	Symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Symptoms causing inability to perform usual social & functional activities	NA
Uveitis	No symptoms AND Detectable on examination	Anterior uveitis with symptoms OR Medical intervention indicated	Posterior or pan-uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions
Visual Changes (assessed from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)

Systemic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acute Allergic Reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with intervention indicated OR Mild angioedema with no intervention indicated	Generalized urticaria OR Angioedema with intervention indicated OR Symptoms of mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR Laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Cytokine Release Syndrome[8]	Mild signs and symptoms AND Therapy (i.e., antibody infusion) interruption not indicated	Therapy (i.e., antibody infusion) interruption indicated AND Responds promptly to symptomatic treatment OR Prophylactic medications indicated for ≤ 24 hours	Prolonged severe signs and symptoms OR Recurrence of symptoms following initial improvement	Life-threatening consequences (e.g., requiring pressor or ventilator support)
Fatigue or Malaise *Report only one*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating symptoms of fatigue or malaise causing inability to perform basic self-care functions
Fever (non-axillary temperatures only)	38.0 to < 38.6°C or 100.4 to < 101.5°F	≥ 38.6 to < 39.3°C or ≥ 101.5 to < 102.7°F	≥ 39.3 to < 40.0°C or ≥ 102.7 to < 104.0°F	≥ 40.0°C or ≥ 104.0°F
Pain[9] (not associated with study agent injections and not specified elsewhere) *Specify location*	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization indicated

[8] Definition: A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and/or shortness of breath.

[9] For pain associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section

Systemic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Serum Sickness[10]	Mild signs and symptoms	Moderate signs and symptoms AND Intervention indicated (e.g., antihistamines)	Severe signs and symptoms AND Higher level intervention indicated (e.g., steroids or IV fluids)	Life-threatening consequences (e.g., requiring pressor or ventilator support)
Underweight[11] *> 5 to 19 years of age*	WHO BMI z-score < -1 to -2	WHO BMI z-score < -2 to -3	WHO BMI z-score < -3	WHO BMI z-score < -3 with life-threatening consequences
2 to 5 years of age	WHO BMI z-score < -1 to -2	WHO Weight-for-height z-score < -2 to -3	WHO Weight-for-height z-score < -3	WHO Weight-for-height z-score < -3 with life-threatening consequences
< 2 years of age	WHO BMI z-score < -1 to -2	WHO Weight-for-length z-score < -2 to -3	WHO Weight-for-length z-score < -3	WHO Weight-for-length z-score < -3 with life-threatening consequences
Unintentional Weight Loss (excludes postpartum weight loss)	NA	5 to < 9% loss in body weight from baseline	≥ 9 to < 20% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)

[10] Definition: A disorder characterized by fever, arthralgia, myalgia, skin eruptions, lymphadenopathy, marked discomfort, and/or dyspnea.
[11] WHO reference tables may be accessed by clicking the desired age range or by accessing the following URLs: http://www.who.int/growthref/who2007_bmi_for_age/en/ for participants > 5 to 19 years of age and http://www.who.int/childgrowth/standards/chart_catalogue/en/ for those ≤ 5 years of age.

Urinary

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Urinary Tract Obstruction	NA	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences

Site Reactions to Injections and Infusions

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Injection Site Pain or Tenderness *Report only one*	Pain or tenderness causing no or minimal limitation of use of limb	Pain or tenderness causing greater than minimal limitation of use of limb	Pain or tenderness causing inability to perform usual social & functional activities	Pain or tenderness causing inability to perform basic self-care function OR Hospitalization indicated
Injection Site Erythema or Redness[12] *Report only one* *> 15 years of age*	2.5 to < 5 cm in diameter OR 6.25 to < 25 cm^2 surface area AND Symptoms causing no or minimal interference with usual social & functional activities	≥ 5 to < 10 cm in diameter OR ≥ 25 to < 100 cm^2 surface area OR Symptoms causing greater than minimal interference with usual social & functional activities	≥ 10 cm in diameter OR ≥ 100 cm^2 surface area OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage OR Symptoms causing inability to perform usual social & functional activities	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
≤ 15 years of age	≤ 2.5 cm in diameter	> 2.5 cm in diameter with < 50% surface area of the extremity segment involved (e.g., upper arm or thigh)	≥ 50% surface area of the extremity segment involved (e.g., upper arm or thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
Injection Site Induration or Swelling *Report only one* *> 15 years of age*	Same as for **Injection Site Erythema or Redness**, *> 15 years of age*	Same as for **Injection Site Erythema or Redness**, *> 15 years of age*	Same as for **Injection Site Erythema or Redness**, *> 15 years of age*	Same as for **Injection Site Erythema or Redness**, *> 15 years of age*
≤ 15 years of age	Same as for **Injection Site Erythema or Redness**, *≤ 15 years of age*	Same as for **Injection Site Erythema or Redness**, *≤ 15 years of age*	Same as for **Injection Site Erythema or Redness**, *≤ 15 years of age*	Same as for **Injection Site Erythema or Redness**, *≤ 15 years of age*
Injection Site Pruritus	Itching localized to the injection site that is relieved spontaneously or in < 48 hours of treatment	Itching beyond the injection site that is not generalized OR Itching localized to the injection site requiring ≥ 48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NA

[12] Injection Site Erythema or Redness should be evaluated and graded using the greatest single diameter or measured surface area.

*Laboratory Values**
Chemistries

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acidosis	NA	pH ≥ 7.3 to < LLN	pH < 7.3 without life-threatening consequences	pH < 7.3 with life-threatening consequences
Albumin, Low (g/dL; *g/L*)	3.0 to < LLN *30 to < LLN*	≥ 2.0 to < 3.0 *≥ 20 to < 30*	< 2.0 *< 20*	NA
Alkaline Phosphatase, High	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Alkalosis	NA	pH > ULN to ≤ 7.5	pH > 7.5 without life-threatening consequences	pH > 7.5 with life-threatening consequences
ALT or SGPT, High *Report only one*	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Amylase (Pancreatic) or Amylase (Total), High *Report only one*	1.1 to < 1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to < 5.0 x ULN	≥ 5.0 x ULN
AST or SGOT, High *Report only one*	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Bicarbonate, Low (mEq/L; *mmol/L*)	16.0 to < LLN *16.0 to < LLN*	11.0 to < 16.0 *11.0 to < 16.0*	8.0 to < 11.0 *8.0 to < 11.0*	< 8.0 *< 8.0*
Bilirubin ***Direct Bilirubin[13], High*** *> 28 days of age*	NA	NA	> ULN with other signs and symptoms of hepatotoxicity.	> ULN with life-threatening consequences (e.g., signs and symptoms of liver failure)
≤ 28 days of age	ULN to ≤ 1 mg/dL	> 1 to ≤ 1.5 mg/dL	> 1.5 to ≤ 2 mg/dL	> 2 mg/dL
Total Bilirubin, High *> 28 days of age*	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN with other signs and symptoms of hepatotoxicity.	≥ 5.0 x ULN with life-threatening consequences (e.g., signs and symptoms of liver failure).
≤ 28 days of age	See Appendix A. Total Bilirubin for Term and Preterm Neonates	See Appendix A. Total Bilirubin for Term and Preterm Neonates	See Appendix A. Total Bilirubin for Term and Preterm Neonates	See Appendix A. Total Bilirubin for Term and Preterm Neonates

*Reminder: An asymptomatic abnormal laboratory finding without an accompanying AE should not be reported to DAIDS in an expedited time frame unless it meets protocol-specific reporting requirements.

[13] Direct bilirubin > 1.5 mg/dL in a participant < 28 days of age should be graded as grade 2, if < 10% of the total bilirubin.

Chemistries

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Calcium, High (mg/dL; *mmol/L*)				
≥ 7 days of age	10.6 to < 11.5 *2.65 to < 2.88*	11.5 to < 12.5 *2.88 to < 3.13*	12.5 to < 13.5 *3.13 to < 3.38*	≥ 13.5 *≥ 3.38*
< 7 days of age	11.5 to < 12.4 *2.88 to < 3.10*	12.4 to < 12.9 *3.10 to < 3.23*	12.9 to < 13.5 *3.23 to < 3.38*	≥ 13.5 *≥ 3.38*
Calcium (Ionized), High (mg/dL; *mmol/L*)	> ULN to < 6.0 *> ULN to < 1.5*	6.0 to < 6.4 *1.5 to < 1.6*	6.4 to < 7.2 *1.6 to < 1.8*	≥ 7.2 *≥ 1.8*
Calcium, Low (mg/dL; *mmol/L*)				
≥ 7 days of age	7.8 to < 8.4 *1.95 to < 2.10*	7.0 to < 7.8 *1.75 to < 1.95*	6.1 to < 7.0 *1.53 to < 1.75*	< 6.1 *< 1.53*
< 7 days of age	6.5 to < 7.5 *1.63 to < 1.88*	6.0 to < 6.5 *1.50 to < 1.63*	5.50 to < 6.0 *1.38 to < 1.50*	< 5.50 *< 1.38*
Calcium (Ionized), Low (mg/dL; *mmol/L*)	< LLN to 4.0 *< LLN to 1.0*	3.6 to < 4.0 *0.9 to < 1.0*	3.2 to < 3.6 *0.8 to < 0.9*	< 3.2 *< 0.8*
Cardiac Troponin I, High	NA	NA	NA	Levels consistent with myocardial infarction or unstable angina as defined by the local laboratory
Creatine Kinase, High	3 to < 6 x ULN	6 to < 10x ULN	10 to < 20 x ULN	≥ 20 x ULN
Creatinine, High **Report only one*	1.1 to 1.3 x ULN	> 1.3 to 1.8 x ULN OR Increase to 1.3 to < 1.5 x participant's baseline	> 1.8 to < 3.5 x ULN OR Increase to 1.5 to < 2.0 x participant's baseline	≥ 3.5 x ULN OR Increase of ≥ 2.0 x participant's baseline
Creatinine Clearance[14] or eGFR, Low **Report only one*	NA	< 90 to 60 ml/min or ml/min/1.73 m^2 OR 10 to < 30% decrease from participant's baseline	< 60 to 30 ml/min or ml/min/1.73 m^2 OR 30 to < 50% decrease from participant's baseline	< 30 ml/min or ml/min/1.73 m^2 OR ≥ 50% decrease from participant's baseline or dialysis needed
Glucose (mg/dL; *mmol/L*)				
Fasting, High	110 to 125 *6.11 to < 6.95*	> 125 to 250 *6.95 to < 13.89*	> 250 to 500 *13.89 to < 27.75*	≥ 500 *≥ 27.75*
Nonfasting, High	116 to 160 *6.44 to < 8.89*	> 160 to 250 *8.89 to < 13.89*	> 250 to 500 *13.89 to < 27.75*	≥ 500 *≥ 27.75*

[14] Use the applicable formula (i.e., Cockcroft-Gault in mL/min or Schwartz, MDRD, CKD-Epi in mL/min/1.73m2). Sites should choose the method defined in their study and when not specified, use the method most relevant to the study population.

*Reminder: Choose the method that selects for the higher grade.

Chemistries

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Glucose, Low (mg/dL; *mmol/L*)				
≥ 1 month of age	55 to 64 *3.05 to <3.55*	40 to < 55 *2.22 to < 3.05*	30 to < 40 *1.67 to < 2.22*	< 30 *< 1.67*
< 1 month of age	50 to 54 *2.78 to < 3.00*	40 to < 50 *2.22 to < 2.78*	30 to < 40 *1.67 to < 2.22*	< 30 *< 1.67*
Lactate, High	ULN to < 2.0 x ULN without acidosis	≥ 2.0 x ULN without acidosis	Increased lactate with pH < 7.3 without life-threatening consequences	Increased lactate with pH < 7.3 with life-threatening consequences
Lipase, High	1.1 to < 1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to < 5.0 x ULN	≥ 5.0 x ULN
Lipid Disorders (mg/dL; *mmol/L*)				
Cholesterol, Fasting, High *≥ 18 years of age*	200 to < 240 *5.18 to < 6.19*	240 to < 300 *6.19 to < 7.77*	≥ 300 *≥ 7.77*	NA
< 18 years of age	170 to < 200 *4.40 to < 5.15*	200 to < 300 *5.15 to < 7.77*	≥ 300 *≥ 7.77*	NA
LDL, Fasting, High *≥ 18 years of age*	130 to < 160 *3.37 to < 4.12*	160 to < 190 *4.12 to < 4.90*	≥ 190 *≥ 4.90*	NA
> 2 to < 18 years of age	110 to < 130 *2.85 to < 3.34*	130 to < 190 *3.34 to < 4.90*	≥ 190 *≥ 4.90*	NA
Triglycerides, Fasting, High	150 to 300 *1.71 to 3.42*	>300 to 500 *>3.42 to 5.7*	>500 to < 1,000 *>5.7 to 11.4*	> 1,000 *> 11.4*
Magnesium[15], Low (mEq/L; *mmol/L*)	1.2 to < 1.4 *0.60 to < 0.70*	0.9 to < 1.2 *0.45 to < 0.60*	0.6 to < 0.9 *0.30 to < 0.45*	< 0.6 *< 0.30*
Phosphate, Low (mg/dL; *mmol/L*)				
> 14 years of age	2.0 to < LLN *0.65 to < LLN*	1.4 to < 2.0 *0.45 to < 0.65*	1.0 to < 1.4 *0.32 to < 0.45*	< 1.0 *< 0.32*
1 to 14 years of age	3.0 to < 3.5 *0.97 to < 1.13*	2.5 to < 3.0 *0.81 to < 0.97*	1.5 to < 2.5 *0.48 to < 0.81*	< 1.5 *< 0.48*
< 1 year of age	3.5 to < 4.5 *1.13 to < 1.45*	2.5 to < 3.5 *0.81 to < 1.13*	1.5 to < 2.5 *0.48 to < 0.81*	< 1.5 *< 0.48*
Potassium, High (mEq/L; *mmol/L*)	5.6 to < 6.0 *5.6 to < 6.0*	6.0 to < 6.5 *6.0 to < 6.5*	6.5 to < 7.0 *6.5 to < 7.0*	≥ 7.0 *≥ 7.0*
Potassium, Low (mEq/L; *mmol/L*)	3.0 to < 3.4 *3.0 to < 3.4*	2.5 to < 3.0 *2.5 to < 3.0*	2.0 to < 2.5 *2.0 to < 2.5*	< 2.0 *< 2.0*

[15] To convert a magnesium value from mg/dL to mmol/L, laboratories should multiply by 0.4114.

