# TITLE PAGE

**Information Type:** ViiV Healthcare Interventional Study Protocol

| | |
|---|---|
| **Title:** | A Phase 4, open-label, single arm study to optimize implementation of CABENUVA for the treatment of HIV-1, for administration in U.S. community-based infusion centers or other alternate sites of administration |

**Protocol Number:** 214747 / Amendment 06

**Compound Number:** GSK1265744, CABENUVA

**Brief Title:** An implementation study using CABENUVA for the treatment of HIV-1, administered in infusion centers or other alternate sites of administration in the U.S.

**Development Phase** Phase 4

**Acronym**: GLACIER - Giving Long Acting CABENUVA in an Infusion centER

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**Approval Date:** 29 Mar 2023

# PROTOCOL AMENDMENT SUMMARY OF CHANGE TABLE

| DOCUMENT HISTORY | | |
|---|---|---|
| **Document** | **Date** | **DNG Number** |
| *Amendment 06* | 29 Mar 2023 | TMF-15719318 |
| *Amendment 05* | 14 November 2022 | TMF-15061935 |
| *Amendment 04* | 6 October 2022 | TMF-15019036 |
| *Amendment 03* | 20 July 2022 | TMF-14758153 |
| *Amendment 02* | 16 March 2022 | TMF-14150714 |
| *Amendment 01* | 19 Nov 2021 | TMF-14150714 |
| Original Protocol | 11 April 2021 | 2020N443730_00 |

**Amendment 01: Overall Rationale for Amendment 1** (See Annex 5: Protocol Amendments)

**Amendment 02: Overall Rationale for Amendment 02** (See Annex 5: Protocol Amendments)

**Amendment 03: Overall Rationale for Amendment 3** (See Annex 5: Protocol Amendments)

**Amendment 04: Overall Rationale for Amendment 4** (See Annex 5: Protocol Amendments)

**Amendment 05: Overall Rationale for Amendment 5** (See Annex 5: Protocol Amendments)

**Amendment 06: Overall Rationale for Amendment 6**

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Global Change | Added Alternate Sites of Administration (ASA) | Add another type of site for CABENUVA administration |
| Section 10.1: Clinical safety laboratory assessments | Revised to state labs should be drawn prior to the first study injections.<br>If an IC/ASA will have labs drawn off-site, added clarity on when the labs should be drawn prior to Baseline/Month 1 Visit | Added clarity to the SOA regarding the collection of labs prior to the Baseline/Month 1 Visit |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Annex 1: Schedule of Activities | Added link to Section 10.1 for Baseline/Month lab assessments | Clarity |
| Annex 5.1: Protocol Amendments | Moved the Table of Changes from Protocol Amendment 05 to Annex 5.1 | Moved according to the Protocol template |

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# LIST OF ABBREVIATIONS

| | |
|---|---|
| ADRs | Adverse drug reactions |
| AE | Adverse event |
| AIF | Alternate Injection Facility |
| AIM | Acceptability of Intervention Measure |
| ALT | Alanine aminotransferase |
| APR | Antiretroviral Pregnancy Registry |
| ARV | Antiretroviral Products |
| ASA | Alternate Site of Administration |
| AST | Aspartate aminotransferase |
| BMI | Body Mass Index |
| c/mL | Copies/milliliter |
| CABENUVA | Cabotegravir LA plus rilpivirine LA |
| CFIR | Consolidated Framework for Implementation Research |
| CI | Confidence Interval |
| CRO | Clinical research organization |
| CSR | Clinical study report |
| DAIDS | Division of acquired immune deficiency syndrome |
| DBR | Database release |
| DDI | Drug-Drug Interaction |
| ECG | Electrocardiogram |
| EDURANT | Rilpivirine |
| eCRF | Electronic case report form |
| FDA | Food and Drug Administration |
| FIM | Feasibility of Intervention Measure |
| FPFV | First participant first visit |
| GCP | Good Clinical Practice |
| GSK | GlaxoSmithKline |
| HCP | Healthcare Provider |
| HIPAA | Health Insurance Portability and Accountability Act |
| HIV | Human immunodeficiency virus |
| IC | Infusion Center |
| ICH | International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| ICF | Informed Consent Form |
| IM | Intramuscular |
| IRB | Institutional Review Board |
| ISR | Injection Site Reaction |
| LAR | Legally Authorized Representative |
| LMP | Last Menses Period |
| LPFV | Last participant first visit |
| M | Month |
| MedDRA | Medical Dictionary for Regulatory Activities |
| PLWHIV | People Living with HIV |
| POCBP | Participants of Child-bearing potential |

