TITLE PAGE

Protocol Title: A Phase IIIb, open-label, hybrid type III trial evaluating implementation strategies for long-acting cabotegravir plus long-acting rilpivirine every two months in HIV-1 infected, virologically suppressed adults in select European healthcare settings.

Protocol Number: 213199 / Amendment 02

Compound Number: GSK1265744

Study Phase: Phase 3

Approval Date: 01-JUL-2021

Short Title: A study evaluating implementation strategies for cabotegravir + rilpivirine long-acting injectables for HIV-1 treatment in European countries.

CARISEL: CAB And RPV Implementation Study in European Locations

Author (s): PPD
PPD

Sponsor Legal Registered Address (excluding US):

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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 Senior Vice President, Head of Research & Development.

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

Medical Monitor and Sponsor Serious Adverse Events (SAE) Name and Contact Information can be found in the Study Reference Manual

Regulatory Agency Identifying Number(s):

IND: 109,678
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SPONSOR SIGNATORY:

Protocol Title: A Phase IIIb, open-label, hybrid type III trial evaluating implementation strategies for long-acting cabotegravir plus long-acting rilpivirine every two months in HIV-1 infected, virologically suppressed adults in select European healthcare settings.

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ViiV Healthcare

Date

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**DNG Number**
Amendment 02	01-JUL-2021	TMF-13794092
Amendment 01	02-DEC-2020	2019N420690_02
Original Protocol (Republishing)	06-MAY-2020	2019N420690_01
Original Protocol	05-FEB-2020	2019N420690_00

Amendment 02 01-JUL-2021

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union due to the change in the allowance of participants becoming pregnant to continue on study.

Overall Rationale for the Amendment:

The primary purposes of this amendment are:

- To allow participants who become pregnant while in the study to remain in the study and not be withdrawn due to pregnancy. Allowing pregnant participants to continue in the study will negate any additional and subsequent fetal exposures to new antiretroviral agents that would occur if the pregnant participant was withdrawn from the study and placed on an oral SOC regimen. An appendix, "Information and Guidance for Managing Pregnant Participants" was inserted as Appendix 15 and all subsequent appendices were renumbered accordingly.
- Detail added around the end of the study and transition to commercial supply or other HAART regimen.
- Removal of the optional collection of cord blood and/or breast milk after delivery.
- Clarification of which participants enter the LTFU phase when CAB+RPV LA marketed product is locally available.
- Medical Device reporting requirement added.
- Clinical and safety references updated.

Other additional edits were made, for clarity and/or correction.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	Added clarifying text; Participants will continue CAB LA + RPV LA until: <u>They have completed the study (reached dose 7, Month 12) and the</u> intervention is locally approved and available for the Investigator to prescribe. Added text confirming the Home Visit Handbook for home visits also provides supplementary information as well as the SRM.	For clarification purposes.
Section 1.1 Long Term Follow-Up (LTFU) Phase Section 4.1. Overall Design Section 4.3.4. LTFU Phase-Following the IM Regimen Only Section 7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal Section 7.1 Discontinuation of Study Intervention	New text added: - 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 <u>before CAB LA + RPV LA marketed product is locally available must enter the LTFU Phase.</u> - Where CAB LA + RPV LA marketed product is locally available,	Transition to marketed product.

	only participants that discontinue the CAB LA + RPV LA regimen for safety-related reasons should enter the LTFU Phase.	
Section 1.3. Schedule of Activities Table	Added new column and footnote w for Safety Follow-Up visit to clarify visit requirements. Prothrombin time (PT)/ partial thromboplastin time (PTT)/international normalized ratio (INR) removed from withdrawal visit. Task added for safety follow-up visit to review transition to commercial product. Footnote b updated to clarify definition of extension phase. Footnote f updated to clarify the assessment of height and body mass index (BMI) are collected at screening only. Footnote g updated to detail pregnancy testing not required for pregnant participants remaining on study.	Transition to marketed product.

	Footnote h updated to clarify the viral load assessments requirement for pregnant patients. Footnote m updated to add safety follow-up requirement if no withdrawal visit.	
Benefit/Risk Assessment Section 2.3.1. Oral CAB and CAB LA (GSK1265744/GSK1265744 LA)	Updated section Potential Risk of Clinical Significance: Drug Induced Liver Injury (DILI) for CAB, Summary of Data/Rationale for Risk text removed: - (total exposure >3100 participants) Summary of Data/Rationale for Risk text updated to include proportion of participants effected; Less than 1%. Removed; All participants with suspected DILI identified to date were receiving oral CAB.	For clarification purposes.
Benefit/Risk Assessment Section 2.3.1. Oral CAB and CAB LA (GSK1265744/GSK1265744 LA)	Updated section Potential Risk of Clinical Significance: Effects in pregnancy seen in non-clinical studies. Summary of Data/Rationale for Risk	To allow participants who become pregnant to remain in the study.

	Animal reproduction studies data updated. Mitigation Strategy updated to allow participants who become pregnant to remain in the study.	
Benefit/Risk Assessment Section 2.3.1. Oral CAB and CAB LA (GSK1265744/GSK1265744 LA)	Updated section: Potential effects in females exposed to dolutegravir during conception and early pregnancy. Summary of Data/Rationale for Risk with data from preliminary analysis of an ongoing birth outcome surveillance study in Botswana involving women exposed to dolutegravir (DTG). Mitigation Strategy updated to allow participants who become pregnant to remain in the study.	To allow participants who become pregnant to remain in the study.
Benefit/Risk Assessment Section 2.3.1. Oral CAB and CAB LA (GSK1265744/GSK1265744 LA) Section 2.3.2 Oral RPV and RPV LA (GSK1265744/GSK1265744 LA) Section 4.3.4. LTFU Phase-Following the IM Regimen Only	Updated section: Development of Resistance following discontinuation of CAB LA. Updated text (HAART) regimens will be prescribed within 1 month (-7 days) after the last Q1M dose or within 2 months (+/-7 days) after the last Q2M dose.	For clarification purposes.

	Updated to differentiate the long term follow-up requirements pre and post commercial availability.	
Benefit/Risk Assessment Section 2.3.2 Oral RPV and RPV LA (GSK1265744/GSK1265744 LA) ORAL RPV	Updated text: For safety and risk mitigation for oral RPV refer to the RPV local prescribing information [Current Edurant Prescribing Information]	For clarification purposes.
Benefit/Risk Assessment Section 2.3.2 Oral RPV and RPV LA (GSK1265744/GSK1265744 LA) RPV LA	Updated text: Systemic reactions following RPV LA injections have <u>been observed in clinical trials. These occur infrequently (in less than 0.5% of participants) and typically begin to resolve within minutes of the injection, some participants have required supportive care. Where timely PK data has been available.</u>	For clarification purposes.
Benefit/Risk Assessment Section 2.3.2 Oral RPV and RPV LA (GSK1265744/GSK1265744 LA) RPV LA	Updated section: Risk of Treatment Failure Updated with text: <u>recently approved EU and under review in other countries</u>. Both IM CAB and RPV have demonstrated antiviral activity in large clinical studies and the two-drug combination dosed <u>Q4W has demonstrated sustained antiviral activity in studies</u>	For clarification purposes.

	200056, 201584 and 201585 and in studies (200056 and 207966) when dosed Q8W.	
Benefit/Risk Assessment Section 2.3.3. Benefit Assessment	Updated list of ongoing studies and duration.	For clarification purposes.
Section 4.2.4 Enhanced Implementation Arm (arm-e) Description	Added text; Face-to-Face injection training: Where new staff join the study the injection training should also be provided face-to-face where possible.	For clarification purposes.
Section 4.3.3 Patient study participant Section: Patient study participants enrollment and Table 7 Dosing Regimen Section 6.1 Study Intervention(s) Administered; Dosing and Administration	End of study clarification; Until after dose 7 (Month 12) when locally approved and commercially available.	
Section 4.3.4. LTFU Phase-Following the IM Regimen Only	New text added: Clarified HAART initiation in months rather than weeks.	Transition to marketed product.
Section 4.5.1.2. Participant Study Participants Section 6.8. Intervention after the End of the Study or Extension Phase	Clarity added around study completion, the extension phase and transition to commercial supplies of CAB LA + RPV LA, or alternate antiretroviral therapy. Added Safety Follow-Up visit details.	Transition to marketed product.

Section 6. Study Intervention	New section added: 6.9. Medical Devices.	Medical Device reporting requirement.
Section 6.7. Treatment of Study Treatment Overdose	Updated the text around IM maladministration should this occur at a home visit. Removed text: (at least 5 days for oral CAB and oral RPV, and 52 weeks for CAB LA and RPV LA. Added text: (number of days will vary by compound – Medical Monitor/ study team can advise)	For clarification Purposes.
Section 7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal	Removed text: Pregnancy (intrauterine), regardless of termination status of pregnancy. Updated text: If a participant is prematurely or permanently withdrawn from the study, and not continuing into the LTFU, the procedures described in the Schedule of Activities Table for the in-clinic Withdrawal visit are to be performed. Where a participant does not complete a withdrawal visit or enter the LTFU, an in-clinic or remote Safety Follow-Up visit will be conducted 4 weeks after the last dose of study	To allow participants who become pregnant to remain in the study. Clarification on withdrawal and safety follow-up visit.

	medication when there are ongoing AEs 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.	
Section 7.1 Discontinuation of Study Intervention	Added text: The start of the 52-week follow-up period begins the day of the last CAB LA and/or RPV LA dose with the first visit at Month 3.	Clarification on start of 52 weeks LTFU phase.
Section 8.4.1. Clinical Evaluation	Added text: 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 15: Information and Guidance for Managing Pregnant Participants.	To allow participants who become pregnant to remain in the study.

	Pregnant participants who remain in the study do not need pregnancy testing during the study, for the duration of their pregnancy.	
Section 8.4.4. Clinical Safety Laboratory Assessments	Text updated: • Prothrombin Time (PT)/International Normalized Ratio (INR)/ Partial Thromboplastin Time (PTT) (screening) • Pregnancy test for women of childbearing potential. • Text added to clarify additional pre-dose PK samples collection for pregnant participants who elect to remain in the study. Text added: Where lab samples are missed in error, including not analysed by the central lab, see the Study Reference Manual (SRM) for guidance on which samples should have subjects brought back in for a central lab retest (local lab only sites require a local retest only). Retesting to be entered as an unscheduled visit in the eCRF.	For clarification purposes.

Section 8.5. Adverse Events and Serious Adverse Events	Added text throughout sections 8.5. and 8.5.1. referring to the new requirement to report Medical Device incidents. New sections added to cover the new requirement to report Medical Device incidents. 8.5.8. Medical Device Deficiencies 8.5.8.1. Time Period for Detecting Medical Device Deficiencies 8.5.8.2. Follow-up of Medical Device Deficiencies 8.5.8.2.1. Prompt Reporting of Medical Device Deficiencies to Sponsor 8.5.8.2.2. Regulatory Reporting Requirements for Medical Device Deficiencies	Added Medical Device incident reporting requirements.
Section 8.5.5. Pregnancy	Added text throughout all sections below to allow subjects who become pregnant to remain in the study: Added text in Section 8.5.5.1. Pregnancy Testing	To allow subjects who become pregnant to remain in the study.

	Added new Section 8.5.5.2. Rationale for Continued Use in Pregnancy Amended Section 8.5.5.3. Time Period for Collecting Pregnancy Information Amended Section 8.5.5.4. Action to be Taken if Pregnancy Occurs	
Section 8.5.5.4. Actions to be taken if Pregnancy occurs	Removed text: Additionally, there will be an optional umbilical cord blood collection at time of delivery, requiring additional parental consent. Cord blood and breast milk samples would be used to better understand the level of PK exposure to the neonate, if any.	Removal of optional umbilical cord blood and/or breast milk PK testing.
Section 8.6. Pharmacokinetics	Added text: Pregnant participants will have additional PK samples collected during the duration of the pregnancy. See Appendix 15: Information and Guidance for Managing Pregnant Participants.	Added PK collection during pregnancy.
Section 9.4.1. Primary Endpoints (S)	Text corrected in the Primary SSP endpoints AIM, IAM, FIM to correctly refer to 'Implementation,' rather that Intervention.	For clarification purposes.

Section 10.1.3. Informed Consent Process	Added text: • 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. • If follow-up information from a treating physician or other licensed medical practitioner is required for a medical device incident with an AE/SAE involving an associated person(s), the Associated Person Safety Reporting Information and Authorization Letter must be signed by the associated person to obtain consent.	To allow patients who become pregnant to remain in the study and medical device deficiency reporting requirements.

Section 10.6.4. Grade 3 Toxicity/Adverse Event	Clarification that a follow-up visit should occur 2-4 weeks after the last dose of IP.	For clarification purposes.
Section 10.6.5.10. Rash Without HSR Symptoms	Updated CAB IB document number	For clarification purposes.
Section 10.7. Appendix 7 Contraceptive Guidance and Collection of Pregnancy Information	Added text throughout section for cases of pregnancy during the study.	To allow patients who become pregnant to remain in the study.
Section 10.9. Appendix 9	New abbreviation added	
Section 10.15. Appendix 15	New appendix added: Appendix 15: Information and Guidance for Managing Pregnant Participants.	To allow participants who become pregnant to remain in the study.
Section 10.16. Appendix 16	New appendix added: Appendix 16: Device Deficiencies: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting in Medical Device Studies.	Medical Device Reporting Requirements.
Section 10.17. Appendix 17	Appendix 17: Protocol Amendment History updated.	

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase IIIb, open-label, hybrid type III trial evaluating implementation strategies for long-acting cabotegravir plus long-acting rilpivirine every two months in HIV-1 infected, virologically suppressed adults in select European healthcare settings.

Short Title: A study evaluating implementation strategies for cabotegravir + rilpivirine long-acting injectables for HIV-1 treatment in European countries.

Rationale:

Cabotegravir long-acting + rilpivirine long-acting (CAB LA + RPV LA) is an investigational HIV-1 treatment regimen administered as two individual intramuscular injections every two months (following an oral lead-in [OLI] period).

The overall objective of the CAB LA + RPV LA clinical development program is to develop a highly effective, well-tolerated, two-drug, long-acting injectable regimen which has the potential to offer improved treatment convenience, compliance and improved quality of life for people living with HIV (PLHIV) compared to current standard of care.

This new HIV treatment will require changes to the current standard of prescribing oral antiretroviral therapies to prescribing and delivering a complete antiretroviral long-acting injectable regimen. As this is a new treatment modality, it is important to understand how to optimize the delivery of CAB LA + RPV LA from a patient, healthcare provider and healthcare system perspective in order to implement into routine care with fewer obstacles. Each country's healthcare system has its own challenges and nuanced differences in the delivery of HIV care. Strategies to support the unique and dynamic contexts for CAB LA + RPV LA implementation is key. As a result, this research study will examine different implementation strategies in different clinic settings across European countries to identify which strategies best meet the needs in each local context. The research in this study will involve both patients receiving the study treatment CAB LA + RPV LA (patient study participants, PSP) as well as the healthcare providers at the investigator site level (staff study participants, SSP).

For PSPs, the study is single-arm, unblinded and interventional, where all patients who fulfil eligibility requirements will be assigned to receive CAB LA + RPV LA and complete assessments as per the study protocol.

For SSPs, the study is two-arm, unblinded, non-interventional and cluster-randomized at the country level. Sites within a given country will be randomized to either the Standard (Arm-s) or the Enhanced (Arm-e) implementation arm. The two arms will involve the provision of overlapping but distinct types of implementation components that are designed to assist in the local implementation of the study drug at each site. Arm-s represents the traditional provider support by a medical science lead and product

materials. Arm-e models a higher level of provider support with added face to face meeting, trainings, and additional touchpoints for administration of CAB LA + RPV LA. The study will evaluate both qualitative and quantitative measures across arm, clinic type, provider type, and country to determine the most effective implementation strategies and to identify barriers and facilitators (including solutions). Clinical data will be collected to monitor safety and efficacy.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
Staff Study Participants (SSP): To evaluate • acceptability • appropriateness • feasibility	Quantitative Change of Acceptability of Implementation Measure (AIM) Score, Implementation Appropriateness Measure (IAM) Score, Feasibility of Implementation Measure (FIM) Score over time assessed quantitatively via questionnaires through Month 12.[a] Qualitative Semi-structured interviews (SSI) assessed qualitatively through Month 12.
Secondary	
Staff Study Participants: To evaluate • Facilitators to implementation • Barriers to implementation • Adaptations/Modifications to address barriers and facilitators	Quantitative: Change of Implementation Leadership Scale (ILS), Change of Implementation Climate Scale (ICS) over time assessed quantitatively via questionnaires through Month 12.[a] Summarize components from Enhanced Implementation & Standard Implementation: • FRAME-IS outcome Months 2 – 12 (monthly) Summarize components from Enhanced Implementation: • CQI 1-hour calls/PDSAs minimum of Months 2-7 (monthly) Qualitative SSIs assessed qualitatively through Month 12.
Patient Study Participants (PSP) To evaluate • Facilitators to implementation	Quantitative: Questionnaires assessed quantitatively through Dose 7.[b]

Objectives	Endpoints
• Barriers to Implementation	Length of patient study participant visit from arrival until departure from clinic assessed at Dose 1, Dose 2, Dose 4, and Dose 5. Qualitative SSIs assessed qualitatively through Dose 7.
To evaluate **Patient Study Participants** experience of delivering CAB LA + RPV LA, including • Acceptability • Appropriateness • Feasibility	Quantitative Change in Acceptability of Intervention Measure (AIM) Score, Intervention Appropriateness Measure (IAM) Score, and Feasibility of Intervention Measure (FIM) Score over time. Assessed via questionnaires at Dose 7. [b] Qualitative SSIs assessed qualitatively through Dose 7.
To evaluate sustainability of CAB LA + RPV LA with **Study Staff Participants** each clinic	Total score of the Clinical Sustainability Assessment Tool (CSAT) at Month 12.
To assess fidelity to CAB LA +RPV LA injection dosing windows	Percentage of injections occurring within target window from the target date.
Evaluate efficacy and safety measures of CAB LA + 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 patient study participants with CVF Incidence and severity of AEs, SAEs and proportion of participants who discontinue treatment due to AEs over time
To assess preference between CAB LA + RPV LA and oral ART medication received prior to entering the study	Preference between CAB + RPV LA and daily oral ART medication (received prior to entering the study) quantitatively assessed via preference questionnaire at Dose 7

a) Month 1 is established by site activation, Month 5 is ~ the 1st patient receiving Dose 3 at the site, Month 12 is ~the 1st patient receiving Dose 7 (last dose) at the site.

b) Dose 1 is the first injection and Dose 7 is the last injection

Overall Design:

This is a single-arm, open-label interventional study in respect to the drug regimen whereby all patients enrolled will receive the same intervention of the CAB LA + RPV LA regimen with a month oral lead in at Day 1 followed by CAB LA + RPV LA injections at Month 1, Month 2 and every 2 months (Q2M) thereafter. For the implementation science aspect, this is a two-arm study where clinics will be randomized to either Enhanced or Standard Implementation Arms at the country level.

For Clinics:

Arm 1: The **Enhanced Implementation Arm** (arm-e) contains the Skilled Wrap-Around Team (SWAT) which is an interactive problem-solving meeting and an introduction to the principles of Continuous Quality Improvement (CQI) with follow-up CQI calls.

Arm 2: The **Standard Implementation Arm (**arm-s**)** will provide sites with the traditional standard practices for each country at the time of product availability provided by a medical science liaison or medical lead.

Both arms will have access to the toolkits aimed to support education and proper administration of CAB LA + RPV LA. We propose a cluster randomized, hybrid type III implementation trial with a mixed methods evaluation. Results from the study will provide best practice recommendations for implementation of CAB LA + RPV LA.

Sample Implementation Assessments:

The proposed study design will identify key barriers (e.g., clinical capacity, injection training, cold chain storage) and facilitators (e.g., existing infrastructure for appointment reminders) to translating CAB LA + RPV LA into routine care by understanding:

1) How do clinical team members and administrators perceive the acceptability, feasibility, and appropriateness of arm-e and arm-s strategies?

2) How do clinical providers (and administrators) perceive the usefulness and ease of use of the toolkit components?

3) How feasible are the two strategies to support rapid implementation of CAB LA + RPV LA in routine care in various countries and archetypes?

4) How prepared are healthcare settings across Europe to incorporate a high volume of patient study participants receiving the CAB LA + RPV LA regimen into their clinical flow in various countries and clinic archetypes?

5) What are the multi-level barriers to, and facilitators of, successful implementation in different countries, by a variety of providers, and by archetype?

Archetypes are descriptors that, in the context of this study, are used to broadly classify the anticipated types of care setting for the study treatment when locally available. **Archetype 1** represents those where study treatment is administered in a hospital-based setting. **Archetype 2** represents those where study treatment will be delivered primarily via (semi-) specialized physician office in primary care. **Archetype 3** represents those where the study treatment will be administered in a broad care setting which is anticipated to trigger new alternative injection facilities.

Sample Effectiveness Assessments:

The study design proposed here allows for simultaneous examination of both implementation and effectiveness outcomes. Throughout the course of the study, viral load suppression and safety markers will be examined to further contribute to our understanding of CAB LA + RPV LA.

Study Aims:

- ✓ **Aim 1:** Evaluate the feasibility, acceptability, and appropriateness of staff study participants to support the integration of CAB LA + RPV LA in a variety of clinical settings.
- ✓ **Aim 2:** Assess patient study participant acceptability, appropriateness, and feasibility of CAB LA + RPV LA treatment.
- ✓ **Aim 3**: Identify multi-level barriers to, and facilitators of, CAB LA + RPV LA implementation and sustainment across Europe experienced by staff study participants and patient staff participants in both arms.
- ✓ **Aim 4:** Assess the safety and effectiveness of CAB LA + RPV LA.

Disclosure Statement: This is a single-arm, open-label interventional study in respect to the drug regimen whereby all patients enrolled will receive the same intervention of the CAB LA + RPV LA regimen. For the implementation science aspect, this is a two-arm study, which will assume a cluster randomization design, where clinics will be randomized to either arm-e or arm-s implementation strategy.

Intervention Groups and Duration:

Study sites

Investigational sites or investigators that have not previously delivered the CAB LA + RPV LA regimen will be preferred for this study. Selection will be based on ability to recruit the desired number of study participants, clinic size, demographic, geographic diversity, and patient population. Sites will be selected in order to cover a wide variety of real-world HIV care settings and classified by the sponsor based on the care delivery system. Sites will be asked to operate through their regular clinic pathways rather than a research pathway wherever possible.

Each clinic selected will be categorized by country, archetype (defined above), number of providers/ staffs, number of patients, and other clinical characteristics that may be considered confounders or influence implementation.
Sites across the following countries: France, Spain, Netherlands, Germany and Belgium will be selected. Exact site number will be based on feasibility assessments with an approximation of 18 sites to be selected.

Site staff participants

Study staff participants will be included that are central to best practices delivery of CAB LA + RPV LA within each local context. This will be decided site by site based on the local clinical infrastructure and practices at each site. At least three staff participants, identified prior to study commencement, will be included at each site.

Data will be collected from study staff participants per Table 2. Informed consent will be obtained prior to any study assessments for study staff participants (where applicable, as determined by local regulatory and compliance requirements).

The total number of staff study participants will be a minimum of approximately 3 per site (~*n*= 54).

Patient study participant

Patient study participants are HIV-1-infected adults that fulfil the eligibility criteria. Each patient study participant will receive CAB LA + RPV LA and clinical assessments throughout the study per the Schedule of Activities (SoA). Data will be collected from patient study participants per Table 1.

A goal of this study is to enroll 20% female participants, as this population is often underrepresented in clinical studies.