Chemistries

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Sodium, High (mEq/L; *mmol/L*)	146 to < 150 *146 to < 150*	150 to < 154 *150 to < 154*	154 to < 160 *154 to < 160*	≥ 160 *≥ 160*
Sodium, Low (mEq/L; *mmol/L*)	130 to < 135 *130 to < 135*	125 to < 130 *125 to < 130*	121 to < 125 *121 to < 125*	≤ 120 *≤ 120*
Uric Acid, High (mg/dL; *mmol/L*)	7.5 to < 10.0 *0.45 to < 0.59*	10.0 to < 12.0 *0.59 to < 0.71*	12.0 to < 15.0 *0.71 to < 0.89*	≥ 15.0 *≥ 0.89*

Hematology

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Absolute CD4+ Count, Low (cell/mm^3; *cells/L*)				
> 5 years of age (not HIV infected)	300 to < 400 *300 to < 400*	200 to < 300 *200 to < 300*	100 to < 200 *100 to < 200*	< 100 *< 100*
Absolute Lymphocyte Count, Low (cell/mm^3; *cells/L*)				
> 5 years of age (not HIV infected)	600 to < 650 *0.600 x 10^9 to < 0.650 x 10^9*	500 to < 600 *0.500 x 10^9 to < 0.600 x 10^9*	350 to < 500 *0.350 x 10^9 to < 0.500 x 10^9*	< 350 *< 0.350 x 10^9*
Absolute Neutrophil Count (ANC), Low (cells/mm^3; *cells/L*)				
> 7 days of age	800 to 1,000 *0.800 x 10^9 to 1.000 x 10^9*	600 to 799 *0.600 x 10^9 to 0.799 x 10^9*	400 to 599 *0.400 x 10^9 to 0.599 x 10^9*	< 400 *< 0.400 x 10^9*
2 to 7 days of age	1,250 to 1,500 *1.250 x 10^9 to 1.500 x 10^9*	1,000 to 1,249 *1.000 x 10^9 to 1.249 x 10^9*	750 to 999 *0.750 x 10^9 to 0.999 x 10^9*	< 750 *< 0.750 x 10^9*
≤ 1 day of age	4,000 to 5,000 *4.000 x 10^9 to 5.000 x 10^9*	3,000 to 3,999 *3.000 x 10^9 to 3.999 x 10^9*	1,500 to 2,999 *1.500 x 10^9 to 2.999 x 10^9*	< 1,500 *< 1.500 x 10^9*
Fibrinogen, Decreased (mg/dL; *g/L*)	100 to < 200 *1.00 to < 2.00* OR 0.75 to < 1.00 x LLN	75 to < 100 *0.75 to < 1.00* OR ≥ 0.50 to < 0.75 x LLN	50 to < 75 *0.50 to < 0.75* OR 0.25 to < 0.50 x LLN	< 50 *< 0.50* OR < 0.25 x LLN OR Associated with gross bleeding
Hemoglobin[16], Low (g/dL; *mmol/L*)[17]				
≥ 13 years of age (male only)	10.0 to 10.9 *6.19 to 6.76*	9.0 to < 10.0 *5.57 to < 6.19*	7.0 to < 9.0 *4.34 to < 5.57*	< 7.0 *< 4.34*
≥ 13 years of age (female only)	9.5 to 10.4 *5.88 to 6.48*	8.5 to < 9.5 *5.25 to < 5.88*	6.5 to < 8.5 *4.03 to < 5.25*	< 6.5 *< 4.03*

[16] Male and female sex are defined as sex at birth. For transgender participants ≥13 years of age who have been on hormone therapy for more than 6 consecutive months, grade hemoglobin based on the gender with which they identify (i.e., a transgender female should be graded using the female sex at birth hemoglobin laboratory values).

[17] The most commonly used conversion factor to convert g/dL to mmol/L is 0.6206. For grading hemoglobin results obtained by an analytic method with a conversion factor other than 0.6206, the result must be converted to g/dL using appropriate conversion factor for the particular laboratory.

Hematology

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
57 days of age to < 13 years of age (male and female)	9.5 to 10.4 *5.88 to 6.48*	8.5 to < 9.5 *5.25 to < 5.88*	6.5 to < 8.5 *4.03 to < 5.25*	< 6.5 *< 4.03*
36 to 56 days of age (male and female)	8.5 to 9.6 *5.26 to 5.99*	7.0 to < 8.5 *4.32 to < 5.26*	6.0 to < 7.0 *3.72 to < 4.32*	< 6.0 *< 3.72*
22 to 35 days of age (male and female)	9.5 to 11.0 *5.88 to 6.86*	8.0 to < 9.5 *4.94 to < 5.88*	6.7 to < 8.0 *4.15 to < 4.94*	< 6.7 *< 4.15*
8 to ≤ 21 days of age (male and female)	11.0 to 13.0 *6.81 to 8.10*	9.0 to < 11.0 *5.57 to < 6.81*	8.0 to < 9.0 *4.96 to < 5.57*	< 8.0 *< 4.96*
≤ 7 days of age (male and female)	13.0 to 14.0 *8.05 to 8.72*	10.0 to < 13.0 *6.19 to < 8.05*	9.0 to < 10.0 *5.59 to < 6.19*	< 9.0 *< 5.59*
INR, High (not on anticoagulation therapy)	1.1 to < 1.5 x ULN	1.5 to < 2.0 x ULN	2.0 to < 3.0 x ULN	≥ 3.0 x ULN
Methemoglobin (% hemoglobin)	5.0 to < 10.0%	10.0 to < 15.0%	15.0 to < 20.0%	≥ 20.0%
PTT, High (not on anticoagulation therapy)	1.1 to < 1.66 x ULN	1.66 to < 2.33 x ULN	2.33 to < 3.00 x ULN	≥ 3.00 x ULN
Platelets, Decreased (cells/mm^3; *cells/L*)	100,000 to < 125,000 *100.000 x 10^9 to < 125.000 x 10^9*	50,000 to < 100,000 *50.000 x 10^9 to < 100.000 x 10^9*	25,000 to < 50,000 *25.000 x 10^9 to < 50.000 x 10^9*	< 25,000 *< 25.000 x 10^9*
PT, High (not on anticoagulation therapy	1.1 to < 1.25 x ULN	1.25 to < 1.50 x ULN	1.50 to < 3.00 x ULN	≥ 3.00 x ULN
WBC, Decreased (cells/mm^3; *cells/L*)				
> 7 days of age	2,000 to 2,499 *2.000 x 10^9 to 2.499 x 10^9*	1,500 to 1,999 *1.500 x 10^9 to 1.999 x 10^9*	1,000 to 1,499 *1.000 x 10^9 to 1.499 x 10^9*	< 1,000 *< 1.000 x 10^9*
≤ 7 days of age	5,500 to 6,999 *5.500 x 10^9 to 6.999 x 10^9*	4,000 to 5,499 *4.000 x 10^9 to 5.499 x 10^9*	2,500 to 3,999 *2.500 x 10^9 to 3.999 x 10^9*	< 2,500 *< 2.500 x 10^9*

Urinalysis

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Glycosuria (random collection tested by dipstick)	Trace to 1+ or ≤ 250 mg	2+ or > 250 to ≤ 500 mg	> 2+ or > 500 mg	NA
Hematuria (not to be reported based on dipstick findings or on blood believed to be of menstrual origin)	6 to < 10 RBCs per high power field	≥ 10 RBCs per high power field	Gross, with or without clots OR With RBC casts OR Intervention indicated	Life-threatening consequences
Proteinuria (random collection tested by dipstick)	1+	2+	3+ or higher	NA

Reference

U.S. Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases, Division of AIDS. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1. [March 2017]. Available from: https://rsc.tech-res.com/docs/default-source/safety/daids-ae-grading-table-mar2017.pdf

10.3. Appendix 3: Liver Safety – Study Treatment Restart or Rechallenge Guidelines

10.3.1. VSLC Guidelines for Drug Restart or Rechallenge after stop for Liver criteria

Drug Rechallenge refers to resuming study treatment following drug induced liver injury (DILI). Because of the risks associated with rechallenge after DILI (see Drug Rechallenge Background below) this should only be considered for a participant for whom there is compelling evidence of benefit from a critical or life-saving medicine, there is no alternative approved medicine available, and a benefit:risk assessment of rechallenge is considered to be favorable (Table 13, Figure 5).

Drug Restart refers to resuming study treatment following liver events meeting stopping criteria **in which there is a clear underlying cause (other than DILI) of the liver event (e.g., biliary obstruction, pancreatic events, hypotension, acute viral hepatitis)**. Furthermore, there should be no evidence of alcoholic hepatitis or hypersensitivity, and the drug should not be associated with HLA markers of liver injury. (Table 14; Figure 6). **As this determination can be difficult, for the purpose of these guidelines, cases should be treated as rechallenges if there is any reasonable likelihood that the liver event is related to study drug. Restarts should be limited to cases in which there is clear evidence that the underlying cause of the liver event is not related to study drug.**

DRUG RECHALLENGE

Background: Following drug-induced liver injury, drug rechallenge is associated with a 13% mortality across all drugs in prospective studies [Andrade, 2009]. Clinical outcomes vary by drug, with nearly 50% fatality with halothane re-administered within one month of initial injury. However, some drugs seldom result in recurrent liver injury or fatality.

Risk factors for a fatal drug rechallenge outcome include:

- hypersensitivity [Andrade, 2009] with initial liver injury (e.g. fever, rash, eosinophilia)
- jaundice or bilirubin >2xULN with initial liver injury (direct bilirubin >35% of total)
- participant currently exhibits severe liver injury defined by: ALT≥3xULN, bilirubin ≥2xULN (direct bilirubin >35% of total), or INR≥1.5
- prior serious adverse event or fatality has earlier been observed with drug rechallenge [Papay, 2009; Hunt, 2010]
- evidence of drug-related nonclinical liability (e.g. reactive metabolites; mitochondrial impairment [Hunt, 2010])

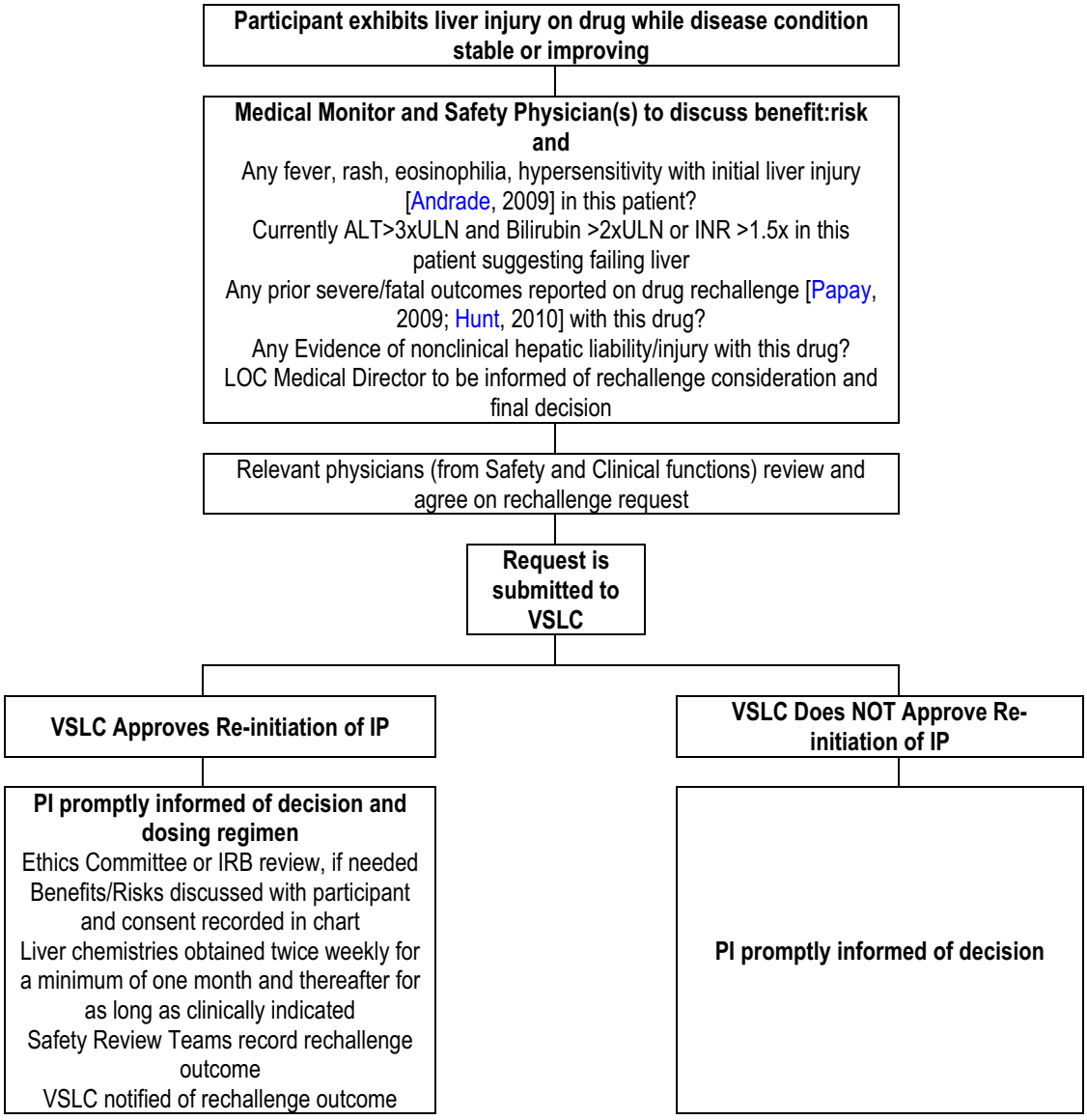
10.3.2. VSLC Decision Process for Drug Rechallenge Approval or Disapproval