| | |
|---|---|
| POT | Plan of Treatment |
| PPD | Pharmaceutical Product Development Inc |
| PVG | Pharmacovigilance |
| Q1 | Quarter 1 |
| Q4 | Quarter 4 |
| QTc | Corrected QT interval |
| QUERI | Quality Enhancement Research Initiative |
| REP | Replicating Effective Programs |
| RNA | Ribonucleic acid |
| SAE | Serious adverse event |
| SGOT | Serum Glutamic-Oxaloacetic Transaminase |
| SGPT | Serum Glutamic-Pyruvic Transaminase |
| SoA | Schedule of Activities |
| SRM | Study Reference Manual |
| SUSAR | Suspected unexpected serious adverse reactions |
| US | United States |
| USPI | United States Prescribing Information |
| VHC | ViiV Healthcare |
| VOCABRIA | Cabotegravir |
| WHO | World Health Organization |

## Trademark Information

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| CABENUVA |
| VOCABRIA |

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# 1. ABSTRACT

**Background/Rationale:** CABENUVA is a 2-drug co-packaged product of cabotegravir plus rilpivirine, both administered as long-acting (LA) intramuscular (IM) once-monthly or every 2-monthly injections is a newly approved treatment for human immunodeficiency virus (HIV). Clinical trial results have shown that CABENUVA administered either once monthly or once every 2-months is non-inferior to the daily oral treatment for HIV.

CABENUVA treatment will require a paradigm shift in how HIV care is delivered, especially in the United States (US). People living with HIV (PLWHIV) will no longer be able to only see their providers one to two times a year for a prescription refill and monitoring visit but will instead attend appointments for their injections once a month. As a result, implementation of CABENUVA in HIV clinical settings in the U.S. poses new health delivery challenges and may require a shift in resources and openness to new ways of delivering and receiving treatment. Expanding where the treatment can be administered, using alternative injection facilities, such as infusion centers (IC) or other alternate sites of administration (ASA), has the potential to address workload capacity with this paradigm shift, and may positively impact treatment engagement and retention for PLWHIV. ICs/ASAs are an appealing option that will help ease the burden of additional appointments, administrative work, and drug ordering in HIV specialty clinics and provide PLWHIV greater flexibility in where they receive their monthly or every 2-month injections.

In this study, the intervention is the process of using an infusion center as the location to receive the CABENUVA IM injections. The acceptability and feasibility of the IC/ASAs to deliver CABENUVA IM injections, will be assessed from the perspectives of the participants, HIV care providers (which could potentially include other Provider clinical staff) and IC/ASA staff. The main objective of this post-approval study is to develop, evaluate and scale-up an implementation blueprint for IM administration of CABENUVA for HIV-1 treatment at ICs/ASAs.

**Study Design**: This is a Phase 4, single arm, open-label, multi-center study examining the administration of CABENUVA IM in infusion centers (ICs) or alternate sites of administration (ASA) in the United States. Additional Infusion Centers (ICs) or ASAs (initiating approximately between November 2022 to Q2 2023) will increase the geographical area in the US and to scale-up of the implementation blueprint.

Participants enrolled in the study will receive commercially available CABENUVA via prescription from their HIV care provider. Participants will be monitored according to usual standard care at their physician's discretion. No more than 120 participants will be recruited. CABENUVA injections will be administered at the ICs/ASAs for 8 months.

The study has two main components. The first component is to conduct a formative evaluation of the feasibility and acceptability of the IC/ASA model by participants, IC/ASA staff and HIV providers and the development of the implementation blueprint. The second component involves a scale-up of the optimized implementation blueprint across all ICs/ASAs in this study.

An Expert Panel will meet to generate an implementation blueprint to guide successful implementation prior to the first participant first visit (FPFV). The blueprint will be optimized over the first 6 months and will be used as a foundation for the enrolment of the remaining participants. As the Expert Panel will complete their assessments Q4 2022, following this timepoint, key IC/ASA staff members involved in decision making and/or overseeing daily operations at the IC/ASA, will be given the opportunity to review and revise both the optimized blueprint and the POT. The blueprint and POT will be reviewed and/or revised as necessary pre-study, at 3-4 months into the study to ensure experience with participants, and at the end of study.