Each site will be asked to recruit enough patient study participants to serve as a reasonable number reflective of a real-world situation. This will be based on feasibility assessment and site capacity to inform subject recruitment allocation, ensuring a balance without compromising study subject safety. This approach will allow sites adequate opportunity to describe the challenges and practical limitations experienced during initial implementation of CAB LA + RPV LA, as well as opportunity to evaluate the resources needed and alternative strategies for successful implementation.

The enrolment period and rate will be monitored continuously and adjustments to the enrolment period and patient distribution may occur based on site feasibility and recruitment.

The maximum number of patient participants included in this study is anticipated to be approximately 450.

Patient study participants Enrollment:

All patient study participants will complete the screening phase of up to 35 days prior to enrollment. Participants may be re-screened once. 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. Informed consent must be obtained prior to any study procedures for patient study participants, including any screening assessment.

HIV-1 infected participants who meet all eligibility criteria will be switched from their pre-baseline regimen to an oral regimen (CAB 30 mg + RPV 25 mg once daily) during the oral lead-in phase. 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 dose of CAB LA (600 mg) + RPV LA (900 mg) injections on the same day (Month 1). The participant will receive the second injections CAB LA (600 mg) + RPV LA (900 mg) one month later (Month 2). All subsequent injections will occur every two months thereafter (Month 4, Month 6, etc). The total length of the treatment phase is approximately one year.

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 injections will be +0 / -7 days from the projected target date (target date is established at Month 1). All subsequent injection windows (starting with Dose 3) will be +7/-7 days from the projected target date. Doses outside of the window *may* be allowed with prior Medical Monitor approval.

Participants will continue CAB LA + RPV LA until:

- They have completed the study (reached dose 7, Month 12) and the intervention is locally approved and available for the Investigator to prescribe
- the participant no longer derives clinical benefit
- the participant meets a protocol-defined reason for discontinuation
- the development of CAB LA and/or RPV LA is terminated
- participant withdraws consent
- participant is withdrawn due to investigator discretion
- participant is withdrawn due to participant or investigator non-compliance
- termination of the study by the Sponsor.

Safety and efficacy assessments will be conducted as per the Schedule of Activities (Section 1.3).

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 long-term follow-up (LTFU) phase of the study.

Long-Term Follow-up (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 before CAB LA + RPV LA marketed product is locally available must enter the LTFU Phase. Participants must remain on suppressive highly active antiretroviral therapy (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.

Where CAB LA + RPV LA marketed product is locally available, only the participants that discontinue the CAB LA + RPV LA regimen for safety-related reasons included in Section 7, must enter the LTFU Phase. Participants transitioning to CAB+RPV LA marketed product or alternative HAART (except due to safety-related reasons) do not need to enter the LTFU Phase.

Dose Modifications

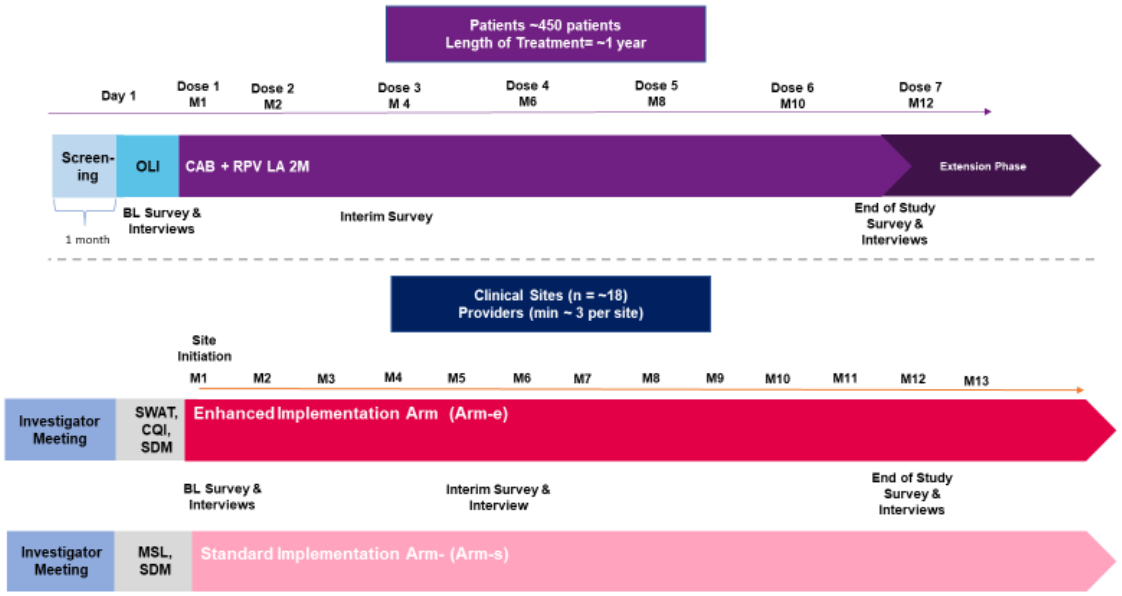
No dose reductions, modifications, or changes in the frequency of any components of each regimen will be allowed during the study beyond what is allowed within the protocol any necessary modifications approved by the study Medical Monitor. Protocol waivers or exemptions are not allowed. Therefore, adherence 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 planned 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 information not mandated in this protocol is provided in the accompanying Study Reference Manual (SRM)and Home Visit Handbook for home visits if applicable in country.

Data Monitoring or Other Committee: No data monitoring committee will be assigned to this study as all subjects are receiving the same regimen (open-label) and appropriate safety medical and laboratory monitoring is included in the study.

1.2. Schema



OLI = Oral Lead In, M=Month CAB = Cabotegravir, RPV = Rilpivirine, CQI = Continuous Quality Improvement; BL = Baseline, SWAT=Skilled Wrap Around Team; CQI= Continuous Quality Improvement; SDM= Study Delivery Meeting; MSL= Medical Science Liaison

1.3. Schedule of Activities (SoA)

Table 1 Schedule of Activities for Patient Study Participants

Procedure	Screening[a] up to 35d	Intervention Period (Month)								Withdrawal[m]	Safety Follow-up Visit[w]	Long Term Follow-up[n]
		Day 1	Month 1	Month 2	Month 4	Month 6	Month 8	Month 10 [b]	Month 12 [b]			
		Oral Lead-in	Dose 1 (D1)	Dose 2 (D2)	Dose 3 (D3)	Dose 4 (D4)	Dose 5 (D5)	Dose 6 (D6)	Dose 7 (D7)			
Written Informed consent	X											
Eligibility Verification	X											
Demography	X											
Physical Exam	X										X[w]	
Medical history	X											
Current medical conditions	X											
Center for Disease Control and Prevention (CDC) HIV-1 Classification	X											
Syphilis serology + reflex Rapid Plasma Reagin (RPR)	X											
Injection site reaction (ISR) assessment			X	X	X	X	X	X	X	X	X	X

Procedure	Screening[a] up to 35d	Intervention Period (Month)							Withdrawal[m]	Safety Follow-up Visit[w]	Long Term Follow-up[n]
		Day 1	Month 1	Month 2	Month 4	Month 6	Month 8	Month 10 [b]	Month 12 [b]			
		Oral Lead-in	Dose 1 (D1)	Dose 2 (D2)	Dose 3 (D3)	Dose 4 (D4)	Dose 5 (D5)	Dose 6 (D6)	Dose 7 (D7)			
Symptom Directed Physical Exam and Medical Assessment[c]		X	X		X		X		X	X		X
HIV-associated Conditions, AE and serious adverse event (SAE) Assessments[d], Con Meds	X	X	X		X		X		X	X	X	X
Vital Signs (blood pressure [BP], heart rate [HR])[e]	X	X	X		X		X		X	X		
Weight, Height & body mass index (BMI)[f]	X	X	X		X		X		X	X		
Clinical Chemistry, Hematology and other Tests[o]	X	X	X	X	X		X		X	X	X[w]	X
HIV-1 RNA and plasma sample for storage[h]	X	X	X	X	X		X		X	X		X
CD4+ count	X	X	X	X	X		X		X	X		X

Procedure	Screening[a] up to 35d	Intervention Period (Month)								Withdrawal[m]	Safety Follow-up Visit[w]	Long Term Follow-up[n]
		Day 1	Month 1	Month 2	Month 4	Month 6	Month 8	Month 10 [b]	Month 12 [b]			
		Oral Lead-in	Dose 1 (D1)	Dose 2 (D2)	Dose 3 (D3)	Dose 4 (D4)	Dose 5 (D5)	Dose 6 (D6)	Dose 7 (D7)			
CD8+ cell count (will be reported at Baseline and Month 12)		X							X			
Urinalysis	X									X		X
Hepatitis Serology[q]	X											
Whole Blood PBMC[p]		X								X		
Prothrombin time (PT)/ partial thromboplastin time (PTT)/international normalized ratio (INR)	X											
Pregnancy Testing Urine (U) or Serum[g]	U	U	U	U	U	U	U	U	U	U		U
Notification of Interview[t]		X										
Oral CAB + RPV Medication Dispensation		X										
CAB LA + RPV LA IM Treatment Administration[i]			X	X	X	X	X	X	X			

Procedure	Screening[a] up to 35d	Intervention Period (Month)							Withdrawal[m]	Safety Follow-up Visit[w]	Long Term Follow-up[n]
		Day 1	Month 1	Month 2	Month 4	Month 6	Month 8	Month 10 [b]	Month 12 [b]			
		Oral Lead-in	Dose 1 (D1)	Dose 2 (D2)	Dose 3 (D3)	Dose 4 (D4)	Dose 5 (D5)	Dose 6 (D6)	Dose 7 (D7)			
Participant Visit Reminder Contact	X	X	X	X	X	X	X	X				
Participant Contact Detail Confirmation	X	X	X	X	X	X	X	X				
Patient Toolkit[s]		X	X	X	X	X						
Record Visit Length[j]			X	X		X	X					
Contraception Counseling[u]										X		X
HAART dispensation[v]										X		X
Patient Questionnaires[k]			X		X				X			
Selected Patient Interviews[l]		X							X			
CCI [redacted]												

Procedure	Screening[a] up to 35d	Intervention Period (Month)								Withdrawal[m]	Safety Follow-up Visit[w]	Long Term Follow-up[n]
		Day 1	Month 1	Month 2	Month 4	Month 6	Month 8	Month 10 [b]	Month 12 [b]			
		Oral Lead-in	Dose 1 (D1)	Dose 2 (D2)	Dose 3 (D3)	Dose 4 (D4)	Dose 5 (D5)	Dose 6 (D6)	Dose 7 (D7)			
Preference Question									X			
Review plan to transition to commercial product or alternative ART[v]											X	

a) A screening visit will be conducted within 35 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) Continue this pattern for visits for the remainder of the study if needed, until CAB LA + RPV LA is locally approved and available. For example, Dose 8 will be conducted as per Dose 6, Dose 9 will be conducted as per Dose 7, Dose 10 will be conducted as per Dose 6 and so on. The exception to this pattern is that no questionnaires, study visit length collection, or patient interviews will be conducted after Dose 7 visit. Visit after Month 12 will be considered, 'extension phase.' See Section 6.8.

c) 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) unless abnormalities are observed. Medical assessments include any decisions the study staff must make for participant management.

d) AE and SAEs will not be proactively assessed at M 2, M 6 and M 10. However, all AEs and SAEs reported by study participants **must** be recorded in eCRF at all visits and reported within required timelines as per Section 8.5.1 .

e) Measure vital signs after about 5 minutes of rest in a semi-supine position.

f) Height and body mass index (BMI) are collected at screening only.

g) A (-) urine pregnancy test is required prior to oral lead-in at day 1 and 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. If (+), participant will need to be withdrawn. A Serum pregnancy test should be performed at any time pregnancy is suspected by the Investigator. Pregnant participants who remain in the study do not need pregnancy testing for the duration of the pregnancy see Appendix 15: Information and Guidance for Managing Pregnant Participants.

h) Plasma for storage samples are collected for possible future analyses. Can be used for back-up in cases of loss/damage in transit, geno/pheno analyses for virologic failures. Only for women becoming pregnant and continuing on CAB LA+RPV LA as if pregnant a plasma HIV-1 RNA test and plasma for storage samples at Month 6 and Month 10 visits are required.

i) All injections are 1 x CAB LA 600 mg IM + 1 x RPV LA 900 mg IM. Doses 1 and 2 are one month apart. Subsequent injections beginning at Dose 3 are every two months. The 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 on the same date of the month as determined by IM Dose 1 visit date, this is the Target Date; where possible, this first injection should be performed within 2 hours of taking the last oral regimen dose. For Dose 2, a dosing window of +0 / -7 days from the target visit date is stipulated. A (+ or -) 7-day window from the target date visit is stipulated for IM dosing beginning at Dose 3. All decisions regarding dose interruption/ resumption must be discussed with the Medical Monitor in advance.**

j) Length of study visit from arrival until departure from clinic will be evaluated. Participant's time of arrival, actual start time of the appointment, and actual end time of the appointment will be collected in the eCRF.

k) Questionnaires should be completed before receiving the injections.

l) Interviews should be conducted before the PSP receives Dose 1 and within 4 weeks of receiving Dose 7. Interviews may be done in person, virtually, or by phone. A minimum of 6 patients per site will be selected for interviews.

m) Withdrawal 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. If visit is not possible ensure a safety follow-up visit is completed.

n) Participants receiving one or more injections with CAB LA and/or RPV LA will be assessed with clinic visits at months 3, 6, 9 and 12 during the Long-Term Follow-Up phase. The start of the 52-week follow-up period begins the day of the last CAB LA and/or RPV LA dose.

o) See Section 8.4.4 for list of tests

p) Whole blood/PBMC collection samples may be used for virologic analyses. PBMCs will be collected at baseline Day1 and at Withdrawal.

q) Hepatitis B (HBsAg), Anti-HBc, Anti-HBsAg, Hepatitis C (anti-HCVAb). A (+) anti-HCVAb will be followed by a confirmatory nucleic acid test for HCV RNA. HBV DNA will only be performed for participants with a (+) anti-HBc and (-) HBsAg and (-) anti-HBs (past and/or current evidence).

r) CCI .

s) At a minimum the study toolkit will be offered at the time pointed noted in the Table 6. However, the toolkit items are intended to be used throughout the study.

t) Notification of interviews may occur between Day 1 or during the 7 days after Day 1.

u) Women of childbearing potential should continue to receive counselling on the need to use adequate contraception for the entirety of the Long-Term Follow-Up period.

v) Investigators must discuss choice of HAART regimen and timing of initiation with the Medical Monitor before initiating.

w) Required when a patient study participant leaves the study following commercial availability of IP, or, if an on-site withdrawal visit is not possible and there are ongoing AEs, SAEs related and not related to study drug, or any laboratory abnormalities that are considered to be AEs or are potentially harmful to the participant, at the last on-study visit. Should be conducted approximately 2-4 weeks after the last dose of IP. Can be completed by remotely, if applicable and tests needed to be done at clinic may not be performed.

Table 2 Schedule of Assessments Table for Staff Study Participants

Assessments			Time (Months)												
	Both Arms	arm- e Only	1[a]	2	3	4	5	6	7	8	9	10	11	12	Until end of study
Informed Consent[g]	X														
Questionnaire	X		X[b]				X[c]							X[d]	
Interviews (SSI)	X		X[b]				X[c]							X[d]	
CQI Calls[e]		X	Initial SWAT Meeting and Intro to CQI	X	X	X	X	X	X						
SWAT[f]		X													
FRAME-IS	X			X	X	X	X	X	X	X	X	X	X	X	
CSAT	X													X	
Provider Toolkit[h]	X		X	X	X	X	X	X	X	X	X	X	X	X	X

a) Month 1 starts at site activation
b) Questionnaire and interview should be conducted prior to the site's first patient receiving their first CAB LA + RPV LA injection at that site.
c) Questionnaire and interview should be conducted within approximately 4 weeks of the site's first patient receiving their third injection.
d) Questionnaire and interviews should be conducted within approximately 4 weeks of the site's first patient receiving their last injection.
e) Intro to CQI calls will occur within four weeks of site activation. Additional CQI calls will be scheduled if deemed necessary.
f) Initial SWAT meeting will occur within four weeks of site activation. Additional SWAT meetings with each site will occur as needed throughout the study.
g) Informed consent will be obtained prior to any study assessments (where applicable, as determined by local regulatory and compliance requirements).
h) At a minimum the study toolkit will be offered at the time pointed noted in the Table 6. However, the toolkit items are intended to be used throughout the study.

2. INTRODUCTION

2.1. Study Rationale

Cabotegravir long-acting + rilpivirine long-acting (CAB LA + RPV LA) is an investigational HIV-1 treatment regimen administered as two individual intramuscular injections every two months (following an oral lead-in [OLI] period).

The overall objective of the CAB LA + RPV LA clinical development program is to develop a highly effective, well-tolerated, two-drug, long-acting injectable regimen which has the potential to offer improved treatment convenience, compliance and improved quality of life for people living with HIV (PLHIV) compared to current standard of care.

This new HIV treatment will require changes to the current standard of prescribing oral antiretroviral therapies to prescribing and delivering a complete antiretroviral long-acting injectable regimen. As this is a new treatment modality, it is important to understand how to optimize the delivery of CAB LA + RPV LA from a patient, healthcare provider and healthcare system perspective in order to implement into routine care with fewer obstacles. Each country's healthcare system has its own challenges and nuanced differences in the delivery of HIV care. Strategies to support the unique and dynamic contexts for CAB LA + RPV LA implementation is key. As a result, this research study will examine different implementation strategies in different clinics settings across European countries to identify which strategies best meet the needs in each local context. The research in this study will involve both patients receiving the study treatment CAB LA + RPV LA (patient study participants, PSP) as well as the healthcare providers at the investigator site level (staff study participants, SSP).

For PSPs, the study is single-arm, unblinded and interventional, where all patients who fulfil eligibility requirements will be assigned to receive CAB LA + RPV LA and complete assessments as per the study protocol.

For SSPs, the study is two-arm, unblinded, non-interventional and cluster-randomized at the country level. Sites within a given country will be randomized to either the Standard (Arm-s) or the Enhanced (Arm-e) implementation arm. The two arms will involve the provision of overlapping but distinct types of implementation components that are designed to assist in the local implementation of the study drug at each site. Arm-s represents the traditional provider support by a medical science lead and product materials. Arm-e models a higher level of provider support with added face to face meeting, trainings, and additional touchpoints for administration of CAB LA + RPV LA. The study will evaluate both qualitative and quantitative measures across arm, clinic type, provider type, and country to determine the most effective implementation strategies and to identify barriers and facilitators (including solutions). Clinical data will be collected to monitor safety and efficacy.

2.2. Background

2.2.1. Treatment Background

The treatment of HIV-1 infection has advanced since the first oral antiretroviral agent (zidovudine, 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, 2019). Moreover, intermittent compliance can result in HIV drug resistance, with subsequent regimens being more complicated to construct.

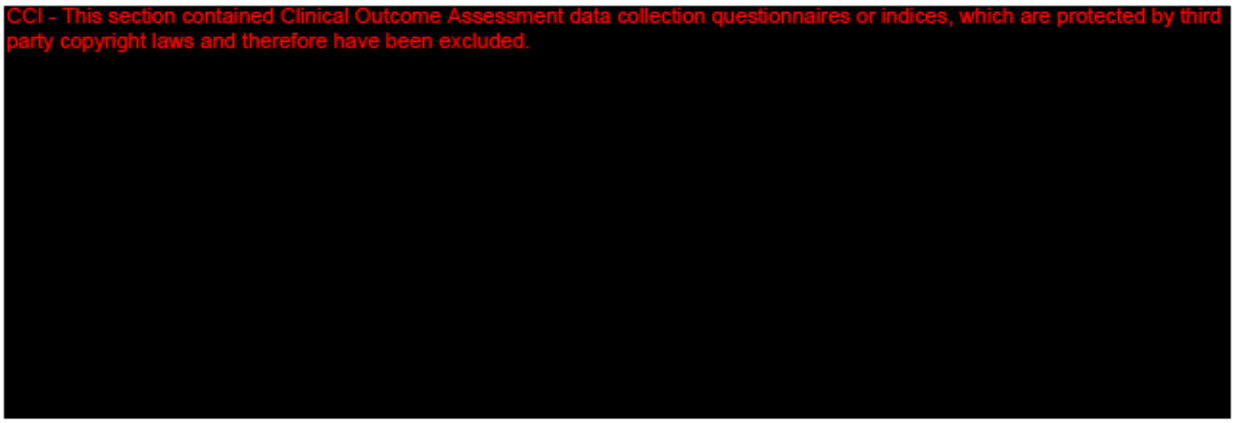
Long-acting injectable versions of drugs are being developed to enable therapy with infrequent dosing injection and represent an emerging paradigm for the treatment of HIV infection. CAB is a potent integrase inhibitor that possesses attributes that allow formulation and delivery as a long-acting product. 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 LA + RPV LA) may offer many potential advantages over daily oral regimens including infrequent dosing that decreases the daily reminder to patients of their HIV status, decreased development of viral resistance due to intermittent compliance with oral agents and overall treatment satisfaction in virologically suppressed patients. Results to date have demonstrated the efficacy of a two-drug regimen of CAB LA + RPV LA as maintenance therapy with several on-going Phase 2 and 3 studies including LATTE-2, ATLAS, FLAIR, and ATLAS 2M [Margolis, 2017].

2.2.2. New Treatment Paradigm

This new HIV treatment will require changes to the current standard of prescribing oral antiretroviral therapies to prescribing and delivering a complete antiretroviral long-acting injectable regimen. 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 new treatment modality for people living with HIV (PLHIV), it is important to understand how to optimize the delivery of CAB LA + RPV LA from the perspective of PLHIV, health care providers (HCP) and the healthcare system. Without a plan that meets the needs of all three of these groups, the implementation of CAB LA + RPV LA may be hindered. Concerns raised about chronic dosing injections include overburdening the health-care system. Additionally, there are concerns that patients will miss scheduled injections also resulting in a fear of inadequate antiretroviral therapy coverage.

The need for pragmatic data is essential to fully understand the barriers and facilitators for delivery of this treatment. The effectiveness of CAB LA + RPV LA has been documented in several Phase 2b studies with several larger Phase 3 studies (ATLAS, ATLAS-2M and FLAIR) and resulted in positive patient-level outcomes. It is critical to understand *how* to effectively implement this treatment to ensure optimal impact on healthcare service system- and patient-level outcomes. Unfortunately, 50% of effective interventions do not make it into routine care, not as a result of lack of effectiveness, but rather a lack of understanding of the contextual factors that make uptake challenging (Bauer, 2019).

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.



(Bauer, 2019).

Implementation science has been deployed across numerous contexts, including the area of long-acting injectable antipsychotics for the treatment of schizophrenia (Kishimoto, 2013). The use of a long-acting antipsychotic injectable medication was a significant paradigm shift within the psychiatric community and required work to address both organizational and attitudinal barriers by physicians in clinical practice. Implementation research began in this area to understand the barriers needed to overcome and support the use of the long-acting injectable, but only after identifying significant difficulties in uptake. The lag between the availability of this injectable and the use of implementation research hindered the rate of adoption and reach of this innovative treatment. Examples where implementation science has been used to improve availability of evidence-based treatment in routine care includes a range of fields including HPV vaccination, cancer care, primary care weight management, and psychotherapy (Soi, 2019; Leeman, 2019; Smith, 2018; Triplett, 2020).