- Principal Investigator (PI) requests consideration of drug rechallenge for a participant receiving compelling benefit from a critical or life-saving drug, who exhibits liver chemistry elevation meeting participant stopping criteria in relation to DILI, with no alternative treatment
- By definition treatment naïve participants will only be considered for rechallenge if they were infected with a multi-resistant virus.
- Medical Monitor and Global Clinical Safety and Pharmacovigilance (GCSP) Physician review the participant's rechallenge risk factors (consultation with the Hepatotoxicity Panel is available) and complete checklist (Table 13).
- The local operating company (LOC) medical directors (ViiV and/or GSK where applicable) should be informed that study drug rechallenge is under consideration and of the final decision, whether or not to proceed.
- The Medical Monitor and GCSP Physician are accountable to review and agree on the following prior to preparing request for rechallenge documentation for presentation to VSLC:
  - Compelling benefit of the investigational product (IP) for this participant and no alternative therapy
    - ***must present source data defining the patient's current resistance profile with documented evidence of extensive drug resistance and previous drug history***
- Relative benefit-risk of drug rechallenge, with consideration of the following high risk factors:
  - Initial liver injury event included: fever, rash, eosinophilia, or bilirubin ≥2xULN (or direct bilirubin >35% of total, if available)
  - Participant currently exhibits severe liver injury defined by: ALT >3xULN, bilirubin >2xULN (direct bilirubin >35% of total, if available), or INR>1.5
  - SAE or fatality has earlier been observed with IP rechallenge
  - IP is associated with known nonclinical hepatic liability/ injury
- Relevant physicians (listed below) must review and agree on action to be taken regarding request for drug rechallenge:
  - Safety Review Team Leader, Safety Development Leader, or Senior Safety Physician
  - Medicines Development Leader (MDL) and Project Physician Leader (PPL)
- Request is taken to full VSLC for final decision

Table 13 Checklist for drug rechallenge for critical medicine (Following drug-induced liver injury, drug rechallenge is associated with 13% mortality across all drugs in prospective studies)

	Yes	No
Compelling benefit of IP for this participant and no alternative therapy. **Provide brief explanation**:		
Relative benefit-risk favorable for drug rechallenge, after considering the **following high risk factors**:		
Initial liver injury event included:		
fever, rash, eosinophilia, or hypersensitivity		
bilirubin≥2xULN (direct bilirubin >35% of total)		
Participant currently exhibits ALT >3xULN, bilirubin >2xULN (direct bilirubin >35% of total, if available), or INR>1.5		
SAE or fatality has earlier been observed with IP rechallenge If yes, please provide brief explanation:		
IP associated with known nonclinical hepatic liability/ injury		
Source data defining the patient's current resistance profile		
Previous drug history		

Figure 5 VSLC process for drug rechallenge approval or disapproval



DRUG RESTART

"Drug restart" can be approved by the VSLC for **transient, defined non-drug-induced** liver injury if no evidence of:

- immunoallergic injury /HLA association with injury
- alcoholic hepatitis

Study drug must be held while labs and evaluation are completed to assess diagnosis.

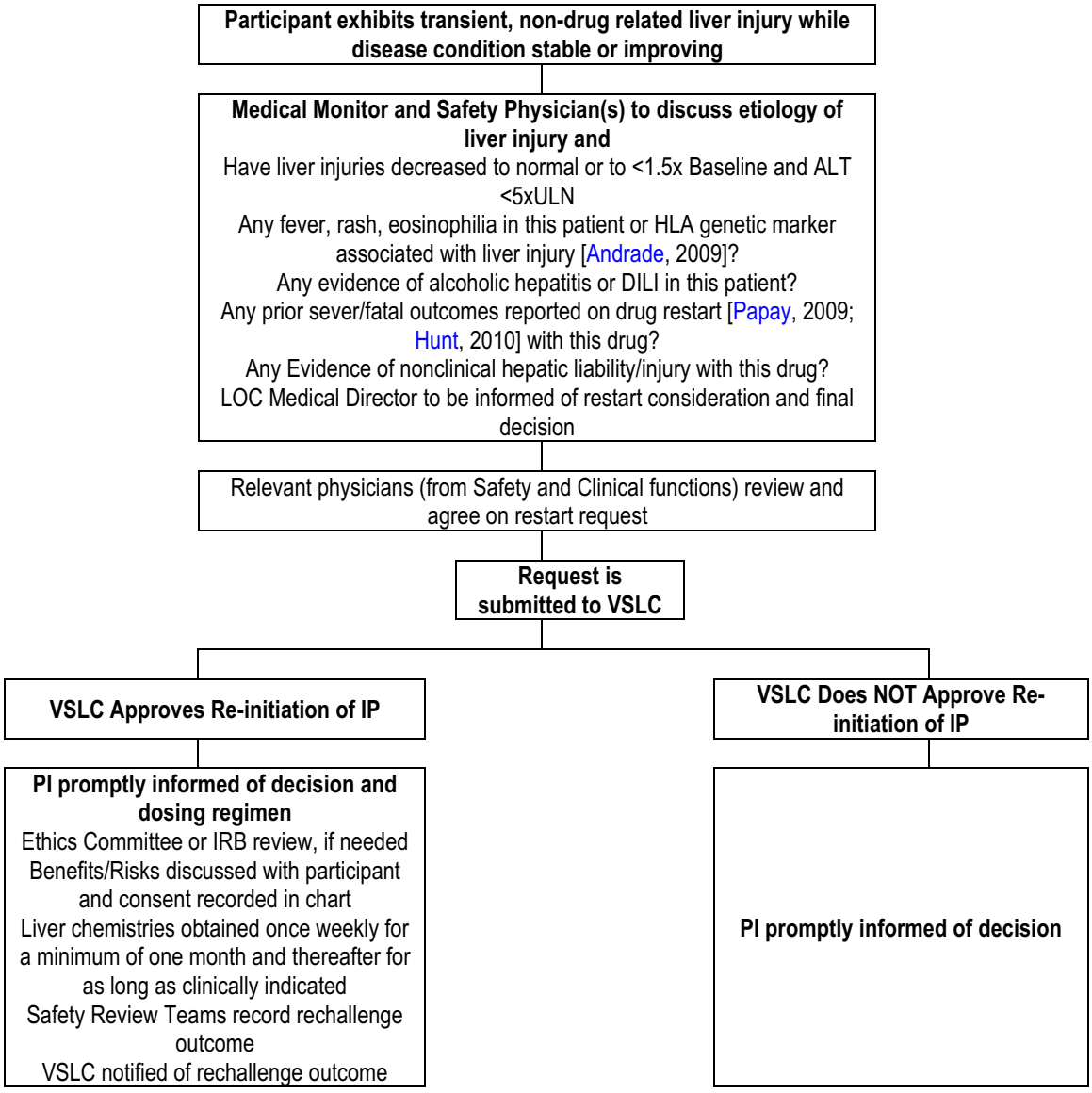
10.3.3. VSLC Decision Process for Drug Restart Approval or Disapproval

- Principal Investigator (PI) requests consideration of drug re-initiation for a participant stable or improving on IP, who exhibits liver chemistry elevation meeting participant stopping criteria, which is transient, non-drug-related, and liver chemistries have improved to normal or are within 1.5x baseline and ALT< 5xULN.
- GSK Medical Monitor and GCSP Physician to review the participant's diagnosis restart risk factors (Hepatotoxicity Panel consultation is available) and complete checklist (Table 14).
  - ***must present source data defining the patient's current resistance profile with documented evidence of extensive drug resistance and previous drug history***.
- The local operating company (LOC) medical director should be informed that study drug restart is under consideration and of the final decision, whether or not to proceed.
- Relevant physicians (listed below) must review and agree on action to be taken regarding request for drug restart:
- Safety Review Team Leader, Safety Development Leader, or Senior Safety Physician
- MDL and PPL
- Request is taken to VSLC for final decision

Table 14 Checklist for Phase III drug restart after well-explained liver injury (e.g. biliary, pancreatic, hypotensive events, congestive heart failure (CHF), acute viral hepatitis), and improvement of liver chemistry to normal or ≤1.5x baseline & ALT<5xULN

	Yes	No
Is participant stable or improving on IP?		
Do not restart if the **following risk factors at initial liver injury**:		
fever, rash, eosinophilia, or hypersensitivity		
drug-induced liver injury		
alcoholic hepatitis (AST>ALT, typically <10xULN)		
IP has an HLA genetic marker associated with liver injury (e.g. lapatinib, abacavir, amoxicillin/clavulanate)		
Source data defining the patients current resistance profile		
Previous drug history		

Figure 6 VSLC process for drug restart approval or disapproval



10.3.4. Medical monitor, GCSP Physician and PI actions for Restart or Rechallenge following VSLC decision

10.3.5. Medical Monitor and GCSP Physician Actions

- Medical Monitor must notify PI of VSLC's rechallenge (or restart) decision and recommended dosing regimen in writing and Medical Monitor must record note in study files.
- The Safety Review Team must record rechallenge (or restart) outcomes and the GCSP Physician must send these to the VSLC (see template below).
- All severe reactions (rechallenge associated with bilirubin>2xULN or jaundice, or INR≥1.5), SAEs or fatalities which occur following a drug rechallenge (or restart) must be immediately reported to Line Management including, VSLC

Chair, VP Global Medical Strategy and EU Qualified Person for Pharmacovigilance.

10.3.6. PI Actions:

- The PI must obtain Ethics Committee or Institutional Review Board approval of drug rechallenge or restart, as required.
- If VSLC approves drug rechallenge or restart, the patient must sign a new informed consent containing a clear description of possible benefits and risks of drug administration including recurrent, more severe liver injury or possible death.
- ***Targeted drug rechallenge or drug restart consent form must be used.***
- The patient's informed consent must be recorded in the study chart, and the drug administered at agreed dose, as communicated by Medical Monitor.
- Liver chemistries must be followed ***twice weekly for 'rechallenge' cases*** and ***once weekly for 'restart' cases*** for a minimum of one month and thereafter for as long as clinically indicated following drug re-initiation. If participant exhibits protocol-defined liver chemistry elevations, IP should be discontinued as protocol specified.
- Medical Monitor and the Ethics Committee or Institutional Review Board must be informed of the patient's outcome following drug rechallenge or restart.

Drug Rechallenge or Drug Restart Outcomes Table Template

To be completed/updated and provided to VSLC with each event recorded across studies and indications

Drug Rechallenge/Restart Outcomes Table – Update with each event

Protocol#	Participant#	Rechallenge or Restart?	Safety outcome*	Drug benefit

Rechallenge/restart safety outcomes:

0 = no liver chemistry elevation

1 = recurrent liver chemistry elevation not meeting participant stopping criteria

2 = recurrent liver chemistry elevation meeting participant stopping criteria

3 = serious adverse event

4 = fatality

10.4. Appendix 4: CDC Classification for HIV-1 Infection (2014)

Note that the CD4+ T-lymphocyte count takes precedence over the CD4+ T-lymphocyte percentage in HIV infection stages 1, 2, and 3. The CD4+ T-lymphocyte should only be considered if the count is missing.

HIV infection, stage 0

Indicates early HIV infection, inferred from a negative or indeterminate HIV test result within 180 days of a positive result. The criteria for stage 0 supersede and are independent of criteria used for other stages.

HIV infection, stage 1

- Laboratory confirmation of HIV infection with no AIDS-defining condition, and
    - CD4+ T-lymphocyte count of ≥500 cells/μL, or
    - CD4+ T-lymphocyte percentage of total lymphocytes of ≥26%.

HIV infection, stage 2

- Laboratory confirmation of HIV infection with no AIDS-defining condition, and
    - CD4+ T-lymphocyte count of 200 to 499 cells/μL, or
    - CD4+ T-lymphocyte percentage of total lymphocytes of 14% to 25%.

HIV infection, stage 3 (AIDS)

- Laboratory confirmation of HIV infection, and
    - CD4+ T-lymphocyte count of <200 cells/μL, or
    - CD4+ T-lymphocyte percentage of total lymphocytes of <14%, or
    - Documentation of an AIDS-defining condition (see below).

Documentation of an AIDS-defining condition supersedes a CD4+ T-lymphocyte count of >200 cells/μL and a CD4+ T-lymphocyte percentage of total lymphocytes of >14%.

HIV infection, stage unknown

- Laboratory confirmation of HIV infection, and
    - No information on CD4+ T-lymphocyte count or percentage, and
    - No information on presence of AIDS-defining conditions.