Some HIV care providers manage their patients in conjunction with other clinic staff members who work with the ICs/ASAs and may be better to complete some study assessments. Thus, in Protocol Amendment 4, the completion of study questionnaires and potential interviews to be completed by the HIV Care Providers could potentially be completed by other clinical staff members.

- Note: the potential for other clinical staff to complete HIV Care Provider questionnaires and potential interviews, will hereafter be represented by HIV Care Providers/clinical staff.

**Objectives**: The primary objective is to evaluate the feasibility of CABENUVA administration at infusion centers from participants.

Secondary objectives include:

- To evaluate feasibility of CABENUVA administration at infusion centers from HIV care providers/clinical staff and IC/ASA staff
- To evaluate feasibility of the process of administering CABENUVA at the infusion center
- To evaluate acceptability of CABENUVA administration at infusion centers from HIV care providers/clinical staff, participants, and IC/ASA staff
- To evaluate feasibility, acceptability and the process of CABENUVA administration at infusion centers from the Expert Panel
- To evaluate perceptions, facilitators, and barriers/concerns by HIV care providers/clinical staff, participants, and IC/ASA staff
- To assess the preference of participants on the location to receive CABENUVA
- To assess the advantages to receive or refer participants to receive CABENUVA at the infusion center from participants and HIV care providers/clinical staff
- To assess the disadvantages about receiving CABENUVA at the infusion center from participants and HIV care providers/clinical staff
- To evaluate the acceptability of receiving and referring participants for CABENUVA injections at infusion centers from participants and HIV care providers/clinical staff

- To evaluate the usefulness of blueprint intervention by IC/ASA staff and the Plan of Treatment (POT) for HIV care providers/clinical staff
- To evaluate overall opinion of receiving and administering the injection at an infusion center by IC/ASA staff, participants and HIV care providers/clinical staff
- To evaluate fidelity to treatment and dosing window

**Analysis Methods**: Implementation science methodology will be used in this study to assess the acceptability and feasibility of an IC/ASA for the delivery of CABENUVA IM injections. This study will evaluate the acceptability and feasibility of our implementation strategy using the Feasibility of Intervention Measure (FIM) and the Acceptability of Intervention Measure (AIM).

In addition to the FIM and AIM, other quantitative questionnaires will be included to address additional constructs related to the study objectives. These questions will cover constructs related to perceptions, facilitators, barriers, usefulness of the blueprint advantages, disadvantages, and processes related to CABENUVA administration at ICs/ASAs. These additional quantitative questionnaires will measure endpoints that are not directly captured by the AIM and FIM.

The primary endpoint in terms of feasibility is the percentage of participants that agree or completely agree (a score of 4 or higher) across all items on the FIM at Month 8. For FIM of participants, HIV care providers/clinical staff and IC/ASA staff at each specified timepoint, the sample percentage and associated 95% confidence interval will be presented.

In addition to summary of FIM scores of participants at different timepoints, the change in FIM scores of each item will be analysed, and the shift table for each item of FIM will be given to display the number of participants who completely disagree (scale=1), disagree (scale=2), neither agree or disagree (scale=3), agree (scale=4), completely agree (scale=5) at Baseline/Month 1 and the shift of these quantities at each timepoint that follows.

The feasibility composite score will be further refined based on the standard process outlined in the blueprint. The exact components of feasibility composite score will be informed by the Expert Panel process to ensure it matches the critical variables identified by all members of the panel.

Subgroup analysis will be performed to evaluate the effect of contextual factors on the variability of responses to feasibility. These factors include, but not limited to, demographic, baseline characteristics, prior clinical experience, initiation method (oral lead in or direct to injection or receiving continuation dose), the number of injections received prior to enrollment and injection option (monthly or every 2-months) for participants, provider type, site type and setting (urban, suburban, rural) for IC/ASA staff, and affiliation for HIV care providers/clinical staff.

The analysis methods for the secondary endpoints of acceptability, and fidelity will be similar to that of the feasibility endpoints.