Within HIV, implementation science has lagged behind other fields. The low uptake of pre-exposure prophylaxis (PrEP) is a prime example where implementation science could have supported a greater uptake in the real world given the significant gap between the number of people recommended for PrEP and the actual number receiving it (hiv.gov; Partners Scale-up Ref). The lag time between availability of an innovation, identification of barriers to translation into the real world through implementation research, and the use of implementation strategies can impact the rate at which the HIV epidemic can be ended. Implementation science can help maximize the impact of an innovation when used proactively in early stages of intervention development and availability.

This study is the first of its kind to examine the use of CAB LA + RPV LA by both healthcare professionals and patients in different clinical care settings in Europe. Incorporating implementation research into CAB LA + RPV LA across Europe will increase the impact of the treatment at a population level. Data in implementation science and CAB LA + RPV LA is in its infancy. While CUSTOMIZE (209493) is an ongoing initial implementation study of CAB LA + RPV LA, results remain forthcoming and only focused on sites in the United States.

Clinical care is a dynamic environment with multiple factors impacting an interventions' success or failure. The proposed approach in this study allows for each site to operate as close to routine care as possible while helping address barriers, supporting facilitators of, and implementation of CAB LA + RPV LA. **Barriers** are any perceived factors that obstruct a site from successfully implementing CAB LA + RPV LA. For example, this might include availability of clinical staff to accommodate additional appointments, lack of injection training or patient education and support. **Facilitators** are any perceived factors that enable successful implementation of CAB LA + RPV LA. Examples of facilitators include existing systems for cold chain storage, previous injector experience with intramuscular injections, and existing patient support applications or communication channels to assist in adherence and education. Despite different overarching components that define the arm-e and arm-s, both strategies leverage existing facilitators and aim to overcome barriers to successful implementation of CAB LA + RPV LA.

Additional examples of implementation strategies at a country level to address identified barriers in the arm-e may be found in a supplemental implementation science handbook.

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 current Investigator's Brochures.

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. (Current Edurant Prescribing Information)

2.3.1. Oral CAB and CAB LA (GSK1265744/GSK1265744 LA)

Since CAB Exposure in humans with and 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)	Less than 1% of participants in the CAB program to date have developed transaminitis (elevated liver transaminases characterized 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.	Exclusion criteria as described in Section 5.2 will prohibit participation of PLHIV 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 and the liver chemistry stopping criteria will be adopted as described in Section 7.1, Section 10.6.2, and Section 10.6.5 of this protocol. Participants will be withdrawn from CAB treatment where no compelling alternative cause is identified and DILI is suspected.
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	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.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	been reported, overall ISRs appear tolerable and have not to date been associated with an excess of participants' withdrawal.	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.
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.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Effects in pregnancy seen in nonclinical 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, 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 15 for additional data regarding CAB and pregnancy. 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).	• Pregnant females are excluded from enrollment in this study and women of childbearing potential (WOCBP) 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. • WOCBP 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 in Appendix 15
Potential effects in women exposed to dolutegravir during	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	• Pregnant females are excluded from enrollment in clinical trials of CAB at this time and women of childbearing potential (WOCBP) are required to adopt

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
conception and early pregnancy	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 became pregnant, 7/3591 neural tube defects (NTD) occurred (0.19%). In comparison, NTDs were identified in 21/19,361 (0.11%) 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	highly reliable means of contraception during participation and throughout long term follow up phases of studies after exposure to CAB LA. • WOCBP 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 15.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
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 1 month (-7 days) after the last Q1M dose or within 2 months (±7 days) after the last Q2M 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 Sponsor will continue to monitor participants in this study who discontinue the LA regimen prior to local availability of CAB LA+ RPV LA for a minimum of 52 weeks from the time of the last LA administration. Post- commercial local availability, the Sponsor will continue to monitor participants in this study who prematurely discontinue a LA regimen for safety reasons 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 CAB and CAB LA, refer to Section 6.6 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	All participants will be informed of prohibited medications throughout the study and updates provided as needed via the informed consent.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	- 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.	
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 overdose with 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, an unscheduled PK sample may be drawn approximately 2 hours post dosing for future evaluation of CAB concentrations.

2.3.2. Oral RPV and RPV LA (GSK1265744/GSK1265744 LA)

ORAL RPV

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

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. Systemic reactions following RPV LA injections have been observed in clinical trials. These occur infrequently (in less than 0.5% of participants) and typically begin to resolve within minutes of the injection, some participants have required supportive care. Where timely PK data has been available, high RPV PK plasma concentrations have been observed which may have resulted from an accidental partial IV injection of RPV. Refer to study protocols for instructions on injection administration. 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 immediat 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.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Rash	Some observations of rash with oral RPV have been reported in clinical studies executed to date (the majority are mild).	Participants with a Grade 1 or 2 rash will be allowed to continue treatment, 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 10.6.5.10 for additional guidance on management of rash.
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 (- 7 days) after the last dose if interruption is prior to Dose 2 and within 2 months (± 7days) after the last injection if interruption is following Dose 2, 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 Sponsor will continue to monitor participants in this study who discontinue the LA regimen prior to local availability of CAB LA+ RPV LA for a minimum of 52 weeks from the time of the last LA administration. Post- commercial local availability, the Sponsor will continue to monitor participants in this study who prematurely discontinue a LA regimen for safety reasons for a minimum of 52 weeks from the time of the last LA administration.

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 RPV and RPV LA, refer to Section 6.6. 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, 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;	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
	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, an unscheduled PK sample may be drawn approximately 2 hours post dosing for future evaluation of RPV concentrations.
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
Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk**	**Mitigation Strategy**

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Risk of Treatment Failure	This study employs a novel 2 drug LA ART treatment regimen dosed Q8W for the treatment of HIV-1 infection recently approved EU and under review in other countries. Both IM CAB and RPV have demonstrated antiviral activity in large clinical studies and the two-drug combination dosed Q4W has demonstrated sustained antiviral activity in studies 200056, 201584 and 201585 and in studies (200056 and 207966) when dosed Q8W. 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 (treatment 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.

2.3.2.1. 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. Site should report any cases of seizure or seizure like events immediately.

2.3.3. 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).

Participants receiving CAB LA + RPV LA are anticipated to benefit from maintenance of virological suppression using LA agents and will not 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 administered Q2M (every two months), has been demonstrated through

Week 256 of the ongoing LATTE-2 (200056) study (ID Week, 2020)) and through Week 96 of the ATLAS 2M (207966) study (CROI, 2021).

2.3.4. Overall Benefit: Risk Conclusion

Considering 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 are justified by the anticipated benefits that may be afforded to virologically suppressed, treatment-experienced participants with HIV-1 infection.

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

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
Staff Study Participants (SSP): To evaluate • acceptability • appropriateness • feasibility	Quantitative Change of Acceptability of Implementation Measure (AIM) Score, Implementation Appropriateness Measure (IAM) Score, Feasibility of Implementation Measure (FIM) Score over time assessed quantitatively via questionnaires through Month 12.[a] Qualitative Semi-structured interviews (SSI) assessed qualitatively through Month 12.
Secondary	
Staff Study Participants: To evaluate • Facilitators to implementation • Barriers to implementation • Adaptations/Modifications to address barriers and facilitators	Quantitative: Change of Implementation Leadership Scale (ILS), Change of Implementation Climate Scale (ICS) over time assessed quantitatively via questionnaires through Month 12.[a] Summarize components from Enhanced Implementation & Standard Implementation: • FRAME-IS outcome Months 2 – 12 (monthly) Summarize components from Enhanced Implementation: • CQI 1-hour calls/PDSAs minimum of Months 2-7 (monthly) Qualitative SSIs assessed qualitatively through Month 12.
Patient Study Participants (PSP) To evaluate • Facilitators to implementation • Barriers to Implementation	Quantitative: Questionnaires assessed quantitatively through Dose 7.[b] Length of patient study participant visit from arrival until departure from clinic assessed at Dose 1, Dose 2, Dose 4, and Dose 5. Qualitative SSIs assessed qualitatively through Dose 7.

Objectives	Endpoints
To evaluate **Patient Study Participants** experience of delivering CAB LA + RPV LA, including • Acceptability • Appropriateness • Feasibility	<u>Quantitative</u> Change in Acceptability of Intervention Measure (AIM) Score, Intervention Appropriateness Measure (IAM) Score, and Feasibility of Intervention Measure (FIM) Score over time. Assessed via questionnaires at Dose 7. [b] <u>Qualitative</u> SSIs assessed qualitatively through Dose 7.
To evaluate sustainability of CAB LA + RPV LA with **Study Staff Participants** each clinic	Total score of the Clinical Sustainability Assessment Tool (CSAT) at Month 12.
To assess fidelity to CAB LA + RPV LA injection dosing windows	Percentage of injections occurring within target window from the target date.
Evaluate efficacy and safety measures of CAB LA + 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 patient study participants with CVF Incidence and severity of AEs, SAEs and proportion of participants who discontinue treatment due to AEs over time
To assess preference between CAB LA + RPV LA and oral ART medication received prior to entering the study	Preference between CAB + RPV LA and daily oral ART medication (received prior to entering the study) quantitatively assessed via preference questionnaire at Dose 7
Tertiary	
CCI [redacted]	

Objectives	Endpoints
CCI [redacted]	

4. STUDY DESIGN

4.1. Overall Design

Study 213199 (**C**abotegravir **A**nd **R**ilpivirine **I**mplementation **S**tudy in **E**uropean **L**ocations -CARISEL) is a cluster randomized, two-arm, open-label, hybrid effectiveness-implementation study designed to evaluate two implementation strategy conditions (Enhanced [Arm-e] vs Standard [Arm-s]) in various clinical settings across five European countries.

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 LA + RPV LA regimen. 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 LA + RPV LA within an interventional clinical trial where the CAB LA + RPV LA regimen is delivered to HIV-1-infected, virologically-suppressed adult patients.

All patients who fulfill eligibility requirements will receive the study treatment of CAB LA + RPV LA and will begin oral therapy with CAB 30 mg + RPV 25 mg once daily for approximately one month to determine individual safety and tolerability prior to receiving CAB LA + RPV LA for an additional 11 months. Total patient study participant duration in the study is approximately 13 months including screening.

Patient participants in CARISEL who successfully complete the study (Dose 7), without meeting study-defined withdrawal criteria, will be given the option to continue to receive CAB LA + RPV LA, administered Q2M in the Extension Phase until the study treatment is either locally approved and commercially available (including through local public/government health sectors), the participant no longer derives clinical benefit, the participant meets a protocol-defined reason for discontinuation or until development of either CAB LA + RPV LA Q2M is terminated. Alternatively, participants can choose to complete study participation and enter the 52-week LTFU phase of the study.

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 before CAB LA + RPV LA marketed product is locally available must enter the 52-week LTFU Phase. Where the CAB LA+ RPV LA marketed product is locally available, only the participants that discontinue the CAB LA+RPV LA regimen for safety-related reasons

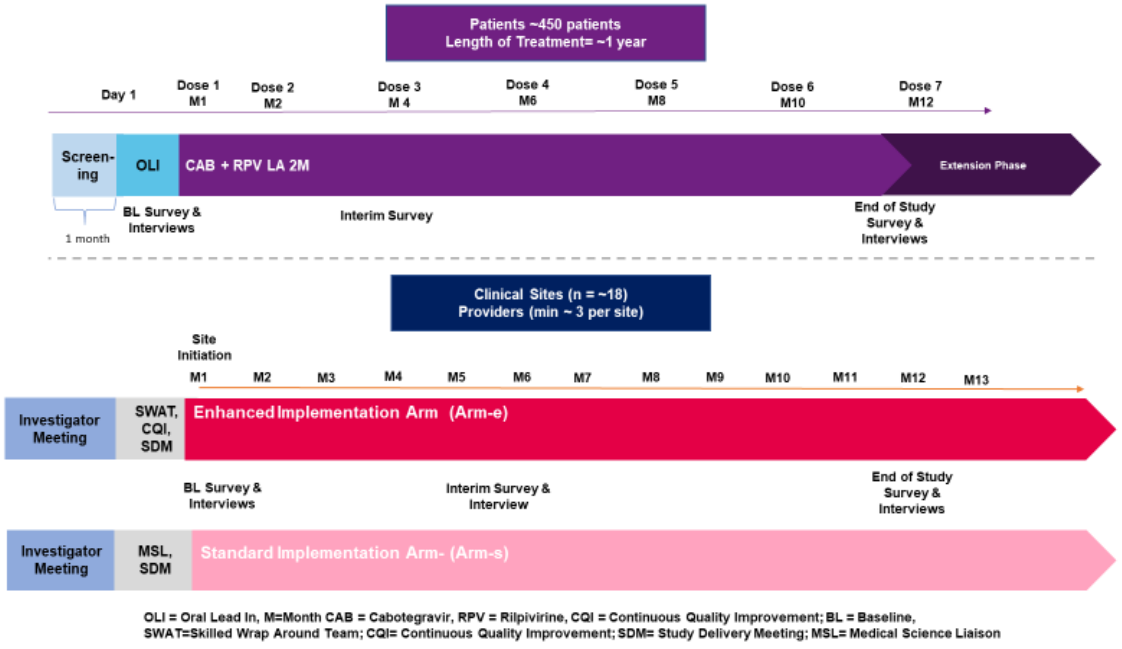
must enter the 52-week LTFU Phase. Those participants must remain on suppressive highly active antiretroviral therapy
(HAART) for at least 52 weeks after the last dose of CAB LA and/or RPV LA.

There are two arms for the providers (arm-e and arm-s) which contain different levels and type of support for the implementation of the HIV Regimen. Different implementation components are found in Table 3. Cluster randomization will be used to randomize sites in each country to either arm-e or arm-s.

Table 3 Implementation Components

	Implementation Component	Arm-e	Arm-s
1	Study Treatment Injection Training	Face-to-face	Virtual
2	Toolkits	X	X
3	SWAT Meeting	X	
4	CQI Meetings (once monthly)	X	

Schema:



4.2. Design of Implementation Research

The proposed study is a cluster-randomized, implementation-effectiveness hybrid type III study. This design allows for a simultaneous focus on both implementation and effectiveness, which allows for maximizing our understanding of how-to best support translation of CAB LA + RPV LA into routine care while continuing to collect effectiveness and safety data. The hybrid type III focuses primarily on the impact of the implementation to get the intervention (CAB LA + RPV LA) into routine care. As a

result, the primary focus of this study is implementation. The secondary focus is on the clinical effectiveness.

To adequately measure the impact of this study, implementation outcomes will be measured in addition to service and patient level outcomes. Implementation outcomes are different from clinical outcomes in clinical trial research. These research outcomes are typically provider and/or system focused and often rely on triangulation of both qualitative and quantitative data. Outcomes can include levels and rates of acceptability, adoption, and fidelity to the clinical intervention and the impact of the implementation strategies on these rates (Proctor, 2011).

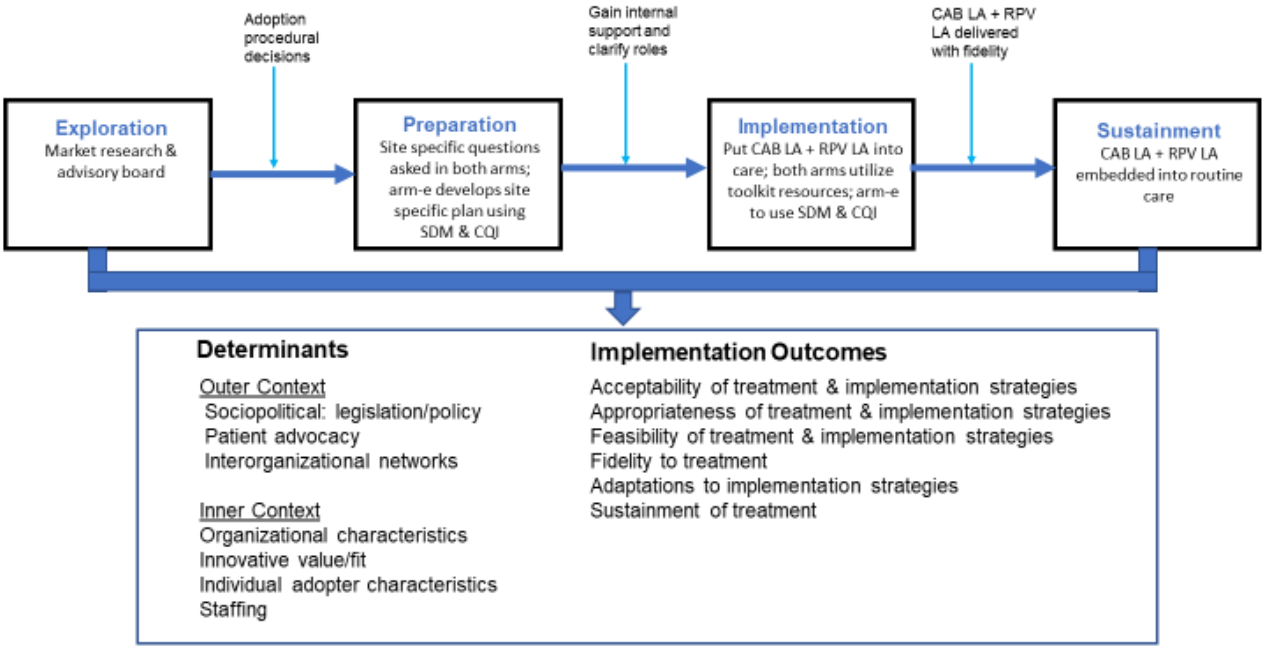
In addition, implementation research focuses on addressing the question of 'what works where, and why.' By identifying factors and processes that negatively and positively affect implementation outcomes, these issues can be effectively addressed in subsequent real-world implementation efforts. The study will allow the tailoring of implementation strategies and clinical support materials to match the specific needs of different clinical settings across Europe. Importantly, the design will also allow for tailoring of strategies within countries to ensure each unique context is understood and considered throughout the study. As a result, this proposal is guided by frameworks that are appropriate to the proposed stage of implementation research, including both a process and determinants framework and an outcomes taxonomy. The chosen frameworks are highly sensitive to the contexts in which the implementation efforts will occur when CAB LA + RPV LA goes to scale in the real world.

4.2.1. Implementation Frameworks:

Implementation research often utilizes multiple frameworks or models to guide the aims, methods (including implementation strategies), and evaluation. In this study, the Exploration, Preparation, Implementation and Sustainment Framework (EPIS, Aarons 2011) is a process and determinants framework that will guide all aspects of the study including study aims, consideration of implementation strategies, and implementation evaluation. This framework will be used in conjunction with the Proctor and colleagues (Proctor, 2011) outcomes guidelines to provide guidance on study design and outcomes (Figure 1).

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 LA + RPV LA is or is not successful across contexts, clinical settings, and implementation strategies. Over 150 implementation frameworks exist, making the choice idiographic to each study. Having a framework that is highly specified operationally and widely used in implementation science is advantageous.

Figure 1 Synergy between frameworks. The EPIS Framework and Proctor guidelines will guide all aspects of the study design and outcomes.



4.2.2. Exploration, Preparation, Implementation, Sustainment (EPIS)

The EPIS Framework emphasizes the central role of context, identification of multi-level barriers, and provides important guidance on both implementation process and determinants. EPIS emphasize the role of services delivery organizations and service systems in which they operate, while being designed to articulate variables that are hypothesized to play key roles in implementation of evidence-based interventions. As a result, EPIS will enable us to not only characterize and explain the ways in which implementation strategies and service system processes have and have not been successful across contexts and settings, but it will also allow us to examine important variables that will be important for implementation sustainment in Europe. Findings from the study will have enough detail to inform the tailoring of implementation strategies, if needed, to enhance the implementation effectiveness of CAB LA + RPV LA once locally available.

EPIS (Aarons, 2011) both guides and describes the implementation process while enumerating common and unique factors that may impact success or failure of implementation efforts. These factors span outer context (system) and inner (organizational) context across phases, as well as factors that bridge the outer and inner context (Aarons, 2011). The inclusion of leadership, considering bridging factors, as well as the nature of the actual innovation provides important guidance for the current study. Leadership is particularly important as it plays a key role in organizational change needed to support successful implementation. Leaders play a number of key roles including and

ability to foster an organizational climate receptive to necessary change. Their implementation support occurs through a variety of outlets including securing funding and resources, and enforcing policies, all of which impact the success of implementation efforts in a local setting.

A recent review (Moullin, 2019) summarizes EPIS use to guide and test theory and process across different countries, health systems, and health problems. EPIS has four phases that align with, and guide, implementation processes. The phases are outlined in Table 4. The current study capitalizes on initial data from the CUSTOMIZE study (209493), as well as the market research done across Europe to provide important information that would otherwise need to be gathered in the Exploration phase. This study will focus on Preparation (e.g., arm-e and arm-s) to identify barriers and facilitators unique to each context) and Implementation (e.g., initiate use of CAB LA +RPV LA in each setting). Given the duration of the study, we are unable to fully examine the Sustainment phase. However, embedded assessment on sustainment will provide sites support to continue to endure the proper procedures for CAB LA + RPV LA in routine care after the study. Including evaluation of sustainment in this study will ultimately support both tailoring of implementation strategies during study, as well as supporting sustained gains using CAB LA + RPV LA at the time of local availability in countries across Europe.

Table 4 EPIS Framework Phases and Definitions (Aarons, 2011)

EPIS Phase	Definition
Exploration	A service system, organization, research group, or other stakeholder(s) consider the emergent or existing health needs of the patients, clients, or communities and work to identify the best evidence-based intervention to address those needs, and subsequently decides whether to adopt the identified evidence-based intervention
Preparation	The primary objectives of this phase are to identify potential barriers and facilitators of implementation at the outer and inner contexts, further assess needs for adaptation, and to develop a detailed plan to capitalize on implementation facilitators and address potential barriers.
Implementation	Evidence-based intervention use is initiated and instantiated in the system and/or organization(s).
Sustainment	The outer and inner context structures, processes, and supports are ongoing so that the evidence-based intervention continues to be delivered, with or without some adaptation, to realize the resulting public health impact of the implemented evidence-based intervention

Proctor Implementation Outcomes (Proctor, 2011):
The evaluation of preparation and implementation from the EPIS framework is on five key implementation outcomes: (1) acceptability, (2) appropriateness, (3) feasibility, (4)

fidelity, and (5) sustainability (see Table 5). According to Proctor, 2011, these outcomes represent key intermediate factors in relation to service system outcomes or clinical outcomes in treatment effectiveness and quality of care research.

The implementation outcomes will be assessed through validated quantitative questionnaires and qualitative interviews (See Section 10.10 and Section 10.11 for a summary of elements to be evaluated in the questionnaires). 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). All five of these outcomes will also be incorporated into the qualitative interviews, which is the standard measurement for implementation outcomes.

Table 5 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.
Sustainability	Extent to which the intervention becomes routinely available/maintained post introduction. The current study will measure each sites capacity to sustain gains made to CAB LA + RPV LA implementation.

4.2.3. Impact of Implementation Strategies on CAB LA + RPV LA

This study offers opportunity to identify the best implementation strategies to support real world uptake. Implementation strategies are methods or techniques used to enhance the adoption, implementation, and sustainability of a clinical program, practice or intervention. Implementation strategies are broadly applicable to a range of context and offer evidence-based approaches to fit dynamic, real world barriers that require problem solving on the implementation journey. The protocol evaluates arm-s, which includes access to patient and HCP facing toolkits, and arm-e which includes Skilled Wrap-around Team (SWAT), Implementation Slide kit, patient and HCP facing toolkits plus a dynamic implementation strategy, CQI. The addition of CQI allows for a more nuanced understanding of the level of support sites may need as they transition to the use of CAB LA + RPV LA in their clinics. CQI can also be incorporated into their routine clinical and organizational culture which is key to success. The two-arm design will 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 across Europe.