Stage-3-defining opportunistic illnesses in HIV infection

- Candidiasis of bronchi, trachea, or lungs
- Candidiasis of oesophagus
- Cervical cancer, invasive

- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (>1 month's duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age >1 month
- Cytomegalovirus retinitis (with loss of vision)
- Encephalopathy, HIV-related
- Herpes simplex: chronic ulcers (>1 month's duration) or bronchitis, pneumonitis, or oesophagitis (onset at age >1 month)
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (>1 month's duration)
- Kaposi's sarcoma
- Lymphoma, Burkitt's (or equivalent term)
- Lymphoma, immunoblastic (or equivalent term)
- Lymphoma, primary, of brain
- Mycobacterium avium complex or Mycobacterium kansasii, disseminated or extrapulmonary
- Mycobacterium tuberculosis of any site, pulmonary, disseminated or extrapulmonary
- Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
- Pneumocystis jirovecii pneumonia
- Pneumonia, recurrent
- Progressive multifocal leukoencephalopathy
- Salmonella septicaemia, recurrent
- Toxoplasmosis of brain, onset at age >1 month
- Wasting syndrome attributed to HIV.

Reference

CDC. Revised Surveillance Case Definition for HIV Infection – United States, 2014. MMWR 2014; 63 (RR-03);1-10.

10.5. Appendix 5: Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

10.5.1. Definition of Adverse Events

Adverse Event Definition:
• An AE is any untoward medical occurrence in a patient or clinical investigation participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

Events <u>meeting</u> AE definition include:
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae). • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE.

Events <u>NOT</u> meeting definition of an AE include:
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the

participant's condition.

- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.5.2. Definition of Serious Adverse Events

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease, etc.).

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:

Results in death

Is life-threatening

NOTE:

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

Requires hospitalization or prolongation of existing hospitalization

NOTE:

- In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

Results in disability/incapacity

NOTE:

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.

- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption

Is a congenital anomaly/birth defect

Other situations:

- Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious.
- Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse

Is associated with liver injury <u>and</u> impaired liver function defined as:

- ALT ≥ 3xULN and total bilirubin* ≥ 2xULN (>35% direct), **or**
- ALT ≥ 3xULN and INR** > 1.5.

* Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥ 3xULN and total bilirubin ≥ 2xULN, then the event is still to be reported as an SAE.

** INR testing not required per protocol and the threshold value does not apply to participants receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.

10.5.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:

Investigators will be required to fill out the specific CV event page of the eCRF for the following AEs and SAEs:

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias
- Valvulopathy
- Pulmonary hypertension

- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularization

10.5.4. Recording of AEs and SAEs

AEs and SAE Recording:

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event.
- The investigator will then record all relevant information regarding an AE/SAE in the eCRF
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK, AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records prior to submission to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms.

10.5.5. Evaluating AEs and SAEs

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and will assign it to one of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities
- Severe: An event that prevents normal everyday activities. - an AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least one of the pre-defined outcomes as described in the definition of an SAE.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and the occurrence of each AE/SAE.
- A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated.
- The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in the determination of his/her assessment.
- For each AE/SAE the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to GSK.**
- The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by GSK to elucidate as fully as possible the nature and/or causality of the AE or SAE.
- The investigator is obligated to assist. This may include additional laboratory tests or investigations, histopathological examinations or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings, including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to GSK within the designated reporting time frames.

10.5.6. Reporting of SAEs to GSK

SAE reporting to GSK via electronic data collection tool
• Primary mechanism for reporting SAEs to GSK will be the electronic data collection tool • If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and fax it to the Medical Monitor. • Site will enter the serious adverse event data into the electronic system as soon as it becomes available. • The investigator will be required to confirm review of the SAE causality by ticking the 'reviewed' box at the bottom of the eCRF page within 72 hours of submission of the SAE. • After the study is completed at a given site, the electronic data collection tool (e.g., InForm system) will be taken off-line to prevent the entry of new data or changes to existing data • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information on a paper SAE form or to the Medical Monitor by telephone. • Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.
SAE reporting to GSK via paper CRF
• Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the Medical Monitor or the SAE coordinator • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable, with a copy of the SAE data collection tool sent by overnight mail • Initial notification via the telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames. • Contacts for SAE receipt can be found at this beginning of the protocol on the Sponsor/Medical Monitor Contact Information page.

10.6. Appendix 6: Toxicity Management

10.6.1. Treatment Interruption Due to an Adverse Event

IP may be interrupted at the discretion of the Investigator and according to the severity of the AE. If one or more antiretroviral medications is held due to toxicity or adverse events, all antiretroviral medications must be held to reduce the risk of development of resistance taking into account both the length of the planned interruption and the pharmacokinetic half-life of each antiretroviral of the regimen, in a way to minimize the risk of development of resistance.

No toxicity-related dose reductions of IP will be allowed. IP should be restarted as soon as medically appropriate; in general, for oral dosing, this should be no longer than 14 days after discontinuation (unless Grade 3 or 4 toxicities persist). Any interruption in therapy during the Maintenance Phase, oral dosing, of greater than 7 consecutive days must be discussed with and agreed by the Medical Monitor prior to resumption of therapy. The Medical Monitor must be contacted upon becoming aware of resumption in therapy, if therapy was resumed without prior approval. **IM dosing is expected to occur during the week in which the participant's projected visit falls (as according to the date of the first injection visit [Month 1]). A +0 / -7 day window is stipulated around the projected dosing date for dosing injections at Month 2 and Month 3. A +7 / -7 day window, from the projected visit date, is allowable from the fourth injections forward for IM dosing but not preferred.** Any interruption outside of this guidance MUST be discussed with the Medical Monitor prior to reinitiating IM IP.

Guidance is provided below on general participant management and IP interruptions based on the severity of the AE. All changes in the IP regimen must be accurately recorded in the participant's eCRF.

10.6.2. Liver Chemistry Stopping and Follow-up Criteria

Liver chemistry threshold stopping criteria have been designed to assure participant safety and to evaluate liver event etiology during administration of study drug and the follow-up phase (See also Section 10.3, Appendix 3). All Phase 3 participants who meet liver stopping criteria will be adjudicated by the ViiV Safety and Labelling Committee (VSLC) – resulting in a case summary, adjudication, and management plan. The VSLC contains an external expert hepatologist, familiar with both DILI and cabotegravir, who will participate in this review. This committee meets on a 3-weekly basis, and can be convened on an ad hoc basis as needed.

Drug Restart Following Transient Resolving Liver Events Not Related to Study Drug

Approval by VSLC for drug restart can be considered where:

Liver chemistries have a clear underlying cause (e.g., biliary obstruction, hypotension, and liver chemistries have improved to normal or are within 1.5 × baseline and ALT <3 × ULN). Ethics Committee or IRB approval of drug restart must be obtained, as required.

If restart of drug is approved by VSLC in writing, the participant must be provided with a clear description of the possible benefits and risks of drug administration, including the possibility of recurrent, more severe liver injury or death.

The participant must also provide signed informed consent specifically for the restart. Documentation of informed consent must be recorded in the study chart.

Study drug must be administered at the dose specified by VSLC.

Participants approved by VSLC for restarting study drug must return to the clinic once a week for liver chemistry tests for a minimum of one month and thereafter for as long as clinically indicated and then laboratory monitoring may resume as per protocol. If protocol defined stopping criteria for liver chemistry elevations are met, study drug must be stopped.

Refer to Section 10.2, Appendix 2, U.S. Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases, Division of AIDS. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1. [March 2017]. Available from: https://rsc.tech-res.com/docs/default-source/safety/daids-ae-grading-table-mar2017.pdf

Refer to Section 10.3.3: Liver Safety – Study Treatment Restart Guidelines for further details.

10.6.3. Grade 1 or Grade 2 Toxicity/Adverse Event

Participants who develop a Grade 1 or Grade 2 AE or toxicity may continue IP at the discretion of the Investigator. (NOTE: See Section 10.6 Appendix 6, Specific Toxicities/Adverse Event Management" for exceptions to this guideline). Participants who choose to withdraw from study due to a Grade 1 or 2 AE should have study withdrawal and follow-up evaluations completed.

Participants who develop ALT ≥3 times ULN while on study must consult with Medical Monitor prior to initiation or continuation of CAB LA and RPV LA.

10.6.4. Grade 3 Toxicity/Adverse Event

Participants who develop a Grade 3 AE or toxicity should be managed as follows:

- If the Investigator has compelling evidence that the Grade 3 AE or toxicity has not been caused by IP, dosing may continue after discussion with the Medical Monitor.
- Participants who develop a Grade 3 AE or toxicity, which the Investigator considers related or possibly related to the IP, should have the IP withheld and be rechecked each week until the AE returns to Grade 2. Once the AE is Grade ≤2, IP may be re-started.
- Should the same Grade 3 AE recur within 28 days in the same participant, the IP should be permanently discontinued and the participant withdrawn from study.

- Participants experiencing Grade 3 AEs requiring permanent discontinuation of IP should be followed weekly until resolution of the AE and to have withdrawal study evaluations completed. A follow-up visit should be performed 4 weeks after the last dose of IP. Any participant receiving at least one dose of CAB LA and /or RPV LA who discontinue IP / Withdraw will initiate treatment with HAART and enter the Long-Term Follow-Up Phase for 52 weeks of follow up.
- Participants with Grade 3 asymptomatic laboratory abnormalities should be investigated for all potential non-drug related causes, and, following discussion with the Medical Monitor, may continue IP if the Investigator has compelling evidence that the toxicity is not related to IP, with the exception of liver chemistry stopping criteria (See Section 10.6.2). Isolated Grade 3 lipid abnormalities do not require withdrawal of IP.

10.6.5. Grade 4 Toxicity/Adverse Event

- Participants who develop a Grade 4 AE or toxicity must have IP permanently discontinued. However, if the Investigator has compelling evidence that the AE is not causally related to the IP, dosing may continue after discussion with and assent from the Medical Monitor. Participants should be rechecked each week until the AE returns to Grade 2.
- Participants experiencing Grade 4 AEs requiring permanent discontinuation of IP should be followed weekly until resolution of the AE and encouraged to complete the withdrawal and follow-up study evaluations as noted above. Any participant receiving at least one dose of CAB LA and /or RPV LA who discontinue IP / Withdraw will initiate treatment with HAART and enter the Long-Term Follow-Up Phase for 52 weeks of follow up.
- Participants with Grade 4 asymptomatic laboratory abnormalities should be investigated for all potential non-drug related causes, and, following discussion with the Medical Monitor, may continue therapy if the Investigator has compelling evidence that the toxicity is not related to IP, with the exception of liver chemistry stopping criteria. An in-clinic follow-up visit will be performed approximately 4 weeks after the last dose of study medication if AEs, SAEs, or laboratory abnormalities considered potentially harmful to the participant are ongoing at the last on-study visit. Isolated Grade 4 lipid abnormalities do not require withdrawal of IP.

Participants should permanently discontinue study drug [and all other concurrent medication(s) suspected in the Investigators causality assessment] for an isolated Grade 3 or 4 rash, except where the etiology of the rash has been definitively diagnosed as NOT attributable to study drug (see below), and the participant should be withdrawn from the study. Participants should be treated as clinically appropriate and followed until resolution of the AE. Every effort should be made to collect as much information as possible about the evolution of the event and any relationship with potentially related medical events (e.g., viral infection) or start of concomitant medication.

The rash and any associated symptoms should be reported as adverse events and appropriate toxicity ratings should be used to grade the events (based on DAIDS toxicity gradings – see Section 10.2 Appendix 2).

However, if the etiology of the rash has been definitively diagnosed as being unrelated to study drug and due to a specific medical event or a concomitant infection or a concomitant non-study medication, routine management should be performed and documentation of the diagnosis provided. In this situation, the study drug should be continued.

Participants in the Follow-Up Phase who are receiving ABC as part of their regimen should be evaluated for the possibility of a clinically suspected ABC HSR and managed appropriately as outlined in the local prescribing information for ABC.

Any participant receiving at least one dose of CAB LA and /or RPV LA who discontinue IP / Withdraw will initiate treatment with HAART and enter the LTFU Phase for 52 weeks of follow-up.

10.6.6. Adverse Event Management

10.6.6.1. Diarrhea

Participants with Grade 1 or 2 diarrhea may continue study treatment without interruption. Participants with diarrhea of any toxicity grade may be treated symptomatically with anti-motility agents; however, the recommended daily dose of the chosen anti-motility agent must not be exceeded. If symptoms persist or get worse on the recommended daily dose of the chosen anti-motility agent then the anti-motility agent must be discontinued and consultation made with the Medical Monitor.

For participants with Grade ≥3 diarrhea that is unresponsive to the recommended dose of the anti-motility agents and for which an alternative etiology (e.g., infectious diarrhea) is not established, the treatment with the anti-motility agent and IP must be interrupted until resolution of diarrhea to Grade ≤2 or Baseline, after which IP and background ART may be resumed after discussion and agreement with the Medical Monitor. If Grade ≥3 diarrhea recurs within 28 days upon the resumption of IP, the IP should be permanently discontinued and the participant withdrawn from the study. Any participant receiving at least one dose of CAB LA and /or RPV LA who discontinue IP / Withdraw will initiate treatment with HAART and enter the LTFU Phase for 52 weeks of follow up.

If loperamide is used for treatment of diarrhea, local prescribing information should be followed with respect to dose and frequency of administration. Loperamide dosing should not exceed local prescribing information.

10.6.6.2. Hypertriglyceridemia/ Hypercholesterolemia

Samples for lipid measurements **must** be obtained in a fasted state according to the Schedule of Activities, Section 1.5. Participants who experience asymptomatic triglyceride or cholesterol elevations may continue to receive IP. Clinical management of participants with hypertriglyceridemia/hypercholesterolemia should **not** be based upon

non-fasting samples (obtained in the fed state). A confirmatory fasting triglyceride and/or cholesterol level should be obtained prior to the institution of medical therapy for hyperlipidemia. Isolated Grade 3 and Grade 4 lipid abnormalities do not require withdrawal of IP.