# 2. BACKGROUND AND RATIONALE

## 2.1. Background

CABENUVA is a 2-drug co-packaged product of cabotegravir plus rilpivirine, both administered as long-acting (LA) intramuscular (IM) injections, is a newly approved treatment for human immunodeficiency virus (HIV). Clinical trial results have shown that CABENUVA administered once monthly and once every 2-months is non-inferior to the daily oral treatment for HIV [Margolis, 2017; Swindells, 2020; Orkin, 2020; Overton, 2020]. Forty-seven percent of healthcare provides (HCPs) believed that "some" patients (25–50%) would be appropriate while nearly one-quarter of HCPs (23%) felt that "many" patients (more than 50%) would be appropriate candidates for LA antiretroviral therapy (ART) [Murray, 2020]. This treatment will require a paradigm shift in how HIV care is delivered, especially in the United States (US). People living with HIV (PLWHIV) will no longer be able to only see their providers one to two times a year for a prescription refill and monitoring visit but will instead attend appointments for their injections once a month or once every 2 months. As a result, implementation of CABENUVA in HIV clinical settings in the U.S. poses new health delivery challenges and may require a shift in resources and openness to new ways of delivering and receiving treatment. Expanding where the treatment can be administered, using alternative injection facilities (AIFs), ICs/ASAs has the potential to address workload capacity with this paradigm shift, and may positively impact treatment engagement and retention for PLWHIV.

ICs/ASAs are an appealing option that will help ease the burden of additional appointments, administrative work, and drug ordering in HIV specialty clinics and provide PLWHIV greater flexibility in where they receive their monthly or every 2-month injections. These facilities have an existing infrastructure that supports a wide range of treatments and can likely be adopted for administration of CABENUVA. Infusion centers exist across the US and have an informal network of sharing information both within the same company of infusion centers, as well as across companies.

Now that CABENUVA is commercially available in the United States, rapidly addressing needs to scale-up availability of the treatment will be important to ensure that those who want the treatment have access to it in a way that works for them and their providers. AIFs, like infusion centers, are a natural option for administering CABENUVA, as they routinely administer injectable treatments to a diverse patient population, have trained medical staff onsite, and have existing infrastructure to ensure communication between the IC/ASA, PLWHIV, and HIV providers. Additionally, these centers are not diagnosis specific, which allows for an added level of privacy during treatment appointments. Generating and testing acceptability and feasibility of an implementation blueprint to understand how this might work in routine care post-approval is an important next step to ensure that implementation of CABENUVA at infusion centers provides optimal care and experience for HIV care providers/clinical staff, PLWHIV, and infusion center staff.

## 2.2. Rationale

This post-approval, Phase 4 study will use an Expert Panel consisting of selected HIV care providers that may refer their PLWHIV to an IC/ASA, key IC/ASA staff members

involved in decision making and/or oversight of daily operations and ViiV Healthcare (VHC) to collaboratively develop an implementation blueprint and a plan of treatment (POT) to establish best practices and standard operating procedures for the administration of CABENUVA at ICs/ASAs (see Section 5.1 for full descriptions of the blueprint and POT). The blueprint will be used to guide the development and/or refinement of the POT which will be reviewed prior to the HIV care provider's first patient with HIV-1 enrolled in the study at the IC/ASA.

Implementation science methodology will be used to assess the acceptability and feasibility of an IC/ASA for the delivery of CABENUVA IM injections. In this study, the intervention is the process of using an infusion center as the location to receive the CABENUVA IM injections. The acceptability and feasibility of the IC/ASA to deliver CABENUVA IM injections, will be assessed from the perspectives of the participants, HIV care providers/clinical staff and IC/ASA staff.

The intention of this post-approval study is to develop, evaluate and scale-up an implementation blueprint for IM administration of CABENUVA for HIV-1 treatment at ICs/ASAs. The study has two main components. The first component is to conduct a formative evaluation of the feasibility and acceptability of the IC/ASA model by participants, IC/ASA staff and HIV providers and the development of the implementation blueprint. The second component involves a scale-up of the implementation blueprint across all ICs/ASAs in this study.

An Expert Panel will meet to generate an implementation blueprint to guide successful implementation prior to the first participant first visit (FPFV). The blueprint will be optimized over the first 6 months and will be used as a foundation for the enrolment of the remaining participants. The Expert Panel will complete all assessments in Q4 2022. The optimized blueprint will be reviewed and potentially revised by key IC/ASA staff members involved in decision making and overseeing daily operations at the IC/ASA.

Participants enrolled in the study will receive commercially available CABENUVA via prescription from their HIV care provider. Participants will be monitored according to usual standard care at their physician's discretion.