4.2.4. Study Arms

Although all sites enrolled in the study will have access to the study toolkits intended to be available at the point when CAB LA + RPV LA is locally available in each country, each site will be cluster randomized to one of two implementation arms. Each is intended to provide sites enough care to support changes needed for CAB LA +RPV LA implementation in the real world. The two conditions are:

1) Enhanced Implementation Arm (arm-e)
2) Standard Implementation Arm (arm-s)

4.2.4.1. Enhanced Implementation Arm (arm-e) Description

In the initial CQI meeting, discussions will occur about how CQI offers a preemptive method to address problems that may ultimately contribute to low rates of CAB LA +RPV LA uptake an intervention and the delivery context is ultimately crucial for sustainability. CQI inherently assumes there will be some deviation from procedures around scheduling, staffing, and other logistics, to ensure fit of the innovation and the context. For CAB LA + RPV LA, this is crucial as each context will likely need to engage in refinement of procedures to improve local fit in the real world outside of efficacy trials. Once study sites are determined and language preferences are identified, it will be determined if these calls are done by country, clinic, or groups of 2-3 clinics that speak the same language.

The other component that is unique to sites in arm-e is access to top challenges anticipated by each country with recommendations for how to overcome these challenges through different implementation strategies. These resources have been developed through information collected during advisory boards as well as discussions with country medical leads. These tailored implementation strategies are not meant to limit what can be done to overcome challenges in each country, but rather to help start discussions with the key stakeholders at each site to begin to overcome challenges from the start of the study. They can be used both in the initial SWAT meeting as well as in the CQI calls.

To understand important modifications and adaptions to the implementation of CAB LA + RPV LA, the FRAME-IS will be completed each month by key staff study participants identified as being aware of daily operations and modifications. This will allow for a nuanced understanding of local changes made to implementation strategies, which will also allow for capturing cultural adaptations that are otherwise difficult to measure, as well as the relationship between different forms of modification and subsequent health and implementation outcomes. Lastly, sites in this condition will also have access to the all the patient- and HCP-facing toolkit items. These tools may vary slightly by country but will be made available to help support capacity planning, storage, and many other variables that may impact CAB LA + RPV LA administration and access.

The Arm-e will contain the following components:

1. Investigator Meeting: All site principal investigators and key staff will attend the investigator meeting that will provide information on effectiveness of CAB LA + RPV LA, study procedures, and an overview of safety information.

2. SWAT Meeting with sponsor team and principle clinic stakeholders: This meeting will occur following the investigator meeting, ideally within the first month of the study. At this meeting, site-specific key personnel (e.g., staff study participants, local leadership, administrators, clinical staff) will work with the SWAT to review the Implementation Slide kit and spend time discussing the rationale for CQI and how it will be used to support implementation in the study. Participants in the CQI calls (2 personnel per site) will be identified and confirmed at this time. Participants for the SWAT meeting will be discussed with the site principal investigator to ensure appropriate people from each site are invited to participate in this meeting.
3. On-demand SWAT meeting: On request, sites will have access to a follow-up SWAT meeting in person to discuss concerns and/or questions about implementation of CAB LA +RPV LA.
4. Monthly Continuous Quality Improvement (CQI) calls: Sites within each country cluster randomized to this condition will attend monthly 1-hour CQI calls together if available. If possible, the key staff at each clinic that participate in the day-to-day injections, medical oversight, and management of CAB LA + RPV LA will attend this call, but a maximum of 2 staff from each site will be included on the calls. This will be determined using information gathered during site selection and confirmed at the initial SWAT meeting. If a barrier is identified that requires an additional staff member attend a CQI call(s), this will be considered on a case by case basis. These calls will be led by a CQI trained leader. During each call, study staff participants will be asked to identify barriers to implementing CAB LA + RPV LA that they identify and work through a Plan, Do, Study, Act (PDSA) cycle on the call. They will then be asked to act on the PDSA cycle between CQI calls to test the success of their strategy at addressing the identified barriers.
5. Face-to-Face injection training: Each site will be provided to an initial face-to-face injection training with the option of adding on virtual injection trainings if requested by the site during the study. Where new staff join the study the injection training should also be provided face-to-face where possible.
6. Monthly FRAME assessment: each month the key stakeholder(s) from each site will be asked whether they made any adaptations to the implementation strategies at their site to assist in implementation of CAB LA + RPV LA. This measurement will also be used to capture additional implementation strategies that were not identified by the study team.
7. Access to toolkit: All sites will have access to both patient level and HCP level toolkits. See Table 6 for list of anticipated toolkit components.
8. Medical science liaison or CAB + RPV Medical Lead will visit each clinic per standard practice in the country.

4.2.4.2. Standard Implementation Arm (arm-s) Description

Following the investigator meeting each site will have a visit with either a medical science liaison or a medical lead (depending on the country) to address investigational product questions. This might include, but is not limited to, discussing the treatment, answering medical questions, and utilization of toolkits components. On-demand visits or calls with a medical representative will be available. Injection trainings will be conducted virtually at the start of the study, with additional training options available as

needed. To capture and understand a site's successful implementation on their own doing a monthly FRAME-IS will be completed by key stakeholders and are intended to capture current successes and barriers. Of note, this condition will not have access to the country specific implementation strategies developed for arm-e.

The Arm-s will contain the following components:

1. Investigator meeting: All site principal investigators and key staff (e.g., nurse, pharmacist) will attend the investigator meeting that will provide information on effectiveness of CAB LA+ RPV LA, study procedures, and an overview of safety information.
2. Medical science liaison or CAB + RPV Medical Lead will visit each clinic per standard practice in the country. These meetings will happen quarterly or at the discretion of the clinic. At this meeting, there will be the option of using the Implementation Slide kit, however, it is not a required part of this arm and is to be decided at the discretion of the Lead.
3. Access to toolkit component: All sites will have access to both patient level and HCP level toolkits components. See Table 6 for list of anticipated toolkit items.
4. Virtual injection training: All sites will have access to a virtual injection training at the start of the study and as needed throughout the study.
5. Monthly FRAME assessment: each month the key stakeholder(s) for each site will identify whether they made any adaptations to the implementation strategies at their site to assist in implementation of CAB LA + RPV LA.

4.2.5. Key Evaluation of Implementation Strategies & Insights

FRAME:

A measurement of implementation strategies in this study will be critical to fully understanding how sites capitalize on facilitators and overcome barriers to CAB LA + RPV LA implementation and make changes to prescribed strategies to best meet local needs. These modifications are rarely systematically captured, ultimately limiting the generalizability of results to new clinical settings. The framework for reporting adaptations and modifications to evidence-based interventions (FRAME; Stirman, 2019) allows the capture of important modifications and adaptations to interventions or implementation strategies occurring at each local site. The FRAME-Implementation Strategy (FRAME-IS) is intended to be used to track changes made specifically to implementation strategies. The FRAME-IS is a measure that can be completed monthly to provide a precise understanding of modifications, the process of modifying or adapting, and the relationship between different forms of modification and subsequent health and implementation outcomes. Given sites are encouraged to figure out how to make CAB LA + RPV LA work for their given clinic, regardless of condition they are in, capturing the nuance for each site will be important for understanding optimal implementation across Europe moving forward. Data from the FRAME-IS can inform a foundation for future optimal implementation in sites with similar characteristics. The FRAME-IS will be used with providers in both arms.

Continuous Quality Improvement (CQI):

CQI is a dynamic implementation strategy that is intended to improve evidence-based practice delivery and quality and will involve study staff participants (Colton, 2000). It is an iterative process of monitoring performance, identifying barriers, generating possible solutions, and implementing changes. The measure and impact of change will be assessed, and modifications can be made (in real time) if a desired outcome is not being achieved. PDSA Cycle supports CQI and allows it to be individualized to the context within each clinic. The participants will be taught how to utilize the CQI process to address these problems and perform mini-experiments to understand what change is most effective to achieve their goals. This will start at the first CQI meeting during the initial SWAT meeting and will continue with hourly calls ~every month for 6 months, with the option to extend. The CQI calls will start by helping identify problems/challenges, generate plans to address the challenges, and identify how to measure the change that results from the plan, so that at each call, staff study participants can discuss progress with the CQI leader and get support if additional iterations are needed. With increased comfort, staff study participants will create PDSA cycles to test, independently of the CQI facilitator.

Study Toolkit:

The study toolkit is a collection of provider-facing and patient-facing materials intended to support the delivery of CAB LA + RPV LA in real-world clinical settings (Table 6). Contents include provider- and patient educational items, nurse/injector training aids, treatment scheduling and capacity planning tools, and patient-directed apps that will be made available as part of the study. In the table below, the toolkit categories are identified. Specific toolkit items will be shared at the investigator meeting. At a minimum, they will be offered at the time pointed noted in the table. However, the toolkit items are intended to be used throughout the study.

Table 6 Study Toolkit Components *

Materials	Objective	Target Audience	Timepoint Offered for Patients and Assessed by Providers
Provider/ Staff Education Materials – Web based	Staff Education	Staff	Month 1monthly through End of Study
Provider/Staff Education materials – Hard copy	Staff Education	Staff	Month 1 monthly through End of Study
Patient Education Materials – Web-based	Patient Education	Patient	Oral Lead-in, Doses 1-3, 5

Materials	Objective	Target Audience	Timepoint Offered for Patients and Assessed by Providers
Patient Education materials – Hard copy	Patient Education	Patient	Oral Lead-in, Doses 1-3, 5
Web-based treatment planner	Scheduling	Staff	Month 1, 2, 4, 6, 8 10
Capacity Planning Tool	Sustainability	Staff	Month 4, 6, 8, 10
Implementation Slide kit	Staff Education/ Capacity Planning	Staff	SWAT meeting or MSL meetings
Patient video	Patient Education	Patient	Oral Lead-in, Dose 1
Injection Training Video	Nurse/Injector Education	Staff/Nurse or Injector	Prior to first injection, throughout the study as needed
In-person Injection Training	Nurse/Injector Education	Enhanced Arm only - Staff/Nurse or Injector	Prior to first injection, throughout the study as needed
Peer to Peer Education	Provider/ Physician Education	Physicians/staff	During enrollment, throughout study as needed
Chatbot	Appointment Adherence and FAQs	Patients (offered at some locations)	Oral Lead-in-End of Study

** Specific toolkits offered in the study will be flexible to ensure the study is offering toolkits consistent what the toolkits that are intended to be offered in routine care.*

While a "toolkit" of supporting elements will be provided in this study, clinical sites will be allowed to choose how they will implement CAB LA + RPV LA delivery in their clinical setting (i.e. nurse visit during clinic hours, pre-post clinic hours, weekend hours, Tues/Thursday clinics, in hospital settings, in pharmacies, at home 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 questionnaires and SSIs. Modifications made to the implementation process or approach during the study, e.g. 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 LA + RPV LA regimen. Investigators will inform the study team of their change and document the reasons why, which will be formally captured by the FRAME-IS in both conditions.

Staff Qualitative Staff Interviews and Quantitative Questionnaires:

Questionnaires and interviews will be administered to the staff study participants at three timepoints:

- Month 1 (established by site activation): Before the first patient receives the first injections at the site
- Month 5: within 4 weeks of the first patient receiving dose 3 at the site.
- Month 12: within 4 weeks of the first patient receiving their last injection (Dose 7) at the site.

Qualitative interviews will be conducted with study staff participants and to assess whether acceptability, appropriateness, fidelity, and sustainability are achievable within each site's setting. Interviews will probe for multilevel barriers to, and facilitators of, CAB LA+RPV LA implementation. Key stakeholder interviews will elicit in-depth information as these individuals have first-hand knowledge of the factors influencing local implementation. The interviews are EPIS-based (Aarons, 2011) which allows for information about characteristics of the adopters, needs and resources of each site, impact of leadership, and factors that might impact the larger system including policy changes at a local and national level.

The interviews for staff study participants will be conducted with up to approximately 4 participants of various disciplines in each clinic that play a critical role (e.g., HIV care providers, nurse/person(s) administering the injections, clinic administrator/manager(s), pharmacists).

An example of a baseline study staff participant qualitative interview can be found in Section 10.12.

The first two questionnaires will take about 15 minutes to complete. The final questionnaire 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 injection, and at the following timepoints based on their current experience administering the injection. The Month 12 assessment will include the CSAT, which may be scheduled in a separate assessment period to ensure thorough completion and support for sites following the conclusion of the study.

With notification or approval by the study team, timing and format of interviews and questionnaires maybe adjusted during times of exceptional circumstances as a result of COVID-19, missed visit. etc.

Details about concepts measured in the staff study participant questionnaires can be found Section 10.11.

Patient Qualitative Interviews and Quantitative Questionnaires:

Qualitative interviews result in valid data when thematic saturation is reached in a sample being examined. Thematic saturation is estimated to occur with 6-12 interviews in the targeted study population (Hamilton, 2019). The number of interviews is set at a minimum of 6 patients interviewed and up to 75% of PSPs enrolled per site to ensure thematic saturation. This will allow for the ability to adjust the number of PSPs at a

given site to appropriately meet site specific saturation. Interviews will be administered to the PSP at two timepoints: before Dose 1 and within 4 weeks of receiving Dose 7.

Selection for Interviews- Given the goal of qualitative data is to understand a specified topic area and gain in-depth contextual understanding rather than generalizability, purposive sampling will be utilized to select patient participants for interviews. Purposive sampling will ensure that the right patient participants are included, and the targeted information/questions can be answered and thematic saturation to be obtained at each site (Hamilton, 2019).

An example of a baseline patient study participant qualitative interview can be found in Section 10.13.

Quantitative Questionnaires. The quantitative implementation data will be collected via questionnaire which will be administered to the patient study participants a Doses 1, 3, and 7 visits (questionnaires to be completed prior to receiving the injections).

Each of the patient questionnaires will take 15-20 minutes to complete. Patient study participants will be asked to answer the questions at Dose 1 based on their current expectations of receiving the CAB LA+RPV LA injections, and at the Dose 3 and 7 timepoints will ask participants to respond based on the current experience receiving the injection during the study.

Details about concepts measured in the patient study participant questionnaires can be found Section 10.10.

With notification or approval by the study team, timing and format of interviews and questionnaires maybe adjusted during times of exceptional circumstances as a result of COVID-19, missed visit. etc.

4.2.6. Country Specific Challenges and Implementation Strategies

Infectious Disease (ID) and HIV care providers were queried on their plan and ability to implement CAB LA + RPV LA effectively into their clinical settings across Europe. Mixed responses suggested that some sites might require more support and some sites many require less support to implement this new intervention well. The level of support may also vary within some countries. However, the exact level of support remains an empirical question, which will be addressed through the two arms of the current study. Some of these unique factors will inevitably be addressed in the both conditions.

Based on initial country feasibility and market research; key challenges by country and potential implementation strategies to address them are may be provided in implementation science handbook.

4.2.6.1. France

Research in France identified several steps for successful CAB LA + RPV LA implementation. First, creation of tools or support for HCPs to identify appropriate patients was noted as critical. Some suggest without efficient transition of administration

of CAB LA + RPV LA to district nurses, there will be a capacity issues in hospitals. If there is a clinic in this study that would be willing to explore the transition of delivering injectables from hospital to a district nurse, facilitating communication between hospitals and district nurses will be important. However, transition to district nurses will take time as they have no previous experience with this type of care, therefore may or may not occur during this study. Last, research indicated that there was additional assessment needed around feasibility due to the 'cold chain' requirement. Both patients and nurses will need to pick up the medication from a pharmacy and transport it to their injection appointment location.

4.2.6.2. Spain

Research from Spain has identified eventual capacity issues post local approval once patient flow increases, and hospital wide resources will become stretched. To address capacity issues resources within hospitals will need to be reallocated. Additionally, communication between the HIV units and other hospital departments will need to be improved to ensure a good user experience. Lastly, like France, HCPs were concerned about patient identification and need additional support.

4.2.6.3. Belgium

In Belgium there are several emerging areas to address for successful implementation of CAB LA + RPV LA. First, a capacity issue is anticipated, and injections will need to be given by health-care providers other than nurses and alternative injection locations will eventually be required to ease capacity of the AIDS reference centers (ARCs). However, this will require a policy change and may happen during the study which will require flexibility of an implementation strategy that embraces dynamic processes for sustainable change. It was also requested that the sponsor provide injection training and education to help with capacity constraints. Patient support is needed to help support adherence, which is anticipated to be achieved through support tools. Lastly, cold chain management is a consideration as the ideal storage scenario would involve dispensation and storage within ARCs. However, this will require legislative change in order to dispense CAB LA + RPV LA from a location other than a community pharmacy. This model will likely involve multiple touchpoints to get the injections to the injector and injection to the patient.

4.2.6.4. Germany

In Germany, CAB LA +RPV LA will be in the outpatient setting with specialized services. There are three models of HIV care in Germany: large private practices with 5-8 physicians with multiple nurses and high capacity; small private practices with 1-3 physicians and limited staffing; and university setting which see a small volume of patients but have a high level of resources. Medication will need to be picked up by patients a pharmacy with a paper prescription from their provider. Additionally, prescriptions are only valid for 30 days, which is anticipated to be a challenge for patients receiving CAB LA+ RPV LA every two-month dosing as the patient will need a

prescription written within 30 days of their injection appointment date. As a result, the product journey will be challenging. Additional potential challenges in Germany include providing appropriate education for clinic staff on CAB LA + RPV LA, as well as discussion about how to schedule appointments and support patient adherence. Lastly, study start will likely overlap with drug being locally available in Germany.

4.2.6.5. Netherlands

In the Netherlands CAB LA + RPV LA is expected to be delivered across hospital-based HIV clinics. Some patients receive care from their general practitioners for related care like viral load tests and PrEP, but in general, care tends to be led by infectious disease physicians and specialist nurse practitioners, both can prescribe medication. Stable patients typically only see their healthcare professionals twice a year, with one of these appointments potentially occurring virtually. Additionally, prescriptions are typically written once every 6-months and patients collect their medication at the outpatient pharmacy every 3-months. As a result, the introduction of CAB LA + RPV LA will require an increase in the frequency of visits (anticipated to impact clinic capacity and nurse time), prescription practices (including the potential of transporting CAB LA + RPV LA), and an economic impact on the hospitals as injection appointments are likely to be considered as an inpatient appointment effecting the hospitals budget.

4.3. Treatment Groups and Duration

4.3.1. Study sites

Investigational sites or investigators that have not previously delivered the CAB LA + RPV LA regimen will be preferred for this study. Selection will be based on ability to recruit the desired number of study participants, clinic size, demographics, geographic diversity, and patient population. Sites will be selected in order to cover a wide variety of HIV care settings. Sites will be asked to operate through their regular clinic pathways rather than a research pathway wherever possible.

Sites will be classified by the sponsor based on care delivery systems such as (but not restricted to) the following:

- Hospitals
- AIDS Reference Centers
- Hospital-based ID clinics
- Community Traveling Clinics (ex. district nurses)
- Community-based
- Sexual Health Clinics

Clinics that include participants from multiple categories (public/private) will be categorized based on the Principal Investigator's determination of most of their patient base. Each clinic selected will be categorized by country, archetype (defined above), number of providers/ staff, number of patients, and other clinical characteristics that may be considered confounders or influence implementation.

Number of Sites:

Sites across the following countries: France, Spain, Netherlands, Germany and Belgium will be selected. Exact site number will be based on feasibility assessments and approximately18 sites will be selected.

4.3.2. Study staff participants

Study staff participants will be included that are central to best practices delivery of CAB LA +RPV LA within each local context. This will be decided based on the local clinical infrastructure and practices at each site. At least three staff participants, identified prior to study commencement, will be included at each site.

Examples of Study Staff Participants whom may participate in the study:

- HIV HCPs
- Nurses
- Staff performing injections
- Clinic Managers
- Administrators (staff involved in resourcing space/ staff or involved in patient scheduling, etc.)
- Pharmacists

Data will be collected from study staff participants per Table 2. Informed consent will be obtained prior to any study assessments for study staff participants (where applicable, as determined by local regulatory and compliance requirements).

All study staff will attend an investigator meeting prior to study start. The purpose of this meeting is to educate healthcare staff on the CAB LA + RPV LA regimen, including the proper administration of the regimen, protocol requirements for all study participants, data collection methods and an overview of available study toolkit. Additionally, an overview of the key protocol objectives and relevant implementation science elements will be reviewed.

Staff study participants will provide input by questionnaires, semi-structured interviews and, FRAME-IS questionnaires, and CQI calls, per the Schedule of Activities Table 2.

Should there be turnover in staff study participants over the course of the study, the replacement staff member will undergo study training per standard practice and continues staff study activities per schedule of assessments.

Number of staff study participants:

Given the unique contexts across the 5 European countries the number and type of staff study participants will vary by site. The total number of staff study participants will be a minimum of approximately 3 per site (~n = 54).

4.3.3. Patient study participant

Patient study participants are HIV-1-infected adults that fulfil the eligibility criteria. Each patient study participant will receive CAB LA + RPV LA and clinical assessments throughout the study per the Schedule of Activities (SoA). Data will be collected from patient study participants per Table 1.

A goal of this study is to enroll 20% female participants, as this population is often underrepresented in clinical studies.

Number of Patient Study Participants:

Each site will be asked to recruit enough patient study participants to serve as a reasonable number in an environment reflective of a real-world situation. This will be based on feasibility assessment and site capacity to inform subject recruitment allocation ensuring a balance without compromising study subject safety. Additionally, this approach will allow sites adequate opportunity to describe the challenges and practical limitations experienced during initial implementation of CAB LA + RPV LA, as well as opportunity to evaluate the resources needed and alternative strategies for successful implementation.

The enrolment period and rate will be monitored continuously and adjustments to the enrolment period and patient distribution may occur based on site feasibility and recruitment.

The maximum number of patient participants included in this study is anticipated to be approximately 450.

Patient study participants enrollment:

All patient study participants will complete the **screening phase** of up to 35 days prior to enrollment. Participants may be re-screened once. 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. Informed consent must be obtained prior to any study procedures for patient study participants, including any screening assessment.

HIV-1 infected participants who meet all eligibility criteria will be switched from their pre-baseline regimen to an oral regimen (CAB 30 mg + RPV 25 mg once daily) during the **oral lead-in phase**. Participants will return to the clinic, and if laboratory and clinical evaluations continue to support progression into the **injection treatment phase** of the study, will take the last dose of their oral regimen (CAB 30 mg + RPV 25 mg) and receive the first dose of CAB LA (600 mg) + RPV LA (900 mg) injections on the same day (Month 1). The participant will receive the second injections CAB LA (600 mg) + RPV LA (900 mg) one month later (Month 2). All subsequent injections will occur every two months thereafter (Month 4, Month 6, etc) for a total of 7 doses of CAB LA

and RPV LA (Table 7). **The total length of the treatment phase is approximately one year.**

Table 7 Dosing Regimen

Oral Lead-in to End of Study+	
CAB + RPV Oral Lead-In	
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 LA + RPV LA Injections	
Dose 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
Dose 2 to Dose 7 (Month 2- End of Study+) two 3 mL injections every two months	• 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
+Until after dose 7 (Month 12) when 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	

The dosing window for the second injections will be +0 / -7 days from the projected target date (target date is established at Month 1). All subsequent injection windows (starting with Dose 3) will be +7/-7 days from the projected target date. Doses outside of the window *may* be allowed with prior Medical Monitor approval.

Participants will continue CAB LA + RPV LA until:

- After dose 7 and when the study intervention is locally approved and available for the Investigator to prescribe. Note if intervention is not locally approved at dose 7 they will continue into the Extension Phase (see Section 6.8).
- the participant no longer derives clinical benefit
- the participant meets a protocol-defined reason for discontinuation
- the development of CAB LA and/or RPV LA is terminated
- participant withdraws consent
- participant is withdrawn due to investigator discretion
- participant is withdrawn due to participant or investigator non-compliance

- termination of the study by the Sponsor.