Please see the Recommendations of the Adult AIDS Clinical Trial Group Cardiovascular Disease Focus Group [for full discussion of management of hyperlipidemia in the context of HIV therapy.

10.6.6.3. Seizures

Several cases of seizure have occurred during the cabotegravir program. These cases have alternate explanations for their occurrence. ViiV Healthcare has reviewed these cases in detail and does not believe they constitute a reasonable likelihood of causation associated with CAB. This assessment is supported by the lack of preclinical signal, class effect or known CNS mechanism, the relatively low frequency of seizures relative to expected rates in both healthy and HIV positive participants and clinical confounders in each case. The Sponsor considers the risk of developing seizures on the study as being no higher than that of the rest of the HIV-1 infected population.

Overall, there is not convincing evidence that cabotegravir 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. However, seizure and seizure-like events are considered as AEs of special interest for close monitoring in studies. Subjects with an unstable or poorly controlled seizure disorder will be excluded from study participation.

Seizures that occur on study should be managed according to the local guidelines on emergency seizure management which may include treatment with benzodiazepines, general supportive treatment, exclusion of metabolic and toxicological abnormalities using laboratory tests, septic workup and excluding underlying structural abnormalities with neuroimaging.

Where seizures occur, the Sponsor would like to better characterize these occurrences to enable systematic analyses.

Investigators are requested to document and report seizure or possible seizure events promptly (within 24 hours of learning of the event) to the Sponsor for evaluation and onward reporting. Data should be documented on the appropriate eCRF seizure page.

10.6.6.4. Creatine Phosphokinase (CPK) Elevation

A Grade 3 or higher elevation in CPK should result in a repeat assessment within 2-4 weeks to ensure the result is transient or due to exercise and will not require a change in study treatment. A history regarding use of drugs known to cause increase of CPK (such as statins) physical activity or exercise preceding the CPK evaluation should be obtained.

Grade 4 elevations in CPK should have a repeat assessment after the participant has abstained from exercise for >24 hours. For persistent Grade 4 CPK elevations that are considered possibly or probably related to the IP, IP should be discontinued and the participant withdrawn from the study. Any participant receiving at least one dose of CAB LA and /or RPV LA who discontinue IP / Withdraw will initiate treatment with HAART enter the LTFU Phase for 52 weeks of follow-up.

10.6.6.5. Lipase Elevations and Pancreatitis

Participants with asymptomatic Grade 1 or 2 elevations in lipase may be followed closely for the development of symptoms.

Participants with asymptomatic Grade ≥3 elevations in lipase that are considered possibly or probably related to IP should have IP interrupted until serum lipase returns to Grade ≤2. The lipase assay should be repeated within 2 weeks of any Grade ≥3 result. Participants with persistence of Grade ≥3 lipase in the absence of other diagnoses or reoccurrence of lipase elevation (at Grade ≥2) following reintroduction of IP should permanently discontinue IP.

Participants with a confirmed diagnosis of clinical pancreatitis that is considered possibly or probably related to IP should have IP held. After complete resolution of the episode, participants may be re-challenged with IP after discussion with the Medical Monitor, only if the Investigator has compelling evidence that the event was not caused by IP. Upon re-challenge, lipase determinations should be performed every 2 weeks for at least 6 weeks after re-initiation of treatment. With any elevation of lipase of Grade ≥2 or any recurrence of symptoms, the participant should discontinue IP and be withdrawn from study.

Any participant receiving at least one dose of CAB LA and /or RPV LA who discontinue IP / Withdraw will initiate treatment with HAART and enter the LTFU Phase for 52 weeks of **follow up.**

10.6.6.6. Decline in Renal Function

Participants who experience an increase in serum creatinine from Baseline of 45 micromoles/liter (μMol/L) (or 0.5 milligrams/deciliter [mg/dL]) should return for a confirmatory assessment within 2 to 4 weeks. A urinalysis and urine albumin/creatinine and urine total protein/albumin ratios should also be done at this confirmatory visit. If the creatinine increase is confirmed, the investigator should contact the study medical monitor to discuss additional follow-up and medical management.

Participants who have a decline in the estimated GFR (using the CKD-EPI method) of >50% from Baseline must return for a confirmatory assessment as soon as possible [Levey, 2009]. A urinalysis and urine albumin/creatinine and urine protein/creatinine ratios should also be done at this confirmatory visit. If the estimated GFR has declined by >50% (confirmed), then study drug should be withheld and the investigator should contact the study medical monitor to discuss the rationale for restarting study drugs (if appropriate). Consideration for confounding factors (e.g., background therapy, other

medications, dehydration, concurrent conditions) should be taken into account, and a nephrology consult may be obtained.

10.6.6.6.1. Proximal Renal Tubule Dysfunctions (PRTD)

PRTD is defined as:

Confirmed rise in serum creatinine of ≥0.5 mg/dL from Baseline AND serum phosphate <2.0 mg/dL;

Either of the above accompanied by any two of the following:

Glycosuria (≥250 mg/dL) in a non-diabetic;

Low serum potassium (<3 mEq/L);

Low serum bicarbonate (<19 mEq/L).

Participants meeting criteria for PRTD must return for a confirmatory assessment within 2 weeks of diagnosis. A urinalysis should also be performed at the time of the confirmatory assessment. If PRTD is confirmed participants should have study drug withheld and the investigator should contact the Study medical monitor to discuss the rationale for restarting study drugs (if appropriate). Consideration for confounding factors (e.g., NRTI backbone, other medications, dehydration, concurrent conditions) should be taken into account, and a nephrology consult may be obtained. If study drug is reinitiated, it should have been withheld for no more than 4 weeks.

10.6.6.7. Proteinuria

Participants with an abnormal urine microalbumin/creatinine ratio (>0.3 mg/mg, >300 mg/g, or >34 mg/mmol) that represents a change from Baseline and no associated increase in creatinine, should have a repeat spot urine microalbumin/creatinine ratio performed within 2-4 weeks. If confirmed, then consideration should be given to additional evaluation after consultation with the study medical monitor. Additional evaluation may include a 24-hour urine protein and creatinine measurement and nephrology referral.

Participants with an abnormal urine albumin/creatinine ratio (>0.3 mg/mg, 300 mg/g, or >34 mg/mmol and representing a change from Baseline) and a serum creatinine increase >45 µmol/L (or 0.5 mg/dL) should have confirmation of both results within 2 weeks. If confirmed, the study medical monitor should be contacted immediately. Agreement on further management should be agreed between the investigator and medical monitor.

10.6.6.8. QTc Prolongation

Participants with an average QTc interval >550 msec from three or more tracings separated by at least 5 minutes should have IP discontinued. These criteria are based on an average QTc value of triplicate ECGs. If an ECG demonstrates a prolonged QT interval, obtain 2 more ECGs over a brief period (~5-10 minutes) and use the averaged QTc values of the 3 ECGs to determine whether the participant should be discontinued

from the study. If an alternative cause of the QT prolongation is determined (e.g., participant receiving drug known to cause prolonged QT or TdP), then IP may be restarted after consultation with, and agreement by, the Medical Monitor.

10.6.6.9. Injection Site Reactions (ISRs)

Injection site reactions will be managed through investigator assessment throughout the study. All ISRs that are either serious, Grade 3 or higher, or persisting beyond 2 weeks must be discussed with the Medical Monitor to determine etiology and assess appropriate continued study participation.

Digital photographs may be documented where possible on all participants who have an injection site reaction, with observable findings, that is either serious or Grade 3 or higher, or that persists beyond 2 weeks. Dermatology will be consulted on all participants who have an injection site reaction considered serious, Grade 3 or above, or if clinically significant and persistent beyond 30 days and others if the Investigator or Medical Monitor feels it is medically necessary.

Details regarding photo collection and any other follow up will be given by the Medical Monitor at the time of assessment.

ISR discomfort can be managed symptomatically (e.g., cold/warm compress, acetaminophen, ibuprofen) if the reaction is interfering with the participant's ability to perform activities of daily living. The required intervention should be documented on the appropriate eCRF page.

10.6.6.10. Allergic reaction

Participants may continue study drug for Grade 1 or 2 allergic reactions at the discretion of the Investigator. The participant should be advised to contact the Investigator immediately if there is any worsening of symptoms or if further systemic signs or symptoms develop. Antihistamines, topical corticosteroids, or antipruritic agents may be prescribed.

Participants with Grade ≥3 allergic reactions that are considered to be possibly or probably related to the study drug should permanently discontinue the CAB LA + RPV LA regimen and the participant should be withdrawn from the study. Participants should be treated as clinically appropriate and followed until resolution of the AE.

10.6.6.10.1. Rash Without HSR Symptoms

Including serious skin reactions such as Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, Erythema Multiforme or rash with significant liver dysfunction.

Participants should be instructed to contact the Investigator as soon as possible if they develop a rash on study.

As many products also cause rash and/or serious skin reactions, all other medicinal products that the participant is receiving should also be reviewed and discontinued as appropriate.

The following guidance is provided for clinical management of participants who experience rash alone in the absence of systemic or allergic symptoms or signs of mucosal or target lesions.

CAB is an analogue of DTG and mild to moderate rash is an expected adverse reaction for DTG-containing ART. Episodes generally occur within the first 10 weeks of treatment, rarely require interruptions or discontinuations of therapy and tend to resolve within two to three weeks. No instances of serious skin reaction, including SJS, TEN and erythema multiforme, have been reported for DTG in clinical trials. For further characterization of HSR and rash observed with DTG-containing ART, please see the current version of the IB [GlaxoSmithKline Document Number RH2009/00003/07].

Rash is an adverse drug reaction (ADR) for RPV. In clinical trials, most rashes emerged during the first 4 weeks of treatment, were transient, and usually mild (Grade 1) to moderate (Grade 2). There were no Grade 4 rashes and none were serious. Treatment-related Grade 3 rash was reported in 0.1% of participants in the RPV group. Treatment-related rash led to permanent discontinuation in 0.1% of participants in the RPV group. No cases of erythema multiforme, SJS or TEN have been reported during clinical development of RPV.

Participants with an isolated Grade 1 rash may continue study drug at the Investigator's discretion. The participant should be advised to contact the Investigator immediately if there is any worsening of the rash, if any systemic signs or symptoms appear, or if mucosal involvement develops.

Participants may continue study drug for an isolated Grade 2 rash. However, study drug (and all other concurrent medication(s) suspected in the Investigators causality assessment) should be permanently discontinued for any Grade ≥2 rash that is associated with an increase in ALT. The participant should be advised to contact the physician immediately if rash fails to resolve (after more than 2 weeks), if there is any worsening of the rash, if any systemic signs or allergic symptoms develop, or if mucosal involvement develops.

10.7. Appendix 7: Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Females of Reproductive Potential (FRP)

A female is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below)

Females in the following categories are not considered FRP

- Premenarchal
- Premenopausal female with ONE of the following:
- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's: review of participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal, highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 15.

Table 15 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen and progestogen-containing) hormonal contraception associated with inhibition of ovulation • oral • intravaginal • transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation • injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • bilateral tubal occlusion
Vasectomized partner *(A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the FRP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)*
Sexual abstinence (*Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*

NOTES:

a. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

Pregnancy Testing

- FRP should only be included after a confirmed menstrual period and a negative highly sensitive serum pregnancy test
- Additional pregnancy testing should be performed as per the study Schedule of Activities Table, Section 1.5. Pregnant participants who remain in the study do not need pregnancy testing during the study, for the duration of their pregnancy.

- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected
- Pregnancy testing will be performed and assayed in the central laboratory OR using the test kit provided by the central laboratory / provided by the sponsor /approved by the sponsor and in accordance with instructions provided in its package insert.
- If pregnancy is confirmed, please see Appendix 8 for details regarding allowing pregnant participants to remain in the study

Collection of Pregnancy Information

The Investigator will collect pregnancy information on **any** participant who becomes pregnant while participating in this study. See Appendix 8 and Section 10.8.1for information to be collected for participants who become pregnant while participating in this study.

Participants who become pregnant while in the study may remain in study and continue scheduled dosing with CAB + RPV LA, once a pregnancy specific ICF addendum is signed by the participant. See Appendix 8 for additional data and information regarding the management of participants who remain in the study while pregnant.

10.8. Appendix 8: Information and Guidance for Managing Pregnant Participants

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10.8.1. Collection of Pregnancy Information

The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study.

- Information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on mother and infant, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in the protocol in Section 10.5.6, Appendix 5. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Females who become pregnant while in the study may remain in study, and continue scheduled dosing with CAB + RPV LA, once a pregnancy ICF addendum is signed by the participant.

10.8.2. Introduction

Pregnancy increases the risk of HIV progression, while HIV increases the risk for maternal complications from pregnancy and poses the risk of perinatal HIV transmission to the unborn fetus. Mother to child transmission (MTCT) of HIV can occur during pregnancy, labor, delivery or postpartum through breastfeeding. In the absence of any interventions, vertical HIV transmission rates approximate 35%, but fall below 5% with effective interventions [WHO, 2010]. In the United States and other developed countries, the risk of perinatal infection has decreased from 25% without intervention to less than 2% with intervention [WHO, 2012]. The HIV-infected mother who breastfeeds her infant while taking ARVs herself or giving ARVs to her infant reduces the risk of transmission to about 2% after 6 months of breastfeeding, or 4% over 12 months [UNAIDS, 2011].

The 2013 WHO Guidelines thus recommend (strong recommendation, moderate-quality evidence) all pregnant and breastfeeding women with HIV should initiate triple ARVs (ART), which should be maintained at least for the duration of mother-to-child transmission risk. Women meeting treatment eligibility criteria should continue lifelong

ART [WHO, 2013]. The global benefits anticipated from ART in pregnant women who are eligible for treatment include treatment of the mother's underlying HIV disease, eliminating pediatric transmission/infection and reducing sexual transmission of HIV

Recent recommendation updates to treatment guidelines have included objectives to increase HIV screening of patients, including pregnant women (noting the importance of adopting HIV screening to be a part of prenatal care).

The ART recommendation for pregnant females prioritizes the health of women over potential risks and increased cost. For females who are on ARV therapy at the time that they become pregnant, the World Health Organization recommends that they continue such therapy if they are responding to the ARV.

In line with this recommendation, this study will allow those females participating in 209493 who are receiving CAB + RPV LA but become pregnant on study, to continue in the study in order to maintain their effective regimen with minimal disruption. The PK of CAB + RPV LA, characterization of the safety of CAB + RPV LA administered during pregnancy, and characterization of maternal, birth and infant outcomes following treatment with CAB + RPV LA will be examined.

10.8.3. Background

At the time of finalizing this protocol, there have been 25 pregnancies reported during the CAB/RPV LA P3 development program (including 6 during PK tail and 5 during OLI) with 8 pregnancies leading to live births (including 3 pregnancies exposed during the PK tail of treatment and 1 pregnancy exposure occurring during CAB oral lead-in) and 5 on-going pregnancies.

- A total of 12 pregnancy losses (11 of these occurring during the first trimester)
- Missed abortions: 2 (one of these was a twin anembryonic pregnancy)
- Elective abortions (no medical indication): 5
- Elective abortion for nausea and vomiting: 1
- Spontaneous abortions: 4 (one late spontaneous abortion at 23/40; severe IUGR, placental insufficiency; presence of risk factors)

No reported congenital anomalies

10.8.4. Benefit/Risk Assessment

Discuss with pregnant participant the benefit-risk of continuing in the study and continuing to receive CAB + RPV LA injections, or being withdrawn from study, as a result of her pregnancy. All participants who chose to stay in the study during pregnancy, and who choose to continue to receive CAB + RPV LA injections will need to sign a pregnancy specific ICF addendum.

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to CAB + RPV LA (CABENUVA) during pregnancy. Healthcare providers are

encouraged to register all pregnant study participants, whether or not they choose to remain in the study, by calling the Antiretroviral Pregnancy Registry [Antiretroviral Pregnancy Registry (APR) Steering Committee] at 1-800-258-4263.

10.8.4.1. Cabotegravir

Cabotegravir use in pregnant females has not been evaluated and there are insufficient human data on the use of during pregnancy to adequately assess a drug-associated risk of birth defects and miscarriage.

The rate of miscarriage is not reported in the APR. The background risk for major birth defects and miscarriage for the indicated population is unknown. The background rate for major birth defects in a U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP) is 2.7%. The estimated background rate of miscarriage in clinically recognized pregnancies in the U.S. general population is 15% to 20%. The APR uses the MACDP as the U.S. reference population for birth defects in the general population. The MACDP evaluates women and infants from a limited geographic area and does not include outcomes for births that occurred at less than 20 weeks' gestation.

Animal Data (pre-clinical)

Cabotegravir was administered orally to pregnant rats at 0, 0.5, 5, or 1,000 mg/kg/day from 15 days before cohabitation, during cohabitation, and from Gestation Days 0 to 17. There were no effects on fetal viability when fetuses were delivered by caesarean although a minor decrease in fetal body weight was observed at 1,000 mg/kg/day (greater than 28 times the exposure in humans at the RHD). No drug-related fetal toxicities were observed at 5 mg/kg/day (approximately 13 times the exposure in humans at the RHD) and no drug-related fetal malformations were observed at any dose.

Cabotegravir was administered orally to pregnant rabbits at 0, 30, 500, or 2,000 mg/kg/day from Gestation Days 7 to 19. No drug-related fetal toxicities were observed at 2,000 mg/kg/day (approximately 0.7 times the exposure in humans at the RHD).

In a rat pre- and postnatal development study, cabotegravir was administered orally to pregnant rats at 0, 0.5, 5, or 1,000 mg/kg/day from Gestation Day 6 to Lactation Day 21. A delay in the onset of parturition and increases in the number of stillbirths and neonatal deaths by Lactation Day 4 were observed at 1,000 mg/kg/day (greater than 28 times the exposure in humans at the RHD); there were no alterations to growth and development of surviving offspring. In a cross-fostering study, similar incidences of stillbirths and early postnatal deaths were observed when rat pups born to cabotegravir-treated mothers were nursed from birth by control mothers. There was no effect on neonatal survival of control pups nursed from birth by cabotegravir-treated mothers. A lower dose of 5 mg/kg/day (13 times the exposure at the RHD) was not associated with delayed parturition or neonatal mortality in rats. Studies in pregnant rats showed that cabotegravir crosses the placenta and can be detected in fetal tissue.

During the pre-clinical development of CAB, there were no positive genotox findings. Embryo-fetal studies also showed no adverse findings including neural tube defects. In a pre and postnatal study, there were some test article-related decreases in F1 pup survival

(87.4% vs 98.9% in control) in the highest dose (1000mg/kg/day) during postnatal days 1-4. No findings in the 0, 0.5 and 5 mg/kg/day doses).

The clinical significance of these finding in humans is unknown.

Human Data

Cabotegravir use in pregnant females has not been evaluated and there are insufficient human data on the use of CAB + RPV LA during pregnancy to adequately assess a drug-associated risk of birth defects and miscarriage.

While there are insufficient human data to assess the risk of neural tube defects (NTDs) with exposure to CAB + RPV LA during pregnancy, NTDs were associated with dolutegravir, another integrase inhibitor. 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 four cases (as of May 2018) of neural tube defects in 426 infants born to mothers who were exposed to DTG-containing regimens from the time of conception. In the same study, no infant born to a woman who started DTG during pregnancy had a neural tube defect, out of 2,824 women. More recently, data from the Tsepamo study was updated. In April 2020, the Tsepamo study team provided interim data from the study, which included available data through to 29 February 2020. Subsequently, the study team presented an updated analysis, including data through to 30 April 2020, at the 23rd International AIDS Society (IAS) Meeting [Zash, 2020].

The latest data from the Tsepamo study included additional data accrued between 1 April 2019 (the cut-off for the last formal analysis) and 30 April 2020. Over this 13-month period, 39,200 additional births were recorded, including 1908 additional exposures to DTG at conception. Two additional NTDs were detected in 1908 (0.10%) deliveries to mothers taking DTG at conception, compared with six NTDs in 4569 (0.13%) deliveries in mothers taking non-DTG regimens at conception, of which five NTDs in 2999 (0.17%) deliveries were to mothers taking efavirenz at conception. The incidence in HIV negative mothers over the 13-month period was 17/30,258 (0.06%).

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. There are insufficient human data on the use of CAB + RPV LA during pregnancy to adequately assess a drug-associated risk of miscarriage or birth defects, including NTDs.

10.8.4.2. Rilpivirine

Animal Data

Rilpivirine was administered orally to pregnant rats (40, 120, or 400 mg/kg/day) and rabbits (5, 10, or 20 mg/kg/day) through organogenesis (on Gestation Days 6 through 17, and 6 through 19, respectively). No significant toxicological effects were observed in embryo-fetal toxicity studies performed with rilpivirine in rats and rabbits at exposures

15 (rats) and 70 (rabbits) times the exposure in humans at the RHD. In a pre- and postnatal development study, rilpivirine was administered orally up to 400 mg/kg/day through lactation. No adverse effects were noted in the offspring at maternal exposures up to 63 times the exposure in humans at the RHD

Human Data

Based on prospective reports to the APR of over 390 exposures to oral rilpivirine-containing regimens during the first trimester of pregnancy and over 170 during second/third trimester of pregnancy, the prevalence of birth defects in live births was 1.3% (95% CI: 0.4% to 3.0%) and 1.1% (95% CI: 0.1% to 4.0%) following first and second/third trimester exposures.

Available data from the APR show no difference in the overall risk of birth defects for rilpivirine compared with the background rate for major birth defects of 2.7% in a U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP)

In a clinical trial, total oral rilpivirine exposures were generally lower during pregnancy compared with the postpartum period. Refer to Edurant Prescribing Information, 2018 for additional information on rilpivirine.

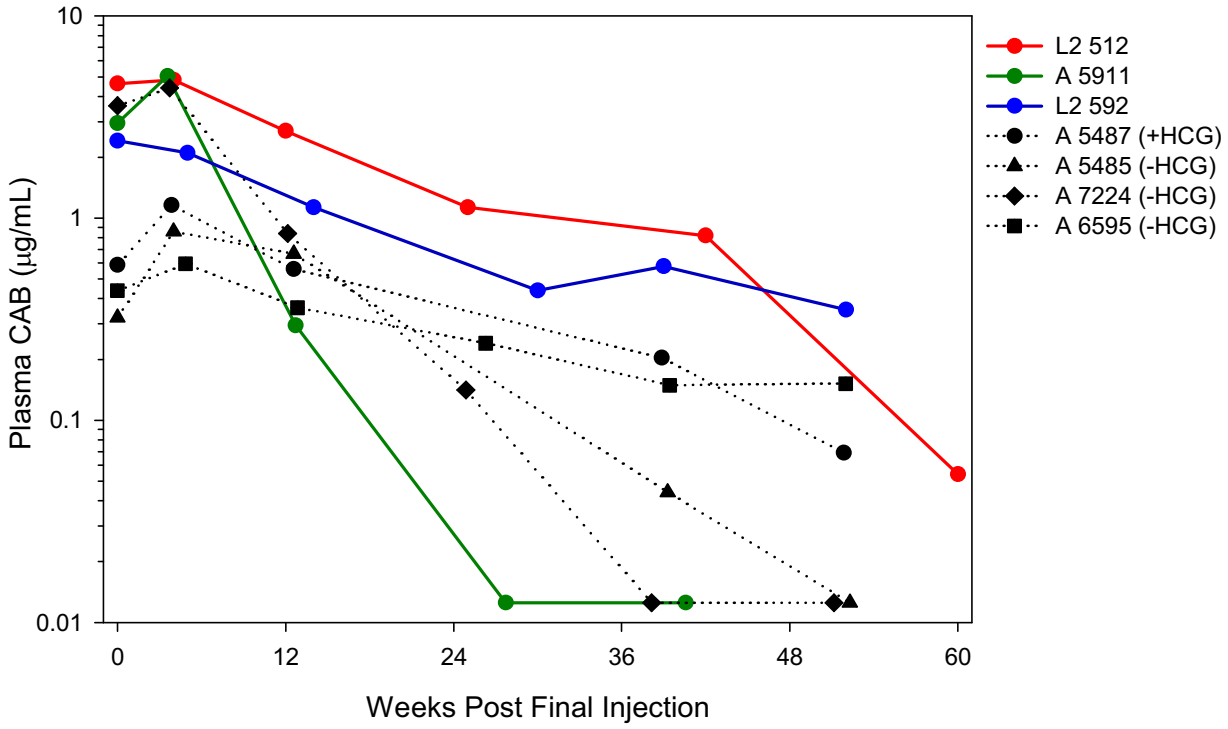
10.8.5. Clinical Considerations

10.8.5.1. Exposure

Lower exposures with oral rilpivirine were observed during pregnancy. Cabotegravir and rilpivirine are detected in systemic circulation for up to 12 months or longer after discontinuing injections of CAB + RPV LA; therefore, consideration should be given to the potential for fetal exposure during pregnancy.

With the change in volume of distribution associated with pregnancy, drug concentrations of CAB and RPV during pregnancy will be assessed in pregnant participants who contiune to receive LA therapy while on study. For these participants, PK samples will be collected up to 4 times throughout the duration of the pregnancy. Additionally, all other scheduled assessments, including viral load monitoring, will continue as reflected in as described in the protocol in the SoA, Section 1.5, Table 3).

Figure 7 LTFU PK in Female and Pregnant Participants (LATTE-2, ATLAS)



10.8.5.2. Use of Supplements with CAB + RPV LA

During pregnancy, additional supplements including vitamins, minerals and other mediations including OTC meds may be prescribed to the pregnant woman. It is important for all female participants who remain in the study to be aware of any potential DDIs that may occur with study medications and other agents used during pregnancy.

10.8.5.2.1. Oral Cabotegravir Only

Antacid products containing divalent cations (e.g., aluminium, calcium and magnesium) must be taken at least 2 hours before or at least 4 hours after CAB.

Concurrent administration of multivitamins is acceptable.

10.8.5.3. Overall Benefit:Risk Conclusion

All medications have AE profiles that must be assessed prior to use, allowing for an appropriate risk/benefit assessment. Additional considerations when using CAB + RPV LA can be found in the protocol in Section 2.3

There is limited data regarding the use of CAB + RPV LA in pregnant females. Based on animal data, the use of CAB + RPV LA is not anticipated to increase the risk of adverse developmental or reproductive outcomes in humans. Available data from the APR show no difference in the overall risk of birth defects for rilpivirine compared with the background rate for major birth defects of 2.7% in a U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP).

Refer to Section 10.8.4.1 for additional data.