Safety and efficacy assessments will be conducted as per the Schedule of Activities (Section 1.3).

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 long-term follow-up (LTFU) Phase of the study.

4.3.4. 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 before CAB LA + RPV LA marketed product is locally available must enter the LTFU Phase. Participants 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.

- **Where the CAB LA + RPV LA Marketed Product is Locally Available**

  Only the participants that discontinue the CAB LA + RPV LA regimen for **safety-related reasons** included in Section 7, must enter the LTFU Phase. Participants must remain on suppressive highly active antiretroviral therapy (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.

  NOTE: Participants who transition to CAB+RPV LA, marketed product or alternative HAART (except due to safety-related reasons) do not need to enter the LTFU Phase.

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 one month (- 7 days) after the last dose if interruption is prior to Dose 2 and within 2 months (± 7days) after the last injection if interruption is following Dose 2, 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.

Long term Follow up phase requirement

Marketed product locally available	Subject WD due to safety-related reasons	LTFU phase required?
No	Yes	Yes
	No	
Yes	Yes	Yes
	No	No, but Safety FU visit required to assess potential safety issues occurred after the last injection see Section 4.5.1.2 Safety Follow-up Visit.

Participants entering the LTFU phase will not complete a Withdrawal visit but will instead move directly into the LTFU Phase as per the schedule of activities. In addition, for participants who withdraw during the LTFU Phase, 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 ensure that participants have access to HAART during the LTFU Phase, 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.

4.4. Justification for Dose

PSPs will evaluate the implementation of the every-2-month CAB LA + RPV LA regimen. Specifically, subjects will receive oral CAB 30 mg once daily + oral RPV 25 mg once daily for 1-month starting on Day 1 followed by CAB LA 600 mg (3mL) + RPV 900 mg (3mL) at Month 2, Month 3 and every 2 months thereafter.

4.4.1. Oral Lead-In Phase

Participants in 213199 will enter the study virologically-suppressed on an oral SOC regimen and will receive oral CAB 30 mg + RPV 25 mg once daily for about one month during the oral lead-in (OLI) 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 of healthy subjects and HIV infected participants. 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]. In the dose-ranging Phase 2b study LAI116482 [(LATTE], oral CAB 10, 30, or 60 mg once daily was co-administered with 2NRTIs for 24 weeks in treatment naïve HIV infected subjects and with the marketed tablet formulation of RPV 25mg once daily as a 2-drug regimen after achieving virologic suppression for an additional 72 weeks; CAB 30 mg once daily and RPV 25 mg once daily was administered to all subjects after Week 96 for an additional 3 years. Rates of virologic suppression through Week 96 (Maintenance) were numerically higher than the EFV-based comparator regimen (Table 8).; GlaxoSmithKline Document Number 2014N216014_00]. Oral CAB 30 mg and RPV 25 mg once daily has been administered as 1-month OLI and 1-2 months oral bridging for planned missed injections in the Phase 2b Study 200056 [LATTE-2] (GlaxoSmithKline Document Number 2013N168152_05) and in Phase 3 studies 201585 [ATLAS] and 201584 [FLAIR] which evaluated Q4W dosing of CAB LA + RPV LA and the Phase 3b Study 207966 [ATLAS 2M] which evaluated both Q8W and Q4W regimens.

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.

4.4.2. 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 3-drug

regimen, for maintenance of virologic suppression in HIV-infected, treatment-naive adults. Following induction with16 weeks of oral CAB + 2 NRTIs, 4 weeks of CAB + 2 NRTIs + oral RPV, eligible participants were 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 9) 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.

Table 9 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)

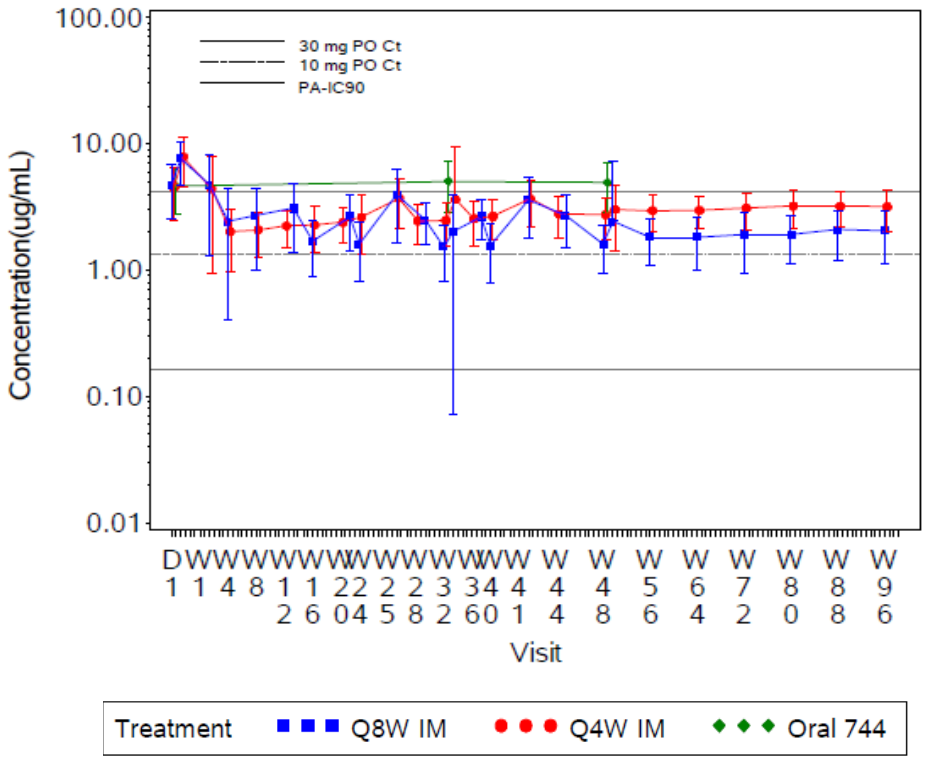
At week 160, 90% of patients receiving intramuscular CAB + RPV every eight weeks and 83% of patients receiving the same regimen every four weeks remained virally suppressed. Of the patients that switched from the comparator regimen of oral CAB + abacavir (ABC)/lamivudine (3TC) to the intramuscular regimen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

The monthly regimen of CAB LA + RPV LA was determined to be noninferior to standard of care in 2 Phase 3 studies – 201585 (ATLAS) and 201584 (FLAIR). The every 2 month regimen was shown to be noninferior to the monthly regimen in Phase 3b Study 207966 (ATLAS 2M).

4.4.2.1. CAB LA Pharmacokinetics

Observed pharmacokinetic data for both CAB LA regimens in LATTE-2 are presented in Figure 2 (Margolis, 2018).

Figure 2 Observed Mean (SD) Concentration-Time Data following CAB LA Q8W and Q4W and Cτ following 30 mg PO QD through Week 96 (200056, LATTE-2)

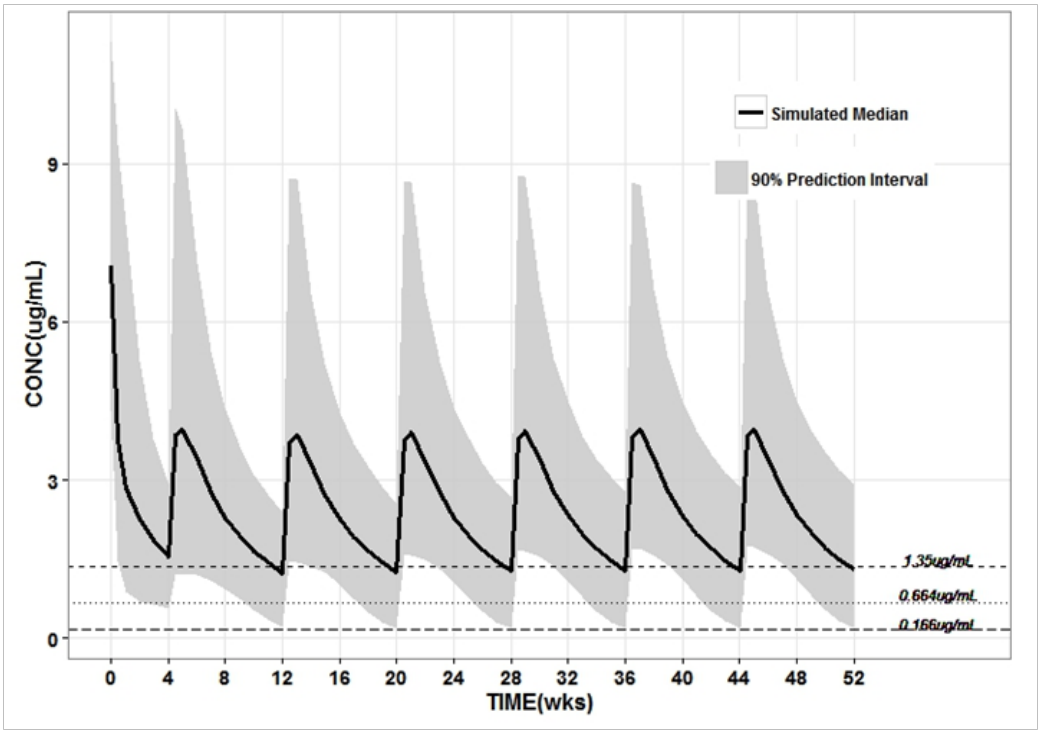


Data Source: Figure 4.1003
Subjects randomized to remain on oral CAB during the Maintenance Phase had predose CAB concentrations obtained on Day 1, Week 32 and Week 48.
Subjects randomized to CAB LA in the Maintenance Phase received their final Induction Phase dose of oral CAB 30 mg once daily as well as their first CAB LA injection on Day1.
CAB 2-h post-injection concentrations were obtained on Day 1 (largely reflecting oral dosing), Week 32 and Week 48.
CAB 1-week post-injection concentrations were obtained on Week 1, Week 25 and Week 41.
CAB 4-week post-injection concentrations reflect either trough concentrations (Q4W) or troughs and mid-cycle concentrations (Q8W) through W48.
All concentrations shown from Week 56 to Week 96 represent troughs regardless of regimen.

The CAB LA 600 mg Q2M regimen is predicted to achieve concentrations above 1.35µg/mL, the geometric mean trough concentration (Cτ) following oral CAB 10mg once daily, which was shown to be efficacious in the LATTE study. The lower bound of the 90% prediction interval is approximately 0.166µg/mL, indicating that 95% of participants on this regimen should remain above the PA-IC_{90} throughout dosing (Figure 3). The CAB LA Q2M regimen consists of identical 600mg doses administered at Day 1, Month 2, and Q2M thereafter. Observed data for the optimized Q2M regimen in

LATTE-2 Extension Phase were consistent with predictions, with a geometric mean CAB trough concentration of 1.58 µg/mL 4 weeks following the reduced 600mg IM loading dose and of 2.03 µg/mL following the fourth injection.

Figure 3 Simulated* Median (90% Prediction Interval [PI]) CAB Plasma Concentrations versus Time for the Optimized CAB LA Q8W Regimen (600 mg IM Day 1, Week 4, Q8W Thereafter)



*Note: current simulations based on interim plasma concentration dataset

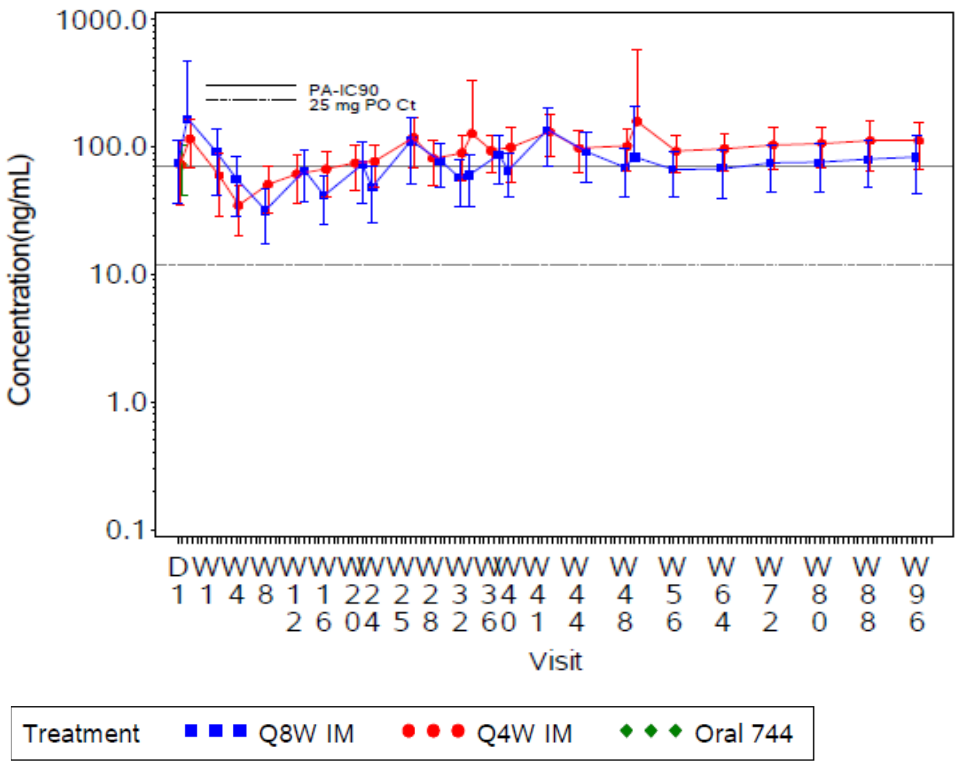
^Study Time and Events include a 4-week oral lead in for subjects transitioning to Q8W from oral SOC. Therefore, Day 1 (time zero) = date of first injections in 207966

A one-week delay in CAB LA dosing for the Q2M regimen at steady state is predicted to result in ~92% rather than 95% of participants achieving trough concentrations above the PA-IC90, which is considered acceptable.

4.4.2.2. RPV LA Pharmacokinetics

Observed PK data for both RPV LA Q4W and Q8W regimens in LATTE-2 are presented in Figure 4. The RPV LA population PK model has been updated to include data from LATTE-2 and from Phase 1 studies in healthy volunteers (Margolis, 2018).

Figure 4 **Observed Mean (SD) Plasma Concentration-Time Data following RPV LA Q8W and Q4W through Week 96 and Day 1 Cτ following RPV 25 mg PO QD (LATTE-2)**



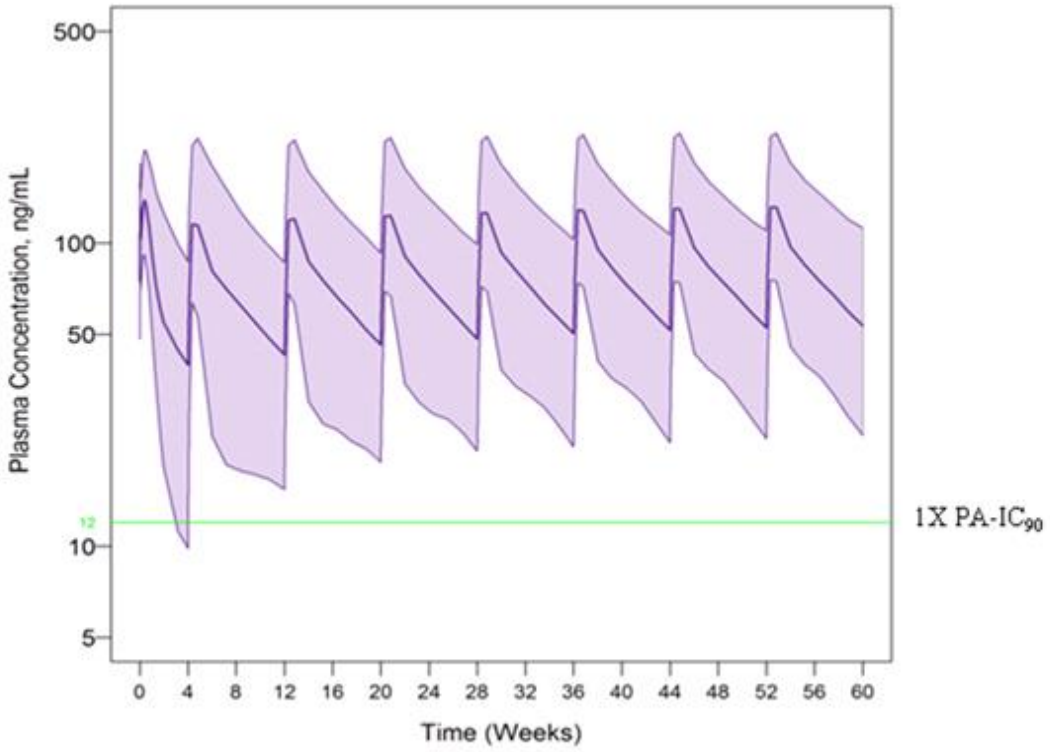
Data Source: Figure 4.1004
Subjects randomized to remain on oral CAB during the Maintenance Phase received their final Induction Phase/Oral lead-in dose of RPV 25mg once daily on Day 1 prior to resuming oral CAB + 2NRTIs.
Subjects randomized to RPV LA in the Maintenance Phase received their final Induction Phase dose of oral RPV 25mg once daily as well as their first RPV LA injection on Day1.
RPV 2-h post-injection concentrations were obtained on Day 1 (largely reflecting oral dosing), Week 32 and Week 48.
RPV 1-week post-injection concentrations were obtained on Week 1, Week 25 and Week 41.
RPV 4-week post-injection concentrations reflect either trough concentrations (Q4W) or troughs and mid-cycle concentrations (Q8W) through W48.
All concentrations shown from Week 56 to Week 96 represent troughs regardless of regimen.

The RPV LA Q2M regimen was selected based on safety and efficacy data from study 200056 (LATTE-2) and supported by modeling and simulation of pharmacokinetic data obtained following administration RPV LA administration in healthy participants (Phase 1 studies C158, and LAI115428 [GlaxoSmithKline Document Number 2011N112455_03]) and in HIV-infected participants (Phase 2 study LATTE-2), the majority of the data coming from 200056 (LATTE-2) (Margolis, 2018).

The RPV LA 900 mg Q2M regimen is predicted to achieve median (90% PI) steady-state Cτ of 54 ng/mL (23-112ng/mL) (Figure 5). With this regimen, 100% of participants remain above the RPV protein-adjusted 90% inhibitory concentration (PA-IC_{90}) during the whole dose interval at steady-state. These data are similar to the observed Week 32

median steady-state Cτ in LATTE-2 for Q8W which was also 54 ng/mL and the mean Cτ was 58 ng/mL. The RPV LA Q2M regimen consists of identical 900 mg doses administered at Day 1, Month 2, and Q2M thereafter. With the second RPV LA dose administered 1 month after the first dose, the anticipated median RPV Cτ at Week 4 (prior to second injection) is 40 ng/mL (versus 30 ng/mL observed prior to second injection at Week 8 in LATTE-2, where the RPV LA dose at Week 4 was not included), with >92% of participants above the RPV PA-IC_{90} of 12 ng/mL. Observed data for the optimized Q2M regimen in LATTE-2 Extension Phase were consistent with predictions, with a geometric mean RPV trough concentration of 49.9 ng/mL 4 weeks following the 900 mg IM loading dose and of 57.5 ng/mL following the fourth injection.

Figure 5 Simulated* Median (90% PI) RPV Plasma Concentrations versus Time Profile for the Optimized RPV LA Q8W regimen (900 mg IM Day)



* Note: current simulations based on interim plasma concentration dataset
^Study Time and Events include a 4 week oral lead in for subjects transitioning to Q8W from oral SOC. Therefore, Day 1 = date of first injections for Study 207966

At steady-state, a one-week delay in dosing for the RPV LA Q2M regimen is predicted to result in a median steady-state Cτ that is approximately 11% lower (48 ng/mL) than for dosing that is administered on schedule, with >99% of subjects still remaining above the RPV PA-IC90. This supports allowance of some flexibility in the dosing regimen similar to what is currently practiced in ongoing LATTE-2 and ATLAS 2M studies.

4.5. End of Study Definition

4.5.1. Study Completion

4.5.1.1. Study Staff Participants

Study Staff participants will have completed the study upon completion of all questionnaires and qualitative interviews after Month 12 evaluations have been completed at their site, per the Schedule of Activities (Section 1.3).

4.5.1.2. 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 have completed all study visits and assessments up to and including Dose 7 (Month 12).

Post Dose 7 (Month 12), they should remain on study (Extension Phase) until; Commercial supplies of the CAB LA + RPV LA regimen become locally available, they are required to initiate alternate antiretroviral therapy at the discretion of their HIV care provider, or until development of CAB LA + RPV LA is terminated.

Until meeting the definition for study completion, participants will continue in the study until the participant no longer derives clinical benefit or the participant meets a protocol-defined reason for discontinuation.

Following commercial availability, 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 care provider.

Safety Follow-up Visit

A safety follow-up visit is required for subjects completing the study when commercial supplies become available, (participant may or may not be transitioning to CAB + RPV LA marketed product). It should be conducted approximately 2-4 weeks after the last dose of IP to assess HIV associated conditions, AEs, Concomitant medications, ISR AEs after the last injection and the plan to transition to marketed product. This visit may be conducted by telephone. Ensure relevant eCRF forms (including the Study Conclusion form) are updated / completed.

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.

Follow-Up visits are not required for successful completion of the study.

5. STUDY POPULATION

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

5.1. Inclusion Criteria

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

- 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.).

- For Germany also refer to country specific requirement Appendix 8 in Section 10.8

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. The use of local laboratory services to assess eligibility is only allowed with prior approval obtained by the study team with agreed guidance (before to initiating the study). 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 35-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 suppressed on a guideline recommended active HAART 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 virologic failure (on treatment HIV-1 RNA ≥200 c/mL). 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 < 6 months prior to Screening and one 6-12 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) 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
6. 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.
OTHER
7. **French participants:** In France, a participant will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a social security category.

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 historical or current CD4+ counts <200 cells/mm3are 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, gluteal implant/ enhancements 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 coinfection 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:

$$(\text{Age} \times \text{AST}) / (\text{Platelets} \times (\text{sqr}[\ \text{ALT}\ ]))$$

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.
Exclusionary Laboratory Values or Clinical Assessments (a single repeat to determine eligibility is allowed)
20. 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, 2015]) by any historical resistance test result (Wensing, 2019) 21. Alanine aminotransferase (ALT) ≥ 5x the upper limit of normal (ULN) or ALT≥ 3x ULN and bilirubin ≥ 1.5 x ULN (with > 35% direct bilirubin) 22. Any verified Grade 4 laboratory abnormality. A single repeat test is allowed during the Screening phase to verify a result 23. Participant has estimated creatinine clearance <50 mL/min/1.73m2 via the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Levey, 2009).
Concomitant Medications
24. 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; 25. Treatment with any of the following agents within 28 days of Day 1: • radiation therapy; • cytotoxic chemotherapeutic agents; • tuberculosis therapy except for 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. 26. Treatment with an HIV-1 immunotherapeutic vaccine within 90 days of Screening. 27. Use of medications which are associated with Torsade de Pointes must be discussed with the Medical Monitor to determine eligibility. (See SRM for a list of relevant medications) 28. 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

COVID-19
29. A participant with known or suspected active COVID-19 infection OR contact with an individual with known COVID-19, within 14 days of study enrollment (WHO definitions Section 10.14.7)

5.2.1. Additional Eligibility Criteria

To assess any potential impact on participant eligibility with regard to safety, the Investigator must refer to the most current 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

Oral Lead-in to End of Study+	
CAB + RPV Oral Lead-In	
Oral Lead-in (Day 1 to Month1) two once daily tablets taken with food	• Take one tablet of CAB 30 mg + RPV 25 mg once daily
CAB LA + RPV LA Injections	
Dose 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
Dose 2 to Dose 7 (Month 2- End of Study+) two 3 mL injections every two months	• 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
+Until after dose 7 (Month 12) when 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 filmcoating. 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 Europe. 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 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 (TMC278, 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 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 LA Packs

CAB LA may be packaged in a pharmacy pack or provided in separate components:

- 3mL fill of CAB LA vial
- Vial adapters, used to draw IP out of the vials into the injection syringes
- Syringes
- Needles (23-gauge, 1.5 inch)
- Printed instructions for use

6.1.1.6. RPV LA Packs

RPV LA may be packaged in a pharmacy pack or provided in separate components:

- 3mL fill of RPV LA vial
- Vial adapters, used to draw IP out of the vials into the injection syringes
- Syringes
- Needles (23-gauge, 1.5 inch)
- Printed instructions for use

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.

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 (ie patient study participant's body position at the time of administration, etc) may also be collected within the eCRF.

At the first dose (injection), participants transitioning from oral CAB + RPV should be dosed with the IM regimen within 2 hours taking the last oral regimen dose where possible.

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

6.3. Measures to Minimize Bias: Randomization and Blinding

For drug distribution purposes, the study will be single-arm, open-label study where all patients who pass screening will be assigned to CAB LA + RPV LA regimen.

For the purposes of implementation science/strategy, this study will be a two-arm study and sites will be either randomized to the Enhanced or Standard implementation strategy.

Cluster randomization will be applied because:

- Evaluation of intervention will be implemented at site level.
- For logistical convenience, and to avoid any contamination that could occur if implementation science interventions were provided for some subjects and not others within each site

Cluster randomization will be used to randomize sites in each country to either arm-e or arm-s. To achieve balanced implementation strategies across the sites, randomization may be stratified by clinic features. This will ensure data can identify whether a certain implementation strategy performs differently within a country or not, as well as between different countries.

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 source records and the 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 and study visits. 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 (including the long-term follow-up phase), and the importance of adhering to treatment regimens. Sites are to have plans in place for adherence counselling 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 if a participant misses any scheduled visit.

6.5. 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 Reference Manual (SRM). The SRM will provide the site personnel with administrative and detailed technical information.

6.5.1. Protocol Permitted Substitutions

6.5.1.1. Oral Bridging- Oral CAB LA + RPV LA

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 LA and RPV LA 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.

6.5.1.2. Oral Bridging- Standard of Care Antiretroviral Therapy (SOC ART)

For patient participants who are unable to attend an IM injection visit nor obtain oral CAB + RPV from the site, 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. Sites must contact the study medical monitor for approval of SOC ART as oral bridging, confirm IM restart

instructions, and to ensure the participant remains appropriate for resumption of IM dosing.

It is important to collect relevant clinical information, including adverse events, from the participant through alternative means, e.g. by telephone contact.

6.5.2. COVID-19

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 participant's ability to attend clinic visits. In some places, medical visits are occurring, and in others, 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 meet this challenge, there are recommendations in Section 10.14 to address access to medicine, staff shortage, shipment of oral medications to patients, and alternative sites of care, etc.

6.5.3. IM Dosing

Participants receiving CAB LA and/or RPV LA are anticipated to be at risk for development of virologic resistance if antiretroviral therapy 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 and RPV decline over time.

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.

Target Date

The patient's 'target date' is determined by their first injection date and ideally is the same date for every injection. For example, if the1st dose (Month 1) is January 15th, then dose 2 (Month 2) will be February 15th, and dose 3 (Month 4) will be April 15th, etc.

Since the first injection visit (Month 1) will determine the future injection visit schedule for participants and ideally be between the 1st and 28th day of the month. 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*.).

Treatment Injections- Months 1 and 2 –one month apart

Participants will take the last dose of their oral (CAB 30 mg + RPV 25mg) and receive the first CAB LA (600mg) + RPV LA (900mg) injections (within 2 hours of the final oral dose of CAB + RPV).

The second dose (CAB LA 600mg + RPV LA 900mg) will be administered one month later (preferable on the same target date as Dose 1). The dosing window for Dose 2 allows administration -7days of the proposed visit date but not later.

Treatment Injections- Months 4- Q2M dosing

Subsequent injections (Dose 3 through 7: CAB LA 600mg + RPV LA 900mg) occur every 2 months. The dosing window is ±7days. The Medical Monitor must be contacted to discuss individual participant case management if a dose must be administered outside of the window.

Nursing Visits for IM Dosing

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. Approval by the medical monitor, the study team and IRB/EC RA as locally required are needed for nursing visits. In cases of nursing visits, where feasible, all assessments should also be performed as per schedule of activity Section 1.3 (Table 1). See the Home-visit Handbook for procedural detail on home visits.

6.5.4. Oral Dosing

Any interruption in therapy (ie due to scheduling conflicts, life circumstances, *etc*.) during any oral dosing period that is greater than 3 consecutive days must be noted on the eCRF Bridging Oral/Oral Study Treatment page. Interruptions greater than 7 consecutive days must also 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.

6.6. 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 6.6.2 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.

6.6.1. 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:

While both oral CAB and RPV have dosing requirements with antacid products containing divalent cations, only oral RPV has requirements for dosing with H2

antagonists. Since co-administration of oral CAB and RPV is required in this study, the most restrictive dosing requirements must be taken into consideration.

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. A list of drugs associated with TdP is available in SRM and can be administered to subjects after consultation with the medical monitor.

6.6.2. 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, 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 SRM). 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.

- Hepatitis C infection therapy is allowed, however, interferon-based HCV therapy or use of any drugs that have a potential for adverse drug:drug interactions with study intervention is prohibited throughout the entire study.

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

6.6.2.1. 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*)

6.6.2.2. Concurrent with oral RPV

In addition to the medications listed in Section 6.6.2, 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.

6.6.3. 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, except for 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.

6.6.4. 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.

6.7. Treatment of Study Treatment Overdose

For participants receiving Oral CAB, any tablet intake exceeding a total daily dose of 30 mg will be considered an overdose. For participants receiving oral RPV, any dose exceeding a total daily dose of 25 mg will be considered an overdose.

For CAB LA and RPV LA, any single dose in excess of the studied doses will be considered an overdose.

Should IM maladministration, specifically overdose or inadvertent IV dosing, be suspected at any time, the participant will stay onsite for approximately 2-3 hours post dose for safety monitoring and an ECG will be performed at 2 hours post dose. If the visit is being performed in the home and further observation or treatment is required at a healthcare facility, the patient study participant should be transported to a clinic or a hospital as required. The Medical Monitor will be notified in the event of a suspected maladministration. Refer to Home-visit Handbook for procedural detail on home visits, where home-visits are locally approved.

In the event of suspected maladministration, additional PK samples will be drawn at 2 hours post dosing for evaluation of CAB and/or RPV concentrations.

For the purposes of this study, an overdose is not an AE (refer to Section 10.5.1) unless it is accompanied by a clinical manifestation associated with the overdose. If the clinical manifestation presents with serious criteria, the event is a SAE (see Section 10.5.2).

If an overdose occurs and is associated with an adverse event requiring action, all study medications must be temporarily discontinued until the adverse event resolves.

The Investigator should use clinical judgement in treating overdose, as ViiV Healthcare is unable to recommend specific treatment.

In the event of an overdose the Investigator or treating physician should:

1. Contact the Medical Monitor immediately
2. Closely monitor the participant for adverse events (AEs)/serious adverse events (SAEs) and laboratory abnormalities until the IP can no longer be detected systemically, (number of days will vary by compound – Medical Monitor / study team can advise).

3. Obtain a plasma sample for pharmacokinetic (PK) analysis if possible within 2 days from the date of the last dose of study treatment if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

6.8. Intervention after the End of the Study or Extension Phase

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 Dose 7 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, this period is termed the, 'Extension Phase.'. Refer to the Schedule of Activities for details on the requirements for these visits (footnote for visit Month 8 and 10)

6.9. Medical Devices

The medical devices to be used in this study are: vial adaptor, syringe and needle. Instructions for medical device use are provided in the Study Reference Manual.

All device deficiencies, (including malfunction, use error and inadequate labelling) shall be documented, and reported by the investigator throughout the clinical investigation (see Section 10.16) and appropriately managed by the sponsor.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

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.

Participants may stop study treatment permanently at any time during the study. The primary reason study treatment is permanently stopped will be collected in the eCRF.

If commercial product is not available when participants complete the Dose 7 visit, they should continue in the CAB LA + RPV LA Extension phase of the study. Should a participant permanently stop study treatment at any time during the study and prior to

commercial product being locally available, they should be advised that it is strongly recommended they enter the Long-Term Follow-Up phase of the study, in the interest of continued safety monitoring. Participants who enter the Extension Phase but permanently discontinue participation when the CAB LA + RPV LA marketed product is locally available must enter the Long Term Follow-Up Phase if they withdraw from the study due to safety-related reasons only.

Any participant not participating in the Long-Term Follow-Up phase after CAB LA + RPV LA study treatment is stopped permanently, will attend a withdrawal visit and be withdrawn from the study. 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 7.1.6 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 10.6.5.1);

- Renal toxicity is met and no compelling alternate cause is identified;
- Corrected QT interval (QTc) >550msec 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, and not continuing into the LTFU, the procedures described in the Schedule of Activities Table for the in-clinic Withdrawal visit are to be performed. Where a participant does not complete a withdrawal visit or enter the LTFU, an in-clinic or remote Safety Follow-Up visit will be conducted 4 weeks after the last dose of study medication when there are ongoing AEs 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), or meet a protocol-defined withdrawal criterion must have IP discontinued. Where the CAB LA + RPV LA marketed product is not locally available, 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 an additional 52 weeks of follow up. The start of the 52-week follow-up period begins the day of the last CAB LA and/or RPV LA dose with the first visit at Month 3. When the CAB+RPV LA marketed product is locally available participants must enter the LTFU Phase if withdrawing for safety related reasons only.

7.1.1. Liver monitoring event – Increased monitoring

A liver monitoring event is an occurrence of predefined liver chemistry changes that triggers increased monitoring of the participant's liver chemistries, but no action is taken with study treatment unless liver chemistry stopping criteria are met.

Liver monitoring event criteria:

- Baseline ALT ≤1.5x ULN: ALT ≥5x ULN and <8x ULN and bilirubin <2x ULN without symptoms believed to be related to liver injury or hypersensitivity.

- Baseline ALT >1.5x ULN: ALT ≥3x baseline and <5x baseline and bilirubin <2x ULN without symptoms believed to be related to liver injury or hypersensitivity

Actions:

- Notify the medical monitor within 24 hours of learning of the abnormality to discuss participant safety.

- Participant can continue study intervention

- Participant must return every 2 weeks for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until resolution or stabilisation (ALT <5x ULN on 2 consecutive evaluations)

- If at any time participant meets the liver chemistry stopping criteria, proceed as described above

7.1.2. Asymptomatic Liver Enzyme Elevations

For asymptomatic subjects who have ALT≥3x ULN, following discussions with medical monitor, ALT and other specific lab tests can be repeated in an unscheduled visit. This may include liver panel tests included in study protocol, even though subject did not meet any liver monitoring or liver stopping criteria.

7.1.3. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Discontinuation of study intervention for abnormal liver tests is required when:

- a participant meets one of the conditions outlined in Section 10.3.1
- when in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules, the Investigator believes study intervention discontinuation is in the best interest of the participant.

Liver Safety Required Actions and Follow up Assessments can be found in Section 10.3.

7.1.4. Temporary Discontinuation

Participants may have a temporary interruption to their study intervention when on oral therapy (oral lead or oral bridging) for management of toxicities. Such interruption of study intervention does not require withdrawal from the study. However, consultation with the Medical Monitor is required.

7.1.5. Restart

If participant meets liver chemistry stopping criteria do not restart the participant with study intervention unless:

- ViiV Healthcare Safety and Labelling Committee (VSLC) approval **is granted**,
- Ethics and/or IRB approval is obtained, if required, and
- Separate consent for treatment restart is signed by the participant.

Refer to Section 10.3.2 for full guidance.

Background

- 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.
- For long-acting agents, a restart may actually be continuation of therapy rather than a true re-start due to the timeframe between dose administration relative to decision making on allowing a restart.

- If protocol defined stopping criteria for liver chemistry elevations are met (Section 10.3), study drug must be stopped. Subjects who meet liver chemistry stopping criteria should not be retreated with investigational product unless an exemption has been approved by the VSLC. The algorithm for restart is described in Section 10.3.2 and summarised in Figure 8.

- If the restart is approved by the VSLC in writing, the subject 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.

- Ethics Committee or Institutional Review Board approval of drug restart must be obtained, as required.

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

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

- Subjects approved by the VSLC for restart of IP 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. Longer durations of close monitoring may be required for long-acting IP.

Refer to Section 10.3.2 for full guidance.

7.1.6. Virologic Failure

Only plasma HIV-1 RNA values determined by the central laboratory will be used to assess virologic failure. The use of local laboratory services to assess virologic failure is only allowed with prior approval (before to initiating the study) obtained by the study team with agreed guidance.

7.1.7. 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.

7.1.8. 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 (except where the use of a local laboratory for study-specific assessments has been reviewed and approved by the sponsor prior to study start). 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.

7.1.8.1. HIV-1 RNA Blips

HIV-1 RNA "blips" are not usually associated with subsequent virologic failure (DHHS, 2019). 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, 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, concomitant medication, intercurrent illness, 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.

7.1.8.2. Suspected Virologic Failure

Upon notification that a participant's HIV-1 RNA plasma level meets the definition of suspected virologic failure (plasma HIV-1 RNA ≥200c/mL), 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 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.

7.1.8.3. 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. Baseline proviral genotyping on Day 1 PBMCs and other genotyping techniques may also be attempted for patient study participants with CVF. 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 etc.

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 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. 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 withdrawal visit should be conducted, as shown in the SoA (see SoA 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 data for further research, the sponsor may retain and continue to use any data collected before such a withdrawal of consent for the study primary research but data will not be used for further research.
- 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 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 are handled as part of Section 10.1.

8. STUDY ASSESSMENTS AND PROCEDURES

Protocol waivers or exemptions are not allowed except for urgent actions to address immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Schedule of Activities Table, 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 1.3.

Laboratory results from the central laboratory services provided by this trial will be used to assess eligibility and scheduled assessments. The use of local laboratory services to assess eligibility is only allowed with prior approval (before to initiating the study) obtained by the study team with agreed guidance.

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. vital signs

2. 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.

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 35 days prior to Oral Lead-in 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 35-day screening period and under no circumstances may the participant be enrolled 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 participant number. A single repeat of a procedure/lab parameter can 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 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

Questionnaires and Interviews for staff study participants should be completed prior to the first Patient Study Participant CAB LA + RPV LA injection.

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 1.3). 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 may 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 1.3) and Laboratory testing specifications (Section 8.4.4).

8.3.3. HIV-Associated Conditions

HIV-associated conditions will be recorded and will be assessed according to the CDC, 2014 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 1.3.
- 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.
- Regular monitoring of hematology, blood chemistry and glucose (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.
    - 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 15: Information and Guidance for Managing Pregnant Participants.
    - 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 1.3).

- 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 1.3).

8.4.4. 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) (Screening)			
Prothrombin Time (PT)/International Normalized Ratio (INR)/ Partial Thromboplastin Time (PTT) (screening)			
Pregnancy test for women of childbearing potential			
Urinalysis (screening, withdrawal/LTFU), 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)			
PK samples maybe collected for maladministration, liver events, pregnancy long-term follow-up or as directed by the medical monitor. Pregnant participants who elect to remain in the study will have additional pre-dose trough PK samples for both CAB and RPV obtained, to be collected within 15 minutes prior to the LA dose, on the day of the study visit see Section 10.15.6.2.			

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, 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 using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) [Levey, 2009].
c) Glucose can be done in a non-fasting or fasted 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 Month 12
f) Urine pregnancy test/ serum pregnancy test will be performed according to the Schedule of Assessments (Table 1).

Where lab samples are missed in error, including not analysed by the central lab, see the Study Reference Manual (SRM) for guidance on which samples should have subjects brought back in for a central lab retest (local lab only sites require a local retest only).

Should a patient be required to return to site provide a re-test lab sample the lab date should entered in the eCRF under an unscheduled visit, if the re-test is conducted on a day that is different to the scheduled visit.

8.4.5. Suicidal Ideation and Behavior 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.

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 Appendix 14 in Section 10.14 for study management information during the COVID-19 pandemic.

Reporting for medical device deficiencies are covered in Section 10.16

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 1.3).
- All AEs will be collected from Day 1 until the follow-up visit at the time points specified in the SoA (Section 1.3).
- 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.
- All AEs and SAEs associated with medical device deficiencies for associated persons (i.e. healthcare professionals) will be collected. The associated person will be provided with a safety reporting information and an authorisation letter, as indicated in Section 8.5.8
- 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. Openended 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.

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

8.5.5.1. Pregnancy Testing

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 1.3) and at any time during the trial when pregnancy is suspected.

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 Section 10.15 for details.

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.

8.5.5.2. 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 15: Information and Guidance for Managing Pregnant Participants

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 WOCBP, 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.

8.5.5.3. 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 (with the exception of pregnancy test) performed as per the Schedule of Activities Table (Section 1.3), including the collection of additional PK samples for CAB and RPV. See Section 10.15 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 enter the LTFU Phase of the study and will be monitored for 52 weeks after the last LA dose. Moreover, an alternative oral HAART will be initiated, at the discretion of the PI and in discussion with the Medical Monitor. If a participant becomes pregnant within 52 weeks of the last dose of study drug the participant should notify the study site.

8.5.5.4. 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 Section 10.15.

Pregnant participants who elect to continue in the study and receive 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.

Participants who become pregnant during the study and elect to continue in the study and receive CAB+RPV LA, will have additional PK samples collected to monitor cabotegravir and rilpivirine exposure levels throughout the pregnancy (see Section 10.15) and at the time of delivery.

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/

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
- 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) 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.

8.5.8. Medical Device Deficiencies

The vial adaptor, syringe, and needles used in the study are classed as medical devices by the US Food and Drug Administration (FDA). To fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detecting and documentation of events meeting the definitions of device deficiency that occur during the study with such devices.

The definition of a medical device deficiency can be found in Section 10.16

NOTE: Medical device deficiencies associated with an SAE will be reported together with an SAE form. AEs associated with a medical device deficiency must be documented in the eCRF.

8.5.8.1. Time period for Detecting Medical Device Deficiencies

Medical device deficiencies that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.

If the investigator learns of any device deficiency at any time after a participant has been discharged from the study, and such device deficiency is considered reasonably related to a medical device provided for the study, the investigator will notify the sponsor within 24 hours.

Medical device deficiencies and any associated AE/SAEs for associated persons (i.e. healthcare professionals) will be collected. The associated person will provided with a safety reporting information and authorisation letter.

The method of documenting Medical Device Incidents is provided in Section 10.16.

8.5.8.2. Follow-up of Medical Device Deficiencies

Follow-up applies to all participants, including those participants who discontinue study treatment or the study, and associated persons.

The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency.

New or updated information will be recorded on the original completed form with all changes signed and dated by the investigator.

Prompt Reporting of Medical Device Deficiencies to Sponsor

Device deficiencies will be reported to the sponsor within 24 hours after the investigator determines that the event meets the protocol definition of a device deficiency.

The medical device deficiency report form will be sent to the sponsor by email.

The sponsor will be the contact for the receipt of device deficiency reports.

Regulatory Reporting Requirements for Medical Device Deficiencies

The investigator will promptly report all deficiencies occurring with any medical device used for CAB+RPV in the study, as described in Section 10.16 in order for the sponsor to fulfil the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

The investigator, or responsible person according to local requirements (e.g., the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of device deficiencies to the IRB/IEC.

8.6. Pharmacokinetics

Pharmacokinetic samples may be collected in cases of maladministration, liver events, to follow-up pregnancy, at plasma HIV 1 RNA retest of SVF, or as directed by the medical monitor.

Pregnant participants will have additional PK samples collected during the duration of the pregnancy. See Appendix 15: Information and Guidance for Managing Pregnant Participants

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. Viral Genotyping and Phenotyping

Whole venous blood samples will be obtained from each participant to provide PBMCs and plasma for storage samples according to the Schedule of Activities Table (see Section 1.3) for potential viral genotypic and phenotypic analyses.

Genotypic and phenotypic analyses may be carried out by Monogram Biosciences using, but not limited to, their Standard PhenoSense and GenoSure testing methods for protease (PRO), reverse transcriptase (RT), and integrase assays.

8.10.1. HIV-1 Polymerase Viral Genotyping and Phenotyping

Participants meeting confirmed virologic failure will have plasma samples tested for HIV-1 PRO and RT genotype and phenotype and HIV-1 integrase genotype and phenotype from samples collected at the time of meeting suspected virologic failure; these results will be reported to the Investigator as soon as available to provide guidance for election of an alternative regimen.

8.11. Health Economics

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

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

The hypotheses on the quantitative aspects of this study is that enhanced implementation strategy is superior than the standard implementation strategy in terms of mean staff study participant (SSP) AIM/IAM/FIM scores. i.e.,

$$H_0: \mu(\text{enhanced}) = \mu(\text{standard}) \text{ vs. } H_1: \mu(\text{enhanced}) > \mu(\text{standard})$$

9.2. Sample Size Determination

The study size is based on practical considerations in terms of feasibility of enrolling an adequate number of sites on each implementation strategy balanced with the desire to have interventions tested across several types of investigative sites; as well as enrolling an adequate number of patient study participants in each site.

Approximately 24 sites (from feasibility process) will be selected from the feasibility process to achieve 18 sites randomly assigned to study implementation strategies and approximately 54 evaluable staff study participants for an estimated total of 27 evaluable study staff participants per implementation strategy group.

Assuming 10% screen failures, it is estimated that with 18 sites approximately 527 patient study participants will be screened to achieve 474 subjects enrolled and 450 evaluable patient study participants completing the study (assumes 5% of patient study participants would be non-evaluable) for an estimated total of 225 evaluable patient study participants per implementation strategy group.

Power to Show Superiority in mean SSP AIM/IAM/FIM scores

Table 10 shows preliminary AIM/IAM/FIM data from the ongoing U.S. implementation study CUSTOMIZE (209493).

Table 10 Staff Study Participants Scores at Month 4 in CUSTOMIZE (209493)

	N	Mean	SD	Median	Observed Range (min-max)	Floor n (%)	Ceiling n (%)	Skewness	Kurtosis
AIM Scale (Total Sample)	24	4.39	0.61	4.13	3.25-5.00	0 (0.0%)	11 (45.8%)	-0.16	-1.58
IAM Scale (Total Sample)	24	4.45	0.59	4.50	3.25-5.00	0 (0.0%)	12 (50.0%)	-0.34	-1.39
FIM Scale (Total Sample)	24	4.32	0.71	4.25	3.00-5.00	0 (0.0%)	11 (45.8%)	-0.47	-1.09

Based on these preliminary data from CUSTOMIZE study, and the given sample size (the number of study participants) , the power to detect a difference of 0.5 between the implementation arms in terms of AIM, IAM and FIM are shown in Table 11.

Table 11 Power to Detect a 0.5 Difference in AIM/IAM/FIM

Endpoint	ARM-S	ARM-E	Delta	SD	Alpha	N(S)	N(E)	Power*
AIM	4.39	4.89	0.5	0.61	0.05	27	27	84%
						36	36	93%

Endpoint	ARM-S	ARM-E	Delta	SD	Alpha	N(S)	N(E)	Power*
IAM	4.45	4.95	0.5	0.59	0.05	27	27	86%
						36	36	94%
FIM	4.32	4.82	0.5	0.71	0.05	27	27	72%
						36	36	84%

*Power calculation using two-sided t-test assuming equal variance.