The use of CAB + RPV LA during pregnancy may offer unique benefits. It is well documented that treatment adherence challenges to oral therapy exists both in the peri-partum and post-partum periods with LA dosing offering an opportunity to overcome such adherence challenges. LA therapy may also help with nausea (50 % mild to moderate) or hyperemesis (2%). Female participants on LA dosing who become pregnant will have exposures throughout pregnancy due to the long half-life and PK tail of CAB/RPV. Pregnant participants who are withdrawn from study and are initiated on an alternative oral ART regimen consisting of either 2 or 3 antiretrovirals to protect the life of the mother and for the prevention of MTCT, potentially expose the fetus to additional ARVs during gestation (in some cases upwards of 5 antiretrovirals).

In summary, taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with CAB + RPV LA are justified by the anticipated benefits that may be afforded to pregnant participants with HIV infection.

Given the risk/benefit ratio for CAB + RPV LA dosing in FRP, coupled with concerns of increasing fetal exposure to several additional antiretrovirals upon participant withdrawal, pregnant participants will be allowed to remain in the study and continue to receive CAB

+ RPV LA injections, once the new pregnancy ICF addendum is signed by the participant.

10.8.6. Study Assessments and Procedures: specific assessments for pregnant participants

Participants who become pregnant while in the study, and who sign the informed consent pregnancy addendum may remain in the study and continue to receive CAB + RPV LA.

Please note: The HIV provider is responsible for HIV care and will collaborate and share information with the subject's obstetric care provider, discuss the subject's participation in this study, the necessary procedures at delivery, to share HIV information, and to collect birth and infant outcomes from the subject's obstetric care provider and/or the pediatric health provider for the infant.

Because obstetric and/or pediatric care will not be specifically provided via this study, the subject must also establish appropriate obstetric and pediatric care (including prenatal care) per local standard of care (SoC) in parallel. It will be necessary for the subject to provide a release of medical information to facilitate collection of pregnancy and pregnancy outcomes by the investigator

All assessments will be conducted in accordance with the protocol, Section 8, and as described in the SoA, Section 1.5, Table 3).

10.8.6.1. Safety Assessments

Pregnancy related complications and diagnoses, and outcomes will be captured as AEs and SAEs as outlined in the protocol in Section 8.5.

Pregnancy complications (e.g., preeclampsia or eclampsia, prolonged hospitalization after delivery, for wound infections etc, seizures) and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

In the event of a pregnancy loss, after the loss is confirmed the subject may continue to receive CAB + RPV LA unless they meet the criteria for confirmed virologic withdrawal. They may continue to CAB + RPV LA until study medications are locally approved and commercially available or until they no longer receive benefit. In this case the subject must agree to use contraception to avoid a 'new' pregnancy (See Appendix 7).

Any SAE occurring in association with the pregnancy brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the study treatment, must be promptly reported to GSK

10.8.6.2. Pharmacokinetics

Refer to Section 8.6 in the protocol.

All pregnant participants who elect to remain in the study will have additional PK sampling obtained. Blood samples for evaluation of plasma concentrations of cabotegravir and rilpivirine will be collected prior to each LA injection throughout the

pregnancy. A final PK sample for cabotegravir and rilpivirine concentrations will obtained at the first postpartum LA visit. All PK samples will be trough levels and will be collected prior to the scheduled LA injection. The pre-dose trough PK sample is to be collected within 15 minutes prior to the LA dose, on the day of the study visit.

Please refer to the SPM for PK sample collection, processing, and shipping instructions. The actual date and time of each PK sample collection will be recorded in the eCRF.

10.8.7. References

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10.9. Appendix 9: Abbreviations and Trademarks

Abbreviations

ADR	Adverse drug reaction
AE	Adverse event
AIDS	Acquired immunodeficiency syndrome
AIM	Acceptability of intervention measure
ALT	Alanine aminotransferase
Anti-HBc	Hepatitis B core Antibody
Anti-HbsAg	Antibodies against Hepatitis B surface Antigen
APR	Antiviral Pregnancy Registry
ARV	Antiretroviral
ART	Antiretroviral therapy
AST	Aspartate aminotransferase
AUC	Area under the curve
AUC(0-τ)	Area under the concentration curve from 0 hours to the time of next dosing
AZT	Azidothymidine (zidovudine)
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CAB	Cabotegravir
CAB LA	Cabotegravir long-acting
c/mL	Copies/milliliter
cART	Combination antiretroviral therapy
CD4	Cluster of Differentiation 4
CD8	Cluster of Differentiation 8
CDC	Centers for Disease Control and Prevention
CFIR	Consolidated framework for implementation research
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
Cmax	Maximum concentration
ConART	Concomitant Antiretroviral Therapy
CONSORT	Consolidated Standards of Reporting Trials
CPK	Creatine phosphokinase
CPMS	Clinical Pharmacology Modelling and Simulation
CRO	Contract research organization
CSR	Clinical Study Report
CV	Cardiovascular
CVF	Confirmed Virologic Failure
DAIDS	Division of Acquired Immunodeficiency Syndrome
DILI	Drug-induced liver injury
DNA	Deoxyribonucleic acid
DRE	Disease-Related Events
DVT	Deep vein thrombosis
ECG	Electrocardiogram
eCRF	Electronic case report form

FIM	Feasibility of intervention measure
FDA	Food and Drug Administration
FRP	Female of Reproductive Potential
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
HAART	Highly active antiretroviral therapy
HbsAg	Hepatitis B surface Antigen
HBV	Hepatitis B virus
HCG	human chorionic gonadotrophin
HCP	Healthcare practitioner
HCV	Hepatitis C virus
HDPE	High density polyethylene
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HSR	Hypersensitivity reaction
IAM	Intervention appropriateness measure
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IDMC	Independent data monitoring committee
IEC	Independent Ethics Committee
IgM	Immunoglobulin M
IM	Intramuscular
INI	Integrase inhibitor
INR	International normalized ratio
INSTI	Integrase strand transfer inhibitor
IP	Investigational Product
IRB	Institutional Review Board
ITT-E	Intent-to-treat exposed
IUD	Intrauterine device
ISR	Injection Site Reaction
LA	Long Acting
LDL	Low density lipoprotein
LFTs	Liver function tests
LTFU	Long-Term Follow-UP
MTCT	Mother-to-Child Transmission
MCV	Mean corpuscular volume
MedDRA	Medical dictionary for regulatory activities
Mg	Milligram
Mg/dL	Milligram per deciliter
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRS	Numeric Rating Scale
NRTI	Nucleoside reverse transcriptase inhibitor
NTF	Note to File
OLI	Oral lead-in
PK	Pharmacokinetic
PLHIV	Persons living with HIV

PP	Per-protocol
PRO	Protease
PRTD	Proximal Renal Tubule Dysfunction
PSAT	Program sustainability assessment tool
PSP	Patient study participant
PSRAE	Possible suicidality-related adverse event
QTc	Corrected QT interval
Q8W	Every 8 weeks
Q4W	Every 4 weeks
RAP	Reporting and Analysis Plan
RBC	Red blood cell
RNA	Ribonucleic acid
RPR	Rapid plasma reagin
RPV	Rilpivirine, Edurant
RPV LA	Rilpivirine long-acting
RT	Reverse transcriptase
SAE	Serious adverse event
SJS	Stevens-Johnson syndrome
SoA	Schedule of activities
SOC	Standard of Care
SPM	Study Procedures Manual
SSI	Semi-structured interview
SSP	Staff study participants
TEN	Toxic epidermal necrolysis
TMC278	Tibotec Medicinal Compound 278
ULN	Upper limit of normal
US	United States
VAPI	Vaccines' Perception of Injection
VSLC	ViiV Safety and Labeling Committee
WBC	White blood cell

Trademark Information

Trademarks of ViiV Healthcare
CABENUVA

Trademarks not owned by ViiV Healthcare
Edurant
Evidera
Genosure
InForm
MedDRA
Monogram Biosciences
PhenoSense

10.10. Appendix 10: Patient Study Participant Surveys

A survey will be administered to the patient study participants at three timepoints:

- Month 1 visit- at the end of the oral dosing period, prior to receiving the CAB+RPV injection.
- Month 4 visit
- Month 12/ End of Study

Each of the patient surveys will include approximately 40-50 questions and will take about 15 minutes to complete. Patients will be asked to answer the questions at Month 1 based on their current expectations of receiving the CAB+RPV injection, and at the Month 4 and 12 timepoints, based on the current experience receiving the injection.

The following concepts are measured in the patient study participant surveys:

- Acceptability of the CAB+RPV injection (AIM)
- Appropriateness of the CAB+RPV injection (IAM)
- Facilitators and barriers to implementation of the CAB+RPV injection
- Utility of patient specific toolkit resources
- Patient satisfaction with current treatment (HIV-TSQs, HIV-TSQc)

Acceptability and appropriateness will be measured by the Acceptability of Intervention Measure (AIM) and Intervention Appropriateness Measure (IAM), which are constructs validated from the Proctor Framework. Reponses are measured using a 5-point Likert scale. (Weiner, 2017)

Additional questions are included to evaluate facilitators and barriers from the patient perspective, and to evaluate the usefulness of the patient specific toolkit resources.

Patient satisfaction will be measured using the validated HIV Treatment Satisfaction Questionnaire (HIV-TSQ), status version (HIV-TSQs), which measures satisfaction with the treatment used in the previous few weeks, and the HIV-TSQ change version (HIV-TSQc), which measures change in satisfaction over time. The HIV-TSQs will be included at all 3 timepoints, while the HIV-TSQc is only measured at Month 12/End of study. (Woodcock, 2006)

10.11. Appendix 11: Staff Study Participant Survey

A survey will be administered to the staff study participants at three timepoints:

- Month 1 – following the investigator meeting, but prior to any patients at the site receiving the CAB+RPV injection
- After the 4th monthly facilitation call
- Month 12/ End of Study

The first two surveys will include approximately 55 questions and will take about 15 minutes to complete. The final survey will include approximately 100 questions and will take about 25 minutes to complete. Staff study participants will be asked to answer the questions at Month 1 based on their current expectations of administering the CAB+RPV injection, and at the following timepoints based on their current experience administering the injection.

The following concepts are measured in the staff study participant surveys:

- Acceptability of the CAB+RPV injection (AIM)
- Appropriateness of the CAB+RPV injection (IAM)
- Feasibility of the CAB+RPV injection (FIM)
- Facilitators and barriers to implementation of the CAB+RPV injection
- Utility of toolkit and study resources
- Experiences and attitudes about the CAB+RPV injection
- Sustainability of the CAB+RPV injection (PSAT) (Month 12 only)

Acceptability, appropriateness and feasibility will be measured by the Acceptability of Intervention Measure (AIM), the Intervention Appropriateness Measure (IAM) and the Feasibility Appropriateness Measure (FIM), which are constructs validated from the Proctor Framework. Reponses are measured using a 5-point Likert scale. (Weiner, 2017)

Additional questions are included to evaluate facilitators and barriers from the site perspective. A series of questions are also included to evaluate the usefulness of toolkit resources, and about staff study participant experiences and attitudes towards implementing the CAB+RPV injection.

Sustainability is measured by the Program Sustainability Assessment Tool (PSAT). The PSAT evaluates the capability of clinics to maintain processes developed to administer CAB+RPV injection in routine clinical settings after the conclusion of this study. (Luke, 2014)

10.12. Appendix 12: COVID-19 Pandemic and Clinical Trial Continuity

Background

The COVID-19 pandemic presents significant logistical challenges for many clinical sites around the world, with variable restrictions being placed on site resources and operations, and on an individual participants ability to attend clinic visits. In some places, medical visits are occurring, and in others, research clinics are operating with only emergency staff.

Based on these challenges, it may be necessary to adopt additional measures and procedures to protect participant safety, and to ensure that there are no gaps in HIV-1 treatment for participants enrolled in this clinical study, through continuous access to antiretroviral therapy.

In order to maintain the scientific integrity of the study, and adhere to updated guidance from regulators, procedures have also been put into place to ensure that the actions taken to mitigate against any impact of COVID-19 are well documented in the trial database.

A "Memo to Investigators" was issued on March 18th, 2020 and served as a record of approved emergency actions being taken within this clinical trial to manage issues related to COVID-19. That memo continues to serve as record of approved actions which can be fully implemented by Investigators, in advance of this protocol guidance. This appendix will remain consistent with the guidance provided within the "Memo to Investigators" and will also serve to provide additional protocol documentation requirements and procedures.

This appendix outlines the measures which are approved for implementation within this clinical trial, to protect patient safety and to ensure the integrity of the clinical trial, as a result of COVID-19 only. These measures may be implemented in accordance with any requirements and expectations set out by local Independent Review Boards/Independent Ethics Committees and National Competent Authorities, as necessary.

This appendix **does not** apply to participant management issues that are unrelated to a specific, and documented, impact from COVID-19.

10.12.1. Changes to Study Visits and Study Procedures

- Where site staff resource is constrained due to COVID-19, IM dosing visits may proceed with limited or no other protocol-defined assessments (e.g. lab tests, questionnaires, etc.). If lab tests will be missed for more than one consecutive visit, the medical monitor must be contacted, to provide guidance for safety monitoring.
- For FRP, point of care pregnancy testing should be performed, prior to IM dosing.
- If central laboratory testing cannot be performed at a particular visit, and monitoring for safety is required, tests may be performed at an appropriately authorised/accredited local laboratory (or other relevant clinical facility), if this

can be done within local restrictions on physical distancing. The site should proactively inform the sponsor about such instances. Local laboratory results may be used to inform safety decisions. Results should be retained in source records.

- When on-site visits are reduced, it is important that the investigator continue collecting relevant clinical information, including adverse events, from the participant through alternative means, e.g. by telephone contact.
- There may be cases where the current principal investigator (PI) of a site is indisposed for a period and may need to delegate parts of his/her duties temporarily, e.g. to a sub-investigator. Any such changes should be documented in the site's source records. Any permanent changes in PI should be communicated to the sponsor.
- There may also be circumstances where immediate actions are required by the sponsor and/or investigator, outside of what is contemplated in the protocol, in order to protect a study participant from immediate hazard. Any such measures will be carefully documented and conducted in accordance with the National Competent Authority (NCA)/IRB/IEC regulations.