As shown in Table 11, with 27 study staff participants (3 per site) surveyed on each arm, the study would have 72%-86% power to detect a 0.5 difference in FIM, AIM and IAM endpoints between ARM-E (Enhanced implementation strategy arm) and ARM-S (Standard implementation arm) assuming data from Table 10 (CUSTOMIZE study) for ARM-S.

And with 36 study staff participants (4 per site) surveyed on each arm, the study would have 84% - 94% power to detect a 0.5 difference in FIM, AIM and IAM endpoints between ARM-E and ARM-S.

Sample Size for Provider Population

An overall average number of 9 sites, per arm, would produces a two-sided 95% confidence interval with a distance from the mean paired difference (e.g. site level mean change from baseline in AIM, IAM or FIM score) to the limits (half-width) that is equal to 0.497 when the estimated standard deviation of the paired differences is 1.0, across sites.

Table 12 Sensitivity Analysis for Sample Size versus Half-Width (Precision)- Two-Sided 95% Confidence Interval (For Number of Sites)

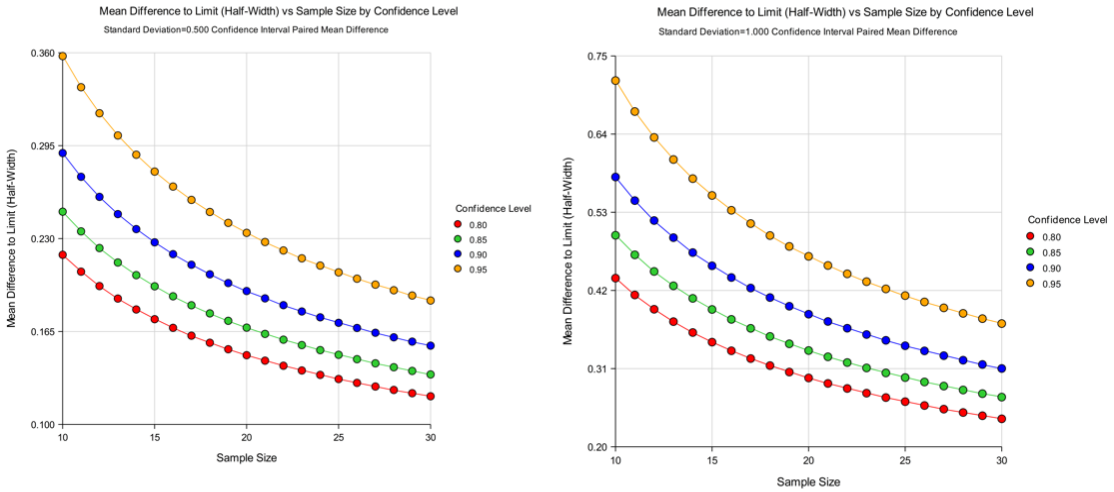
Sample Size	Actual Distance from Mean Difference to Limits (Precision)	
	SD=0.5	SD=1.0
10	0.358	0.715
11	0.336	0.672
12	0.318	0.635
13	0.302	0.604
14	0.289	0.577
15	0.277	0.554
16	0.266	0.533
17	0.257	0.514
18	0.249	0.497
19	0.241	0.482
20	0.234	0.468

A sample size of 27 providers, per arm, produces a two-sided 95% confidence interval with a distance from the mean paired difference to the limits (half-width) that is equal to 0.396 when the estimated standard deviation of the paired differences is 1.0.

Table 13 Sensitivity Analysis for Sample Size versus Half-Width (Precision)-Two-Sided 95% Confidence Interval (for Number of Providers)

Sample Size	Actual Distance from Mean Difference to Limits (Precision)	
	SD=0.5	SD=1.0
21	0.228	0.455
22	0.222	0.443
23	0.216	0.432
24	0.211	0.422
25	0.206	0.413
26	0.202	0.404
27	0.198	0.396
28	0.194	0.388
29	0.190	0.380
30	0.187	0.373

Figure 6 Sensitivity Analysis for Sample Size versus Half-Width (Precision)-Two-Sided 95% Confidence Interval (for Sites and Providers)



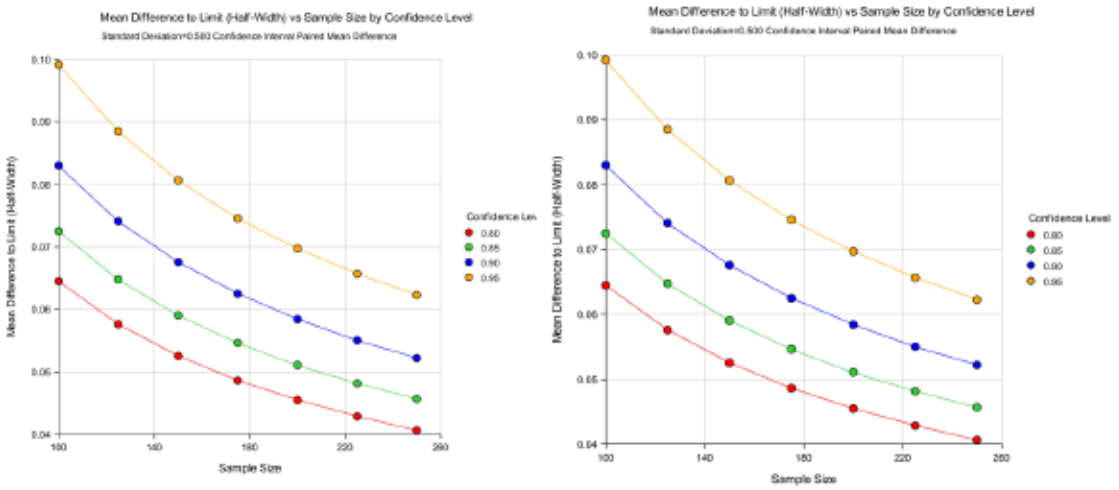
Sample Size for Patient Population

A sample size of 225 patient subjects per implementation strategy group produces a two-sided 95% confidence interval with a distance from the mean paired difference to the limits that is equal to 0.131 when the estimated standard deviation of the paired difference is 1.

Table 14 Sensitivity Analysis for Sample Size versus Half-Width (Precision)-Two-Sided 95% Confidence Interval (for Patients)

Sample Size	Actual Distance from Mean Difference to Limits (Precision)	
	SD=0.5	SD=1.0
100	0.099	0.198
125	0.089	0.177
150	0.081	0.161
175	0.075	0.149
200	0.070	0.139
225	0.066	0.131
250	0.062	0.125

Figure 7 Sensitivity Analysis for Sample Size versus Half-Width (Mean Diff to Limit) versus Sample Size - Patients (Multiple Confidence Levels)



As explained in other parts of this protocol, launching CAB LA + RPV LA in the real world may present challenges that were not observed in a clinical trial setting. Therefore, in addition to the primary analyses which focuses on study staff participants data, statistical analyses of patient outcome endpoints will be performed to evaluate changes in study patients' satisfaction score results, to allow a formal comparison between the two implementation strategies.

CCI [redacted]

9.3. Population Analyses

The following key populations are defined. Any further population definitions will be detailed in the RAP:

Population	Definition / Criteria
Intent-To-Treat - Exposed (ITT-E)	• All assigned patient participants who received at least one dose of study treatment. • This population will be based on the treatment the subject was randomized to (All subjects were assigned to the same drug regimen in this study) • Any participant who receives a participant number will be considered to have been assigned.
Safety	• All assigned participants who received at least one dose of CAB Oral + RPV Oral or CAB LA + RPV LA. • All patients receive the same drug regimen, CAB LA + RPV LA

9.4. Statistical Analyses

There will be two main reporting and analysis timeframes. First, will be the primary complete analyses which will be conducted when the last study participant has completed their CAB LA + RPV LA study treatment up to Dose 7. All study staff participant (site-level) questionnaire and interview data, plus all study participant (subject-level) data will be included in this reporting and analysis effort.

Once all study participants have completed the study, final analyses of the data will also be conducted

The statistical analysis plans will be finalized prior to DBL and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of endpoints. Analysis on patient

study participant data will account for sites that patients are nested in. The reporting analysis plan will provide further details of the analyses.

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

Qualitative interview data will be summarized by a third party and reported as part of the overall study results (CSR). Details of these analyses will be described in a separate analysis plan provided by the CRO partner under GSK's oversight.

Qualitative Analytic Strategy and Data Integration. The EPIS-informed qualitative data collected from both the study staff participants and the providers are embedded within the quantitative outcome of the study for expansion, development, and convergence. All qualitative data will be recorded, transcribed, translated if necessary, cleaned. Data will be entered into a qualitative data management software and any notes from calls made to study staff team that are related to study outcomes will be compiled and analyzed. The Clinical Research Organization or an identified expert consultant will be responsible for coding all qualitative assessments for use in the evaluation of feasibility, acceptability, appropriateness, barriers and facilitators of future implementation, and potential modification suggestions to implementation strategies. Established procedures to enhance validity will be used, including development of an audit trail documenting analytical decisions. All coding decisions will be noted for further review. Rater agreement will be assessed through a second rater coding a subset of the data, and agreement will be reported. We will also use a check-coding model where the primary coder will code and recode a percentage of the same material to ensure there is over a 90% consistency.

A theory-driven approach to explore the relationship between the findings and the EPIS framework will be followed. The goals, objectives and key research questions will guide all aspects of the qualitative analyses. Using content analysis, we will identify analytical categories to describe and explain observations. Our work will occur in five stages outlined in Mays et al. framework approach to qualitative analysis: 1) Familiarization, 2) Identifying a Thematic Framework, 3) Indexing, 4) Charting, and 5) Mapping and Interpretation. Codes will be derived deductively by identifying categories at the beginning of the research (e.g., elements of the EPIS framework) and inductively by identifying those that emerge gradually from the data. Operational definitions of each code will be used and through constant comparison, updates to the coding model will occur throughout to support efforts to index the data and lead to further refinement. In the charting and mapping phases, we will integrate the qualitative and quantitative data for expansion, development, and convergence, and based on our research questions, themes, commonalities and variations in themes, and findings related to training, feasibility, acceptability, and fidelity-related issues will be examined. Data integration will assist a fine-grained understanding of processes and characteristics that may influence effectiveness and implementation outcomes of CAB LA+ RPV LA in sites across Europe.

9.4.1. Primary Endpoint(s)

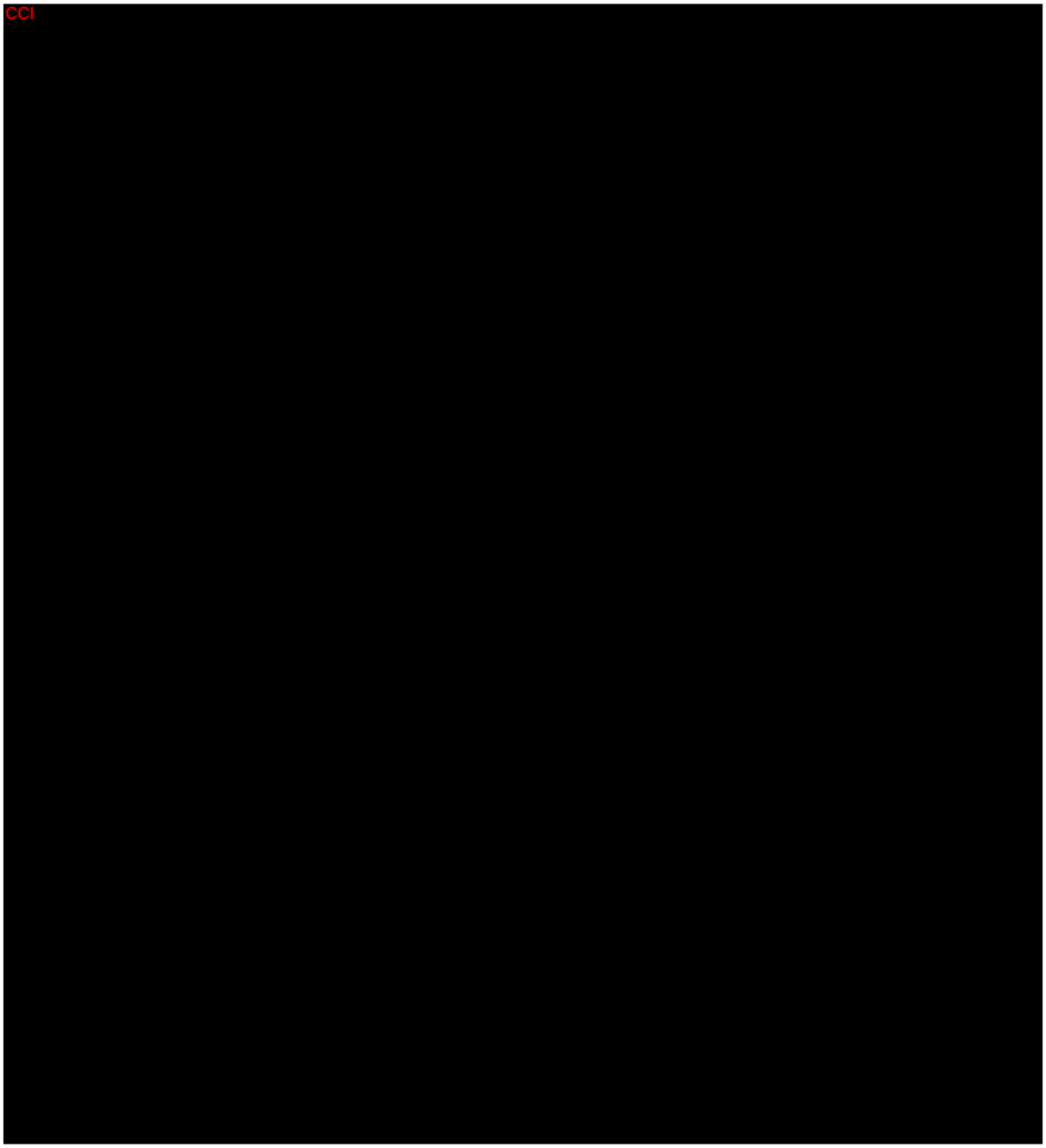
Endpoint	Statistical Analysis Methods
<u>Staff Study Participants (SSP):</u> Change from baseline at Month 12 in Acceptability of Intervention Measure (AIM), Intervention Appropriateness Measure (IAM), and Feasibility of Intervention Measure (FIM)	Acceptability of Implementation Measure (AIM), Implementation Appropriateness Measure (IAM), and Feasibility of Implementation Measure (FIM) will be summarized using descriptive statistics including 95% confidence intervals. Data will be summarized by month of study/injection visit and by implementation strategy as actual values and change from baseline. Mean AIM, IAM and FIM scores will be compared between the two implementation arms. In addition, distribution of AIM, IAM and FIM items scores will also be compared. P-values will be reported for these comparisons. Responses will also 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 and for subject level outcomes markers of demographic and baseline characteristics.

9.4.2. Secondary Endpoint(s)

Endpoints	Statistical Analysis Methods
Staff Study Participants (SSP)	
Change of Implementation Leadership Scale (ILS), Change and Implementation Climate Scale (ICS) over time assessed quantitatively via questionnaires through Month 12	Implementation Leadership Scale (ILS), and Implementation Climate Scale (ICS) will be summarized using descriptive statistics including 95% confidence intervals. Data will be summarized by month of study as actual values and change from baseline. Responses will also 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 and for subject level outcomes markers of demographic and baseline characteristics.
FRAME-IS outcome Months 2 – 12 (monthly)	Responses from the FRAME-IS outcome will be summarized by month.
Patient Study Participants (PSP)	
Length of patient study participant visit from arrival until departure from clinic assessed at Dose 1,Dose 2, Dose 4, and Dose 5.	The length of patient study participant visit will be determined from the time of arrival to time of departure and summarized using descriptive statistics including 95% confidence intervals.
Change in Acceptability of Intervention Measure (AIM) Score, Intervention Appropriateness Measure (IAM) Score, and Feasibility of Intervention Measure (FIM) Score over time. Assessed via questionnaires at Dose 7. [b]	Acceptability of Intervention Measure (AIM), Intervention Appropriateness Measure (IAM), and Feasibility of Intervention Measure (FIM) will be summarized using descriptive statistics including 95% confidence intervals. Data will be summarized by month of study/injection visit and by implementation strategy as actual values and change from baseline. Mean AIM, IAM and FIM scores will be compared between the two implementation arms. In addition, distribution of AIM, IAM and FIM items scores will also be compared. P-values will be reported for these comparisons. Responses will also be summarized overall and by site type. Exploratory analyses will be undertaken to assess the variability of responses by factors

Endpoints	Statistical Analysis Methods
	including but not limited to site type, setting and for subject level outcomes markers of demographic and baseline characteristics.
Study Staff Participants: Total score of the Clinical Sustainability Assessment Tool (CSAT) at Month 12	Total score of the Clinical Sustainability Assessment Tool (CSAT) will be summarized using descriptive statistics including 95% confidence intervals. Data will be summarized by month of study as actual values and change from baseline.
Percentage of injections occurring within target window from the target date.	Percentage of injections occurring within target window from the target date, will be summarized at Month 12, including 95% confidence intervals The patient's 'target date' is determined by their first injection date
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 patient study participants with CVF Incidence and severity of AEs and SAEs over time and the proportion of participants who discontinue treatment due to AEs over time	The proportion of participants with HIV-1 RNA <50 c/mL, based on the snapshot algorithm, will be summarized at Dose 7, with 95% confidence intervals The proportion of participants with HIV-1 RNA >= 50c/mL, respectively, based on the snapshot algorithm, will be summarized at Dose 7, with 95% confidence intervals. Summary of proportion of participants with confirmed virologic failure (CVF) over time using the FDA Snapshot algorithm in the ITT-E population Incidence of treatment-emergent genotypic and phenotypic resistance to CAB and RPV in patient study participants with CVF will be summarized at Dose 7, with 95% confidence intervals Incidence and severity of AEs and SAEs over time, will be summarized, with 95% confidence intervals. Proportion of participants who discontinue treatment due to AEs over time will be summarized.

Endpoints	**Statistical Analysis Methods**
Preference between CAB + RPV LA and daily oral ART medication (received prior to entering the study) quantitatively assessed via preference questionnaire at Dose 7	The proportion of participants preferences between CAB + RPV LA and daily oral ART medication (received prior to entering the study) with be summarized at Dose 7.
Reported injection site reactions over time	Reported injection site reactions over time will be summarized
Absolute values and changes in laboratory parameters over time	Absolute values and changes in laboratory parameters over time will be summarized, with 95% confidence intervals



9.4.4. Other Analyses

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

For clinics, baseline clinic characteristics will be collected and analyzed for potential confounders. Additionally, endpoints may be analyzed by study arm, by country, clinic archetype and by provider type.

9.5. Interim Analyses

One or more interim analysis will be conducted to provide early evaluation of the implementation science primary and key secondary objectives. No changes to the study conduct will occur.

Completed staff and patient participant questionnaire and interview data collected at the time of the interim data cut, will be included in the analyses. In addition, a limited number of eCRF datasets will be included in order to describe the characteristics of the patient study participants enrolled.

The timing of the interim/s will be based on when a sufficient number of staff study and/or patient study participant questionnaires and interviews have been completed.

No formal criteria for stopping or amending the study based on interim analysis results will be made.

An interim Reporting and Analysis Plan will describe the planned analyses in greater detail.

9.6. Data Monitoring Committee

No data monitoring committee will be assigned to this study as all subjects are receiving the same regimen (open-label) and appropriate safety medical and laboratory monitoring is included in the study.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

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.
- If follow-up information from a treating physician or other licensed medical practitioner is required for a medical device incident with an AE/SAE involving an associated person(s), the Associated Person Safety Reporting Information and Authorization Letter must be signed by the associated person to obtain consent.

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 who will be required to give consent for their data to be used as described in the informed consent.
- 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 data management monitoring plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data. Detailed information about study data collection and management process including systems used can be found in the study Data Management Plan.
- Guidance on completion of CRFs will be provided in CRF completion guidelines.
- Quality tolerance limits (QTLs) will be pre-defined in the quality tolerance limits plan to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during the study and deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.
- 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 Paediatric 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 utilized 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

DAIDS, 2017

10.3. Appendix 3: Liver Safety: Required Actions, Follow-up Assessments and Study Intervention Restart Guidelines

Study treatment refers to all drugs evaluated in the study and therefore includes ViiV study intervention and non-ViiV ART therapies that can be used in combination with ViiV products or other ART interventions.

A liver stopping event is an occurrence of predefined liver chemistry changes (ALT, bilirubin and or INR) that trigger discontinuation of study treatment and requirement of additional actions and follow up assessments to be performed.

A liver monitoring event is as an occurrence of predefined liver chemistry changes (ALT, bilirubin and or INR) that triggers increased monitoring of the participant's liver chemistries, but no action is taken with study treatment unless liver chemistry stopping criteria are met.

10.3.1. Liver chemistry stopping criteria and Required Actions and Follow-up Assessments

Study treatment or Investigational Product must stop immediately when participant meets one of the criteria described in below:

Liver Chemistry Stopping Criteria - Liver Stopping Event	
If baseline ALT ≤ 1.5x ULN	
ALT-absolute	ALT ≥ 8x ULN
ALT Increase	ALT ≥ 5x ULN but <8x ULN persists for ≥2 weeks (with bilirubin <2x ULN and no signs or symptoms of acute hepatitis or hypersensitivity)
Bilirubin[1, 2]	ALT ≥ 3x ULN **and** bilirubin ≥ 2x ULN (>35% direct bilirubin)
Cannot Monitor	ALT ≥ 5x ULN but <8x ULN and cannot be monitored every 1 - 2 weeks
Symptomatic[3]	ALT ≥ 3x ULN with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity
If baseline ALT > 1.5x ULN	
ALT-absolute	ALT ≥ 5x baseline OR > 500 U/L (whichever occurs first)
ALT Increase	ALT ≥ 3x baseline but <5x baseline persists for ≥2 weeks (with bilirubin <2x ULN and no signs or symptoms of acute hepatitis or hypersensitivity)

Liver Chemistry Stopping Criteria - Liver Stopping Event	
Bilirubin[1, 2]	ALT ≥ 3x baseline OR > 300 U/L (whichever occurs first) **and** bilirubin ≥ 2x ULN
Cannot Monitor	ALT ≥ 3x baseline but <5x baseline and cannot be monitored every 1 - 2 weeks
Symptomatic[3]	ALT ≥ 3x baseline and symptoms (new or worsening) believed to be related to liver injury or hypersensitivity.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study intervention for that participant if ALT ≥3x ULN **and** bilirubin ≥2x ULN.Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥3x ULN **and** bilirubin ≥2x ULN (>35% direct bilirubin) **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required, and the threshold value stated will not apply to participants receiving anticoagulants.
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia).

Required Actions and Follow up Assessments following ANY Liver Stopping Event	
Actions	**Follow Up Assessments**
• Immediately discontinue study intervention. • Report the event to the Medical Monitor **within 24 hours**. • Complete the liver event eCRF and complete an SAE data collection tool if the event also meets the criteria for an SAE**[2]**. • Complete the liver imaging and/or liver biopsy eCRFs if these tests are performed. • Perform liver event follow up assessments. • Monitor the participant until liver chemistries resolve, stabilise, or return to within baseline (see **MONITORING** below).	Make every attempt to carry out liver event follow-up assessments at the central laboratory as described below: • Viral hepatitis serology, including: • Hepatitis A immunoglobulin M (IgM) antibody; • HBsAg and hepatitis B core antibody; • Hepatitis C RNA; • Hepatitis E IgM antibody. • Cytomegalovirus IgM antibody. • Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing).

Required Actions and Follow up Assessments following ANY Liver Stopping Event	
Actions	**Follow Up Assessments**
• **Do not restart** participant with study intervention unless allowed per protocol and VSLC approval **is granted** (refer to Section 10.3.2.2). • If restart is **not allowed or not granted**, permanently discontinue study intervention and may continue participant in the study for any protocol specified follow up assessments. **MONITORING:** • Make every reasonable attempt to have participants return to clinic within **24 hours** for repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments. • Monitor participants twice weekly until liver chemistries resolve, stabilise or return to within baseline. • A specialist or hepatology consultation is recommended.	• Syphilis screening. • Drugs of abuse screen, including alcohol. • Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James, 2009]). The site must contact the Medical Monitor when this test is required. • Blood sample for pharmacokinetic (PK) analysis, obtained within 60 hours of last dose[4]. • Serum CPK and lactate dehydrogenase (LDH). • Fractionate bilirubin, if total bilirubin ³1.5x ULN. • Obtain complete blood count with differential to assess eosinophilia. • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Gamma glutamyl transferase [GGT], glutamate dehydrogenase [GLDH], and serum albumin • International normalized ratio (INR) • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging

Required Actions and Follow up Assessments following ANY Liver Stopping Event	
Actions	**Follow Up Assessments**
	and/or Liver Biopsy eCRF forms. • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, fatigue, decreased appetite, nausea, vomiting, abdominal pain, jaundice, fever, or rash as relevant on the AE report form. • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake eCRF.

CPK - creatine phosphokinase
1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study intervention for that participant if ALT ≥3x ULN **and** bilirubin ≥2x ULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥3x ULN **and** bilirubin ≥2x ULN (>35% direct bilirubin) **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required and the threshold value stated will not apply to participants receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. Record the date/time of the PK blood sample draw and the date/time of the last dose of study intervention prior to blood sample draw on the eCRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

10.3.2. Study Intervention Restart after Stopping for Liver Criteria

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. cholecystolithiasis, acute viral hepatitis, leptospirosis; syphilitic 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. (Figure 8, Table 16)

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.

If participant meets liver chemistry stopping criteria do not restart participant with study treatment unless:

- ViiV Healthcare Safety and Labelling Committee (VSLC) approval **is granted**
- Ethics and/or IRB approval is obtained, if required, and
- Separate consent for treatment restart is signed by the participant

> If VSLC approval to restart subject with study treatment **is not granted**, then subject must permanently discontinue study treatment and may continue in the study for protocol-specified follow up assessments (Section 10.3).

10.3.2.1. 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.

CCI

CCI

CCI

[redacted]

CCI

10.4. Appendix 4: CDC Classification for HIV-1 Infection (CDC, 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/□L, 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.
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

10.5. 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/selfharming 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 NOT 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 persistent or significant disability/incapacity

- 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 with 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 SAE 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 events should usually be considered serious.
- Examples of such events include 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

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

Adverse events that occur during the trial should be evaluated by the Investigator and graded according to the Division of AIDS (DAIDS) toxicity scales (See Section 10.2 "Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events"). Additional information regarding detecting, documenting and reporting AEs and SAEs are available in Section 10.5 and Section 8.5.

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 considering 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 Treatment 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] or called Target Date). A +0 / -7 day window is stipulated around the target date for dosing injections at Month 2. A +7 / 7 day window, from the projected target date, is allowable from the third injections forward.** 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. 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 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 followup evaluations completed.

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

10.6.3. 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 2-4 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 10.6.5.1). Isolated Grade 3 lipid abnormalities do not require withdrawal of IP.

10.6.4. 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 FollowUp 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 2-4 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).

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.

10.6.5. Specific Toxicities/ Adverse Event Management

General guidelines for the management of specific toxicities that are considered to be associated with treatment of HIV patients.

Participants who permanently discontinue study drug for reasons of toxicity should be followed weekly until resolution of the AE and encouraged to complete the withdrawal and Follow-up study evaluations as noted in Section 8.5.3

10.6.5.1. 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.

For a complete listing of stopping and follow-up criteria refer to Section 10.3.1.

10.6.5.2. 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.

10.6.5.3. 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 preclinical 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.

10.6.5.4. 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.

10.6.5.5. 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.

10.6.5.6. 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.

10.6.5.7. 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.

10.6.5.8. 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.

10.6.5.9. 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.

10.6.5.10. 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 CAB IB. 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 Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

- 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 17.

Table 17 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[b] • injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b] • 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 WOCBP 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.

b. A highly effective method of contraception should be utilized from 30 days prior to the first dose of study medication, throughout the study, and for at least 52 weeks after discontinuation of CAB LA and RPV LA.

Pregnancy Testing

- WOCBP 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.
- 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 15 for details regarding allowing pregnant participants to remain in the study

10.7.1. Collection of Pregnancy Information

- The Investigator will collect pregnancy information on **any** participant who becomes pregnant while participating in this study. See Appendix 15 and Section 10.15.1 for 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 Section 10.15 for additional data and information regarding the management of participants who remain in the study while pregnant.
- 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 this section. 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.

10.8. Appendix 8: Country-specific requirements

Germany

This requirement has been included based on request from the lead Ethics committee to specify that participants would have an expected individual benefit from enrollment in the study

- A participant will be eligible for inclusion in this study if he/she meets all eligibility criteria and for whom an individual benefit can be expected.

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
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
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
Cmax	Maximum concentration
ConART	Concomitant Antiretroviral Therapy
CONSORT	Consolidated Standards of Reporting Trials
CPK	Creatine phosphokinase
CRO	Contract research organization
CSAT	Clinical Sustainability Assessment Tool
CSR	Clinical Study Report
CV	Cardiovascular
CVF	Confirmed Virologic Failure
CQI	Continuous Quality Improvement
DAA	Direct-Acting Antivirals
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
FRAME	Framework for Reporting Adaptations and Modifications-Enhanced
FRAME-IS	FRAME-Implementation Strategy
FRP	Female of reproductive potential
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
HAART	Highly active antiretroviral therapy
HBV	Hepatitis B virus
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
ICS	Implementation Climate Scale
ID	Infectious Disease
IDMC	Independent data monitoring committee
IEC	Independent Ethics Committee
IgM	Immunoglobulin M
ILS	Implementation Leadership Scale
IM	Intramuscular
INI	Integrase inhibitor
INR	International normalized ratio
IP	Investigational Product
IRB	Institutional Review Board
ITT-E	Intent-to-treat exposed
IUD	Intrauterine device
ISR	Injection Site Reaction
LA	Long-Acting
LFTs	Liver function tests
LTFU	Long-Term Follow-UP
MCV	Mean corpuscular volume
MedDRA	Medical dictionary for regulatory activities
Mg	Milligram
Mg/dL	Milligram per deciliter
MRHD	Maximum Recommended Human Dose

NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRS	Numeric Rating Scale
NRTI	Nucleoside reverse transcriptase inhibitor
OLI	Oral lead-in
PDSA	Plan, Do, Study, Act
PK	Pharmacokinetic
PLHIV	Persons living with HIV
PREP	Pre-exposure prophylaxis
PRO	Protease
PRTD	Proximal Renal Tubule Dysfunction
PSP	Patient study participant
PSRAE	Possible suicidality-related adverse event
QTc	Corrected QT interval
Q2M	Every 2 months
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
SRM	Study Reference Manual
SSI	Semi-structured interview
SSP	Staff study participants
SWAT	Skilled Wrap-Around Team
TEN	Toxic epidermal necrolysis
TOC	Table of Contents
TMC278	Tibotec Medicinal Compound 278
ULN	Upper limit of normal
US	United States
VSLC	ViiV Safety and Labeling Committee
WBC	White blood cell
WOCBP	Woman of Childbearing Potential

Trademark Information

Trademarks of ViiV Healthcare
None

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

10.10. Appendix 10: Patient Study Participant Questionnaires

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

- Acceptability of the CAB+RPV injection (AIM)
- Appropriateness of the CAB+RPV injection (IAM)
- Feasibility of the CAB LA + RPV LA injection (FIM)
- Utility of patient specific toolkit resources
- CCI
- Facilitators and barriers to CAB LA + RPV LA related to time spent in appointments to receive the injections will be measured at Dose 1, 3, and 7.
- Preference

Acceptability, appropriateness, and feasibility will be measured by three brief 4-item measures (Weiner, 2017): the Acceptability of Intervention Measure (AIM), the Intervention Appropriateness Measure (IAM) and the Feasibility Intervention Measure (FIM). The AIM, IAM, and FIM access implementation outcomes identified in the Proctor Framework which are constructs of a 5-point Likert scale validated from the Proctor Framework. Reponses are measured using a 5-point Likert scale

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

CCI

CCI [redacted]

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

CCI [redacted]

CCI

[redacted]

Construct	Example Question
CCI [redacted]	

Construct	Example Question
Outer Context	
CCI [redacted]	

Construct	Example Question
CCI [redacted]	

*Note: constructs are taken from the preparation and implementation phase. All constructs from implementation phase are noted with *.*

CCI

[redacted]

Construct	Example Questions
CCI	[redacted]

10.14. Appendix 14: 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.

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.

10.14.1. 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 WOCBP, 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.

10.14.2. 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.

10.14.3. 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)

Oral bridging with CAB + RPV

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 6.5.1. 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.

10.14.4. 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.

10.14.5. 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.

10.14.6. COVID-19 Specific Data Capture

10.14.6.1. Capturing COVID-19 Specific Protocol Deviations

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

10.14.6.2. 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.

10.14.7. WHO Case Definitions

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.

10.15. Appendix 15: Information and Guidance for Managing Pregnant Participants

10.15.1. 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 8.5. 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.

10.15.2. 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 WHO, 2013 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 CARISEL 213199 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.

10.15.3. Background

At the time of finalizing this protocol, there have been 25 pregnancies reported during the CAB/RPV LA Phase 3 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

10.15.4. Benefit/Risk Assessment

Investigator to 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, 2013] at 1-800-258-4263.

10.15.4.1. 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 (1000 mg/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, preliminary findings from an unscheduled analysis of a birth outcomes surveillance study conducted in Botswana (Tsepamo Study) and presented in May 2018 showed a higher than expected number of neural tube defects (NTDs) among newborns whose mothers were exposed to DTG based ART at conception. DTG is a different molecule in the same integrase class of medications as CAB. As of May 2018 four cases of neural tube defects were identified 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. Updated analysis of interim data from the Tsepamo study became available in 2019 and more recently in 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%).

As of the Tsepamo April 2020 analysis, seven cases of neural tube defects were reported in 3,591 deliveries (0.19%) to mothers taking dolutegravir -containing regimens at the time of conception, compared with 21 cases in 19,361 deliveries (0.11%) to mothers taking non- dolutegravir containing regimens at the time of conception (Prevalence Difference 0.09%; 95% CI -0.03, 0.30). Since the first analysis the estimated prevalence of neural tube defects with DTG exposure at conception has decreased in magnitude from 0.94% to 0.19%. In the same study, no increased risk of neural tube defects was reported in women who started dolutegravir during pregnancy. Two out of 4,448 deliveries (0.04%) to mothers who started dolutegravir during pregnancy had a neural tube defect, compared with five out of 6,748 deliveries (0.07%) to mothers who started non-dolutegravir -containing regimens during pregnancy.

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.

10.15.4.2. 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 the current Edurant Prescribing Information for additional information on rilpivirine.

10.15.5. Clinical Considerations

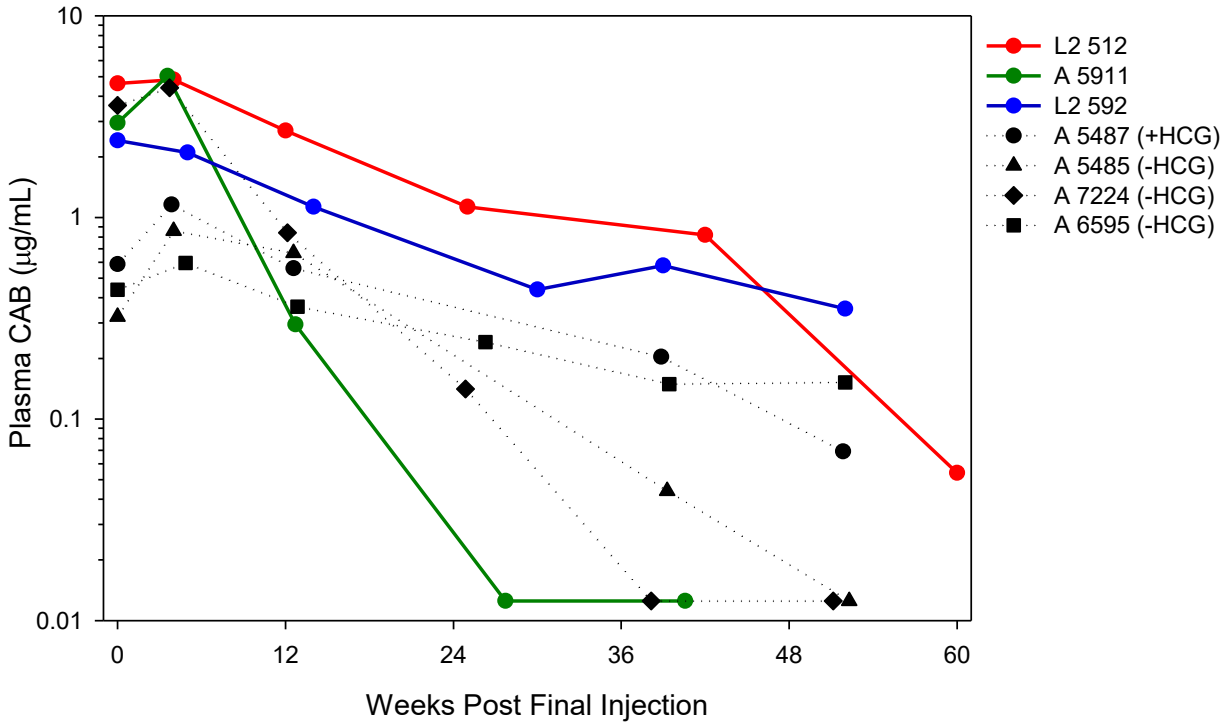
10.15.5.1. Exposure

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, plasma PK

samples of CAB and RPV will be obtained at every study visit for Q8W and Q4W during the pregnancy. Additionally, all other scheduled assessments, including viral load monitoring, will continue as reflected in as described in the protocol in the Time and Events Table (see Section 1.3)

Figure 9 LTFU PK in Female and Pregnant Participants (LATTE-2, ATLAS)



10.15.5.2. 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.

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.

10.15.5.3. 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 10.15.4.1 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 WOCBP, 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.

10.15.6. 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, as described in the protocol in the Schedule of Activities Table (see Section 1.3)

Viral Load Assessments

Women who become pregnant while on study and consent to stay on study will have VL testing obtained at every study visit during pregnancy and at the first post-partum visit. Timing of subsequent VL assessments are performed, as described in the protocol in the Schedule of Activities Table (see Section 1.3)

10.15.6.1. 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

10.15.6.2. 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 laboratory manual 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.

10.15.7. References

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10.16. Appendix 16: Device Deficiencies: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting in Medical Device Studies

The definitions and procedures detailed in this appendix are in accordance with ISO 14155, European Medical Device Regulation (MDR) 2017/745 for clinical device research, and the US Food and Drug Administration (FDA) combination product reporting rule, 21 CFR 4, Subpart B.

Both the investigator and the sponsor will comply with all local medical device reporting requirements for medical devices.

The detection and documentation procedures described in this protocol apply to all medical devices used in the study (see Section 6.9 for the list of medical devices).

10.16.1. Definition of Device Deficiency

Device Deficiency Definition
• A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and information supplied by the manufacturer.

10.16.2. Recording and Follow-Up of Device Deficiencies

Device Deficiency Recording
• When a device deficiency occurs, with or without an associated AE/SAE, it is the investigator's responsibility to review all applicable documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event. • The investigator will then record all relevant device deficiency information on the appropriate form. If applicable, any associated AE or SAE will be documented in the participant's medical records, in accordance with the investigator's standard clinical practice. • There may be instances when copies of medical records for certain cases are requested by the sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor. • The investigator will attempt to fully describe the device deficiency and provide details on any treatment provided. • For device deficiencies, it is very important that the investigator describe any corrective or remedial actions taken to prevent the deficiency's recurrence. o A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent the recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence.

Assessment of Intensity of associated AE/SAEs
• If an AE or SAE is associated with a device deficiency, the investigator will make an assessment of intensity for each AE or SAE as outlined in Section 8.5
Follow-up of device deficiency
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature of the device deficiency and any associated AE or SAE as fully as possible • New or updated information regarding the device deficiency will be recorded in the originally completed medical device deficiency report form. • If there is an associated SAE with the device deficiency, the investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

10.16.3. Reporting of Medical Device Deficiencies for participants

• Reporting to GSK
• NOTE: There are additional reporting obligations for medical device deficiencies that are potentially related to SAEs that must fulfil the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies. • Medical device deficiencies that are not related to an AE or SAE should be reported via email to PPD , using the medical device deficiency report form. • If the medical device deficiency is related to a non-serious AE and not linked to an SAE, please send the medical device deficiency report form via email to PPD only. The eCRF for the subject should also be updated with AE information, as outlined in Section 8.5 • If the device incident is linked to an SAE, please email the medical device deficiency report form, within 24 hours, to **both** PPD (or fax +44(0)20 8754 7822) **and** PPD . The SAE form should also be reported, as outlined in Section 8.5. The eCRF for the subject should also be updated with the SAE information. • GSK will review all device deficiencies and determine and document in writing whether they could have led to an SAE. These device deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by national regulations. • Contacts for Medical Device Deficiency reporting can be found in the medical device deficiency report form.

10.16.4. Reporting of Medical Device Deficiencies for Associated Person

- **Reporting to GSK**

If an Associated Person (i.e. a healthcare professional) experiences a device deficiency, the medical device deficiency information and any associate AE/SAE information will be reported to GSK. The associated person will be provided with the safety reporting information and authorization to contact physician letter.

If follow up information is required, authorization to contact physician (or other licensed medial practitioner) must be signed to obtain consent.

- Medical device deficiencies that are not related to an AE or SAE should be reported via email to PPD, using the medical device deficiency report form.
- If the medical device deficiency is related to a non-serious AE and not linked to an SAE, please send the medical device deficiency report form with details of the associated AE via email to PPD only.
- If the device incident is linked to an SAE, please email the medical device deficiency report form, within 24 hours, to **both** PPD (or fax +44(0)20 8754 7822) **and** PPD. The associated SAE form should also be reported to PPD (or fax +44(0)20 8754 7822).
- GSK will review all device deficiencies and determine and document in writing whether they could have led to an SAE. These device deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by national regulations.
- Contacts for Medical Device Deficiency reporting can be found in the medical device deficiency report form.

10.17. Appendix 17: Protocol Amendment History

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

Amendment 01- 02-DEC-2020

Overall Rationale for the Amendment 01:

Changes were made to correct discrepancies in the document and to update the statistical section based on Ethics Committee requirement.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis Section 2.3.1 Oral CAB and CAB LA (GSK1265744/GSK1265744 LA) Section 4.3 Treatment Groups and Duration	Updated HAART therapy initiation during LTFU from 'within 4 weeks' to 'within 8 weeks (+/-7 days) after the last Q2M injection'	Correction
Section 1.3 Schedule of Activities (SoA)	PSP SoA • Added footnote regarding AE/SAE assessment for M 2, M 6 and M 10 visits • Updated footnote regarding CAB LA + RPV LA IM treatment to clarify where possible IM Dose 1 to be dosed within 2 hours of taking the last oral regimen dose • Updated footnote related to recording of visit length • RPR updated as 'Syphilis serology + reflex RPR' SSP SoA • Checkpoint for Provider Toolkit deleted for 'arm- e Only'	Clarification
Section 2.3.1 Oral CAB and CAB LA (GSK1265744/GSK1265744 LA)	Deleted duplicate text under 'ISRs' Clarification added under mitigation strategy for development of resistance	Correction Clarification
Section 1.1 Synopsis Section 4.3 Treatment Groups and Duration	Deleted text 'a single repeat viral load to determine eligibility may be allowed ONLY after consultation with the medical monitor".	Correction
Section 5.1 Inclusion Criteria	Deleted text 'single repeat allowed' from plasma HIV-1 RNA criteria	Correction
Section 6.4 Study Intervention Compliance	Updated text to reflect, the date and time of each dose administered in the clinic will be recorded in the participant's source records and the eCRF.	Clarification
Section 6.5 Dose Modification Section 6.6 Concomitant Therapy	Interchanged Section 6.5 and Section 6.6	For better flow and presentation

Section 6.5.3 IM Dosing	Added text under nursing visit that 'in cases of nursing visits, where feasible, all assessments should also be performed as per SoA'	Clarification
Section 7.1.5 Restart Section 10.3 Appendix 3: Liver Safety: Required Actions, Follow-up Assessments and Study Intervention Restart Guidelines	Deleted study intervention rechallenge after stopping treatment for liver criteria	Ethics Committee requirement
Section 8.4.1 Clinical Evaluations	Deleted lipid assessment which is not performed in this study	Correction
Section 8.4.4 Clinical Safety Laboratory Assessments	Removed RPR assessment at Baseline Updated urinalysis to be done at screening and withdrawal/LTFU Updated PT/ PTT/ INR to be done at withdrawal/LTFU Updated footnote regarding glucose assessment which can be done in a non-fasting or fasted state	Correction
Section 8.6 Pharmacokinetics	Added text regarding PK sample to be collected at plasma HIV 1 RNA SVF re-test	Clarification
Section 9.1 Statistical Hypotheses	Added hypotheses testing on the quantitative aspects of the study, considering enhanced implementation strategy is superior than the standard implementation	Ethics Committee requirement
Section 9.2 Sample Size Determination	Added 'Power to Show Superiority in mean SSP AIM/IAM/FIM scores'	Ethics Committee requirement
Section 9.4.1 Primary Endpoint(s) Statistical Analysis Methods Section 9.4.2 Secondary Endpoint(s) Statistical Analysis Methods	Updated SSP and PSP Statistical Analysis Methods with details of AIM/IAM/FIM scores comparison between the two implementation arms	Ethics Committee requirement
Section 10.1.7 Data Quality Assurance	Added text 'Detailed information about study data collection and management process including systems used can be found in the study Data Management Plan.'	Clarification
Section 10.5.2 Definition of Serious Adverse Events	Updated SAE definition	SAE definition was truncated and replaced with complete definition

Section 10.6.5 Specific Toxicities/ Adverse Event Management	Deleted 'Section 10.6.5.3 Hypertriglyceridemia/ Hypercholesterolemia' and 'Section 10.6.5.9 Proteinuria'	Correction as lipid assessments are not performed in this study and urinalysis is not performed while on study treatment
Section 10.8 Appendix 8: Country-specific requirements	Added country specific requirement for Germany	Ethics Committee requirement
Section 10.9 Appendix 9: Abbreviations and Trademarks	Updated table for abbreviations and trademarks	Correction
Section 10.10 Appendix 10: Patient Study Participant Questionnaires	Updated measurement timing of PSP questionnaires as per original SoA	Correction
Section 10.14 Appendix 14: COVID-19 Pandemic and Clinical Trial Continuity	Deleted text related to "Memo to Investigators" issued on March 18th, 2020 which served as a record of approved emergency actions being taken within prior on-going clinical trial to manage issues related to COVID-19 and not applicable to this new study.	Correction
Section 11 References	Deleted reference Mugwanya, 2018 Updated reference Wensing, 2019	Correction

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