10.12.2. Changes to Informed Consent

Informed consent should continue per normal procedure and as described in the main body of the protocol, to the extent possible. However, there may be circumstances where re-consent of participants is needed, and a physical signature on site is not possible. In these cases, alternative ways of obtaining such re-consent should be considered, such as the participant sending a picture of his/her written consent to the investigator, or the investigator contacting the participant by telephone or video call and obtaining verbal consent, supplemented with email confirmation.

Any updated informed consent form or other subject-facing materials should be provided to participants by e-mail, mail or courier before re-consent is obtained. Any consent obtained this way should be documented in source records and confirmed by way of normal consent procedure at the earliest opportunity when participants attend their next on-site study visit.

Any alternative informed consent procedure must be undertaken only after site IRB/Ethics Committee agreement and approval.

10.12.3. Permissible Use of Antiretroviral Therapy

In order to minimize the risk of gaps in HIV-1 antiretroviral therapy (ART) for participants impacted by COVID-19 in the clinical trial, the following options can be considered with regards to ART dosing, in order of preference:

1. Where possible, and safe to do, please continue to prioritize IM dosing visits in order to keep the participants on the protocol-defined regimen

    a. Qualified healthcare professionals (HCPs) trained on study procedures can administer IM injections outside of the study clinic setting (e.g. home, nursing facility, hospital), assuming this can be done safely, without compromising investigational product preparation/handling/storage/accountability requirements and done in accordance with local requirements. Please seek approval by the study team on a case-by-case basis.

2. If a participant is not able to attend an IM injection visit due to COVID-19 related restrictions, the gap in IM dosing should be covered with oral ART, until IM dosing can resume. Participants should be reminded of the importance of adhering with daily oral dosing. Two options can be approved for oral bridging therapy in consultation with the Medical Monitor, listed in order of preference:

    a. Oral CAB + RPV
        i. Investigator should request availability of oral CAB + RPV supplies, prior to pursuing option b.
    b. Oral standard of care (SOC) commercial ART (prescribed locally)

<u>Oral bridging with CAB + RPV</u>

The protocol permits oral bridging to cover planned missed injections with oral CAB + RPV, only until IM dosing can be resumed. The start date of oral bridging should be within the dosing window for the missed IM dosing visit. This recommendation can be used to accommodate requests for oral dosing due to COVID-19. Oral bridging recommendations should be followed as per protocol Section 6.6.1.1. The process and required information for requesting oral bridging can be found in your Study Reference/Procedure Manual. Please continue to reach out to your study medical monitor for approval of oral bridging, in order to document use and to ensure expeditious shipment of oral CAB + RPV to your site.

Participants who use oral CAB + RPV as short-term oral bridging are permitted to return to IM dosing, on protocol, once the COVID-19 conditions permit resumption of site activities.

The investigator should reach out to the medical monitor to confirm IM restart instructions, and to ensure the participant remains appropriate for resumption of IM dosing. If oral bridging with CAB/RPV is anticipated to continue for >2 months, additional approval and guidance should be obtained from the medical monitor to continue with oral bridging therapy. Loading/Re-initiation doses of CAB + RPV IM may be required, depending on the length of oral bridging.

Oral bridging with Standard of Care Antiretroviral Therapy (SOC ART)

For participants impacted by COVID-19, where the participant is unable to receive IM injections, and oral CAB + RPV is not available for use, oral bridging with any commercially available, guideline-recommended, SOC ART regimen is permitted. The start date of oral bridging should be within the dosing window for the missed IM dosing visit. Please reach out to your study medical monitor for approval of SOC ART as oral bridging, in order to document the use of commercially available SOC ART within the study.

Participants who use oral SOC ART as short-term oral bridging as a result of COVID-19 will not be considered formally withdrawn insofar as they wish to continue on the study. Individuals who bridge with SOC ART will be permitted to return to IM dosing, on study, once the COVID-19 conditions permit resumption of site activities.

The investigator should reach out to the medical monitor to confirm IM restart instructions, and to ensure the participant remains appropriate for resumption of IM dosing. If oral bridging with SOC ART is anticipated to continue for >2 months, additional approval and guidance should be obtained from the medical monitor to continue with oral bridging therapy. Loading/Re-initiation doses of CAB + RPV IM may be required, depending on the length of oral bridging.

10.12.4. Direct-To-Patient (DTP) Shipment of Oral Study IP

If a participant is unable to travel to the clinic, either to receive IM injections or to be dispensed oral bridging, sites are encouraged to consider DTP shipments of drug, from the site, to the participant, to ensure access to medicines.

- If the study site is considering DTP shipment of oral CAB + RPV investigational product (IP), the site must first verify if DTP IP dispensing by investigators/hospital pharmacies is locally permitted and whether it requires regulatory and/or local ethics pre-approval, or post-hoc notification.
- The study participant should express his/her agreement for DTP shipment and the sharing of their personal information with any third-party couriers (as applicable), in accordance with local requirements. This agreement should be documented in source records.
- Oral CAB + RPV IP can be shipped at ambient temperatures via ground transport without a temperature monitoring device, with low risk of temperature excursions. Sites are encouraged to use discretion in determining the need for in-transit temperature monitoring based on the labelled storage requirements and the planned mode of transport and apply this as appropriate. Shipment of oral CAB + RPV via air courier continues to require appropriate temperature monitoring. For shipment conditions of oral medications other than oral CAB + RPV, please consult the product labelling.
- In all cases IP accountability must be maintained, and all DTP dispensing documentation should be reflected in source records and dispensing logs per GCP.

- Please refer to your CRA or local study manager for support with the DTP process, ensuring reference to current sponsor guidance and arrangement of a courier that can support shipment of IMP directly to participants.

10.12.5. COVID-19 Experimental Agents

If any treatments for COVID-19 are planned for a study participant, please consult with the study medical monitor to ensure that relevant drug interactions are considered and to ensure that continued study participation remains appropriate.

10.12.6. COVID-19 Specific Data Capture

10.12.6.1. Capturing COVID-19 Specific Protocol Deviations

In order to summarise the impact of COVID-19 in a systematic way and in line with regulatory authorities' recommendations, any study-level impact around COVID-19 will be documented as a protocol deviation. This will include the permissible actions summarized in this Appendix, which are taken to protect patient safety, including the use of CAB + RPV or SOC ART as oral bridging as well as missed visits and assessments as a result of logistical challenges resulting from COVID-19.

Although the conduct of remote visits and the continuity of antiretroviral therapy, via oral bridging, are being utilized to protect patient safety, these events fall outside of the intent of the original protocol design, may have an impact on data interpretation, and thus will be characterized as protocol deviations for the purposes of data summary and analysis.

Any protocol deviations resulting from COVID-19 will be clearly identified as such within the protocol deviation description and summarised separately.

Please refer to your study procedure manual for specific details on capturing protocol deviations as a result of COVID-19.

10.12.6.2. Capturing COVID-19 Specific AEs and SAEs

It is important for the study team to describe COVID-19 related adverse events/serious adverse and their impact on study data and outcomes. Standardization of case definitions will facilitate future data analysis.

Please use the following guidance:

1. AEs should continue to be evaluated as to whether they meet SAE criteria as defined in the protocol, and if so, submitted according to established SAE reporting requirements. SAEs and AEs should be submitted following usual study procedures and timelines.

2. When an in-person clinic visit is not possible, please conduct a remote telehealth visit to assess for, and document any AEs/SAEs.

3. Investigators should use the WHO definition to classify COVID-19 cases. The definition below, released March 20, 2020, represents a time point for standardized collection. We recognize definitions are likely to continue to evolve. When reporting both serious and non- serious adverse events (related to COVID-19 infection, investigators should use the following Verbatim terms:
    a) Suspected COVID-19 infection; or
    b) Probable COVID-19 infection; or
    c) Confirmed COVID-19 infection

4. Sites should contact the study Medical Monitor for questions related to definitions and reporting, and decisions around impact to study drug continuation.

5. A new COVID-19 infection Case Report Form will be added to the eCRF to collect additional details about the reported COVID-19 AE or SAE data. It is important to collect the correct information from each participant reporting a COVID-19 AE or SAE. Therefore, please use the CRF templates to help you collect this information, once available.

WHO Case Definition - March 20, 2020 Version (https://www.who.int/publications-detail/global-surveillance-for-human-infection-with-novel-coronavirus-(2019-ncov))
:

Suspected case:

A. A patient with acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g., cough, shortness of breath), AND a history of travel to or residence in a location reporting community transmission of COVID-19 disease during the 14 days prior to symptom onset;

OR

B. A patient with any acute respiratory illness AND in contact (see definition of "contact" below) with a confirmed or probable COVID-19 case (see definition of contact) in the last 14 days prior to symptom onset;

OR

C. A patient with severe acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g., cough, shortness of breath; AND requiring hospitalization) AND in the absence of an alternative diagnosis that fully explains the clinical presentation.

Probable case:

A. A suspect case for whom testing for the COVID-19 virus is inconclusive (Inconclusive being the result of the test reported by the laboratory).

OR

B. A suspect case for whom testing could not be performed for any reason.

Confirmed case:

A person with laboratory confirmation of COVID-19 infection, irrespective of clinical signs and symptoms.

Covid-19 Contact:

A contact is a person who experienced any one of the following exposures during the 2 days before and the 14 days after the onset of symptoms of a probable or confirmed case:

1. Face-to-face contact with a probable or confirmed case within 1 meter and for more than 15 minutes;
2. Direct physical contact with a probable or confirmed case;
3. Direct care for a patient with probable or confirmed COVID-19 disease without using proper personal protective equipment; OR
4. Other situations as indicated by local risk assessments.

Note: for confirmed asymptomatic cases, the period of contact is measured as the 2 days before through the 14 days after the date on which the sample was taken which led to confirmation.

10.13. Appendix 13: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment 2 15-MAY-2020

Overall Rationale for the Amendment: The purpose of this amendment is to include an Appendix related to COVID-19 Pandemic and Clinical Trial Continuity. This appendix will replace the previous Appendix 11, and "Protocol Amendment History," will be included as Appendix 12.

Section # and Name	Description of Change	Brief Rationale
Section 6.2 Preparation/Handling/ Storage/Accountability Section 6.6.1.1. Oral Bridging Section 8. Study assessments and procedures Section 8.5. Adverse Events and Serious Adverse Events	Added reference to COVID-19 Section 10.11, Appendix 11	To link Appendix 11 to the main body of the protocol
Section 10.11 Appendix 11: COVID-19 Pandemic and Clinical Trial Continuity	Added Appendix	To summarize COVID-19 related patient management updates that were previously communicated in a memo to investigators

Amendment 1 02-APR-2019

- **Overall Rationale for the Amendment:** The reasons for this amendment include: addition of exclusion criterion regarding known major resistance mutations at Screening, clarification of timing for collection of visit length, removal of consent requirement for study staff, correction to allowable window around the Month 3 dosing visit, clarification of pregnancy testing requirements at Screening, clarification of wording to allow a single re-screen per subject, removal of color of vial stopper in product description to allow flexibility of

packaging for cabotegravir and rilpivirine suspension, clarification of ECG collection during the study, clarification of wording to allow qualitative analyses to be performed by a CRO under GSK oversight.

Section # and Name	Description of Change	Brief Rationale
Section 1.2 Objectives and Endpoints and Section 3 Objectives and Endpoints	Added time points where visit length is collected (Month 1, Month 5 and Month 11)	To provide specificity when these data will be collected
Section 1.3 Overall Design	Deleted wording to require written consent from study staff	Because there is no risk to study staff, consent is not required.
Section 1.5 Schedule of Activities	Clarification of footnote "b" re: study visit length collection not being collected following Month 11, footnote "i" re: dosing window and removal of consent requirement for study staff in Table 4.	Study visit length will not be collected after Month 12, the Month 3 dosing window is corrected to +0/-7 days from the projected visit date, and consent requirement for study staff has been removed.
Section 5.1 Inclusion Criteria	Urine pregnancy test is stipulated for females of childbearing potential at the Screening visit.	Urine pregnancy test is stipulated at Screening. Serum pregnancy test should be performed if pregnancy is suspected.
Section 5.2 Exclusion Criteria	New Exclusion Criteria added. "Any evidence of primary resistance based on the presence of any major known INI or NNRTI resistance-associated mutation, except for K103N by any historical resistance test result	This exclusion criterion has been added to prevent subjects with known relevant mutations which could affect virologic response from being included in the study.
Section 5.4 Screen Failures and Section 8.1 Screening Assessments	Minor wording changes to clarify that subjects may be re-screened only one time.	Minor wording to clarify rescreening requirements.

Section # and Name	Description of Change	Brief Rationale
Section 6.1.1.3 and Section 6.1.1.4	Color (grey) of rubber vial stopper has been removed to allow flexibility of packaging.	A color change in vial stopper color is anticipated during the course of this study.
Section 8.4.1 Clinical Evaluations and Section 8.4.4 Electrocardiograms	ECG requirements have been clarified to require ECG at Screening and not at Day 1	Minor wording modification to clarify ECG requirements for study entry.
Section 9.4 Statistical Analyses	Wording added to allow qualitative analyses to be performed by Evidera or other CRO partner under GSK's oversight	This wording has been changed to allow flexibility in CRO vendor for the qualitative analyses in this study, as well as to confirm that all work will be carried out under GSK oversight.

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