As a result, this study will examine the impact of the implementation blueprint and POT in enhancing the uptake of infusion centers by HIV care providers/clinical staff and patients with HIV-1 as the location they use to provide CABENUVA IM injections for their PLWHIV.

## 2.3. Benefit/Risk Assessment

Refer to the most recent USPI CABENUVA USPI for more detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of CABENUVA CABENUVA USPI.

# 3. OBJECTIVES AND ENDPOINTS

| Objectives | Endpoints |
|---|---|
| *Primary* | |
| To evaluate feasibility of CABENUVA administration at infusion centers from participants | • Proportion of participants that agree or completely agree (a score of 4 or higher) across all items on the FIM at Month 8 |
| *Secondary* | |
| To evaluate feasibility of CABENUVA administration at infusion centers from participants, HIV care providers/clinical staff and IC/ASA staff | • Proportion of participants that agree or completely agree (a score of 4 or higher) across all items on the FIM at Month 1, Month 3<br>• Proportion of HIV care providers/clinical staff that agree or completely agree (a score of 4 or higher) across all items on the FIM at Month 1, Month 4 and at Month 8<br>• Proportion of IC/ASA Staff that agree or completely agree (a score of 4 or higher) across all items on the FIM prior to Month 1, at Month 3, and Month 8<br>• Change over time in the FIM at Month 3 and Month 8 with participants<br>• Change over time in the FIM at Month 4 and Month 8 with HIV care providers/clinical staff<br>• Change over time in the FIM at Month 3, and Month 8 with IC/ASA staff<br>• Summary of other quantitative questionnaires assessed with participants at Month 1, Month 3, and Month 8<br>• Summary of other quantitative questionnaires assessed with HIV care providers/clinical staff at Month 1, Month 4 and Month 8<br>• Summary of other quantitative questionnaires assessed with IC/ASA staff prior to Month 1, at Month 3, and at Month 8 |

| Objectives | Endpoints |
|---|---|
| | • Qualitative interviews assessed at Month 8 with participants, HIV care providers/clinical staff and IC/ASA staff |
| To evaluate feasibility of the process of administering CABENUVA at the infusion center | • Summary of composite score of the feasibility process indications through Month 8<br>• Change over time through Month 8 in the composite score and each item of composite score. |
| To evaluate acceptability of CABENUVA administration at infusion centers from HIV care providers/clinical staff, participants, and IC/ASA staff | • Proportion of HIV care providers/clinical staff that agree or completely agree (a score of 4 or higher) across all items on the AIM at Month 1, Month 4 and Month 8<br>• Proportion of participants that agree or completely agree (a score of 4 or higher) across all items on the AIM at Month 1, Month 3and Month 8<br>• Proportion of IC/ASA staff that agree or completely agree (a score of 4 or higher) across all items on the AIM prior to Month 1, at Month 3, and Month 8<br>• Change of HIV care providers/clinical staff over time in the AIM at Month 4 and Month 8<br>• Change of participants and IC/ASA staff respectively over time in the AIM at Month 3, and Month 8<br>• Summary of other quantitative questionnaires assessed with HIV care providers/clinical staff at Month 1, Month 4 and Month 8<br>• Summary of other quantitative questionnaires assessed at Month 1, Month 3, and Month 8 with participants<br>• Summary of other quantitative questionnaires assessed prior to Month 1, at Month 3 and Month 8 with IC/ASA staff<br>• Qualitative interviews assessed at Month 8 with participants, HIV care |

| Objectives | Endpoints |
|---|---|
| | providers/clinical staff and IC/ASA staff |
| To evaluate feasibility, acceptability and the process of CABENUVA administration at infusion centers from the Expert Panel | • Proportion of Expert Panel that agree or completely agree (a score of 4 or higher) across all items on the FIM and AIM respectively prior to FPFV, and at Month 3 and Month 6<br>• Change of Expert Panel over time in FIM and AIM respectively through Month 6<br>• Summary of other quantitative questionnaires assessed with Expert Panel prior to FPFV, and at Month 3 and Month 6<br>• Qualitative interviews assessed with Expert Panel prior to FPFV and at Month 6 |
| To evaluate perceptions, facilitators, and barriers/concerns by participants, HIV care providers/clinical staff, and IC/ASA staff | • Summary of participant other quantitative questionnaires at Month 1, Month 3 and Month 8<br>• Summary of IC/ASA staff other quantitative questionnaires prior to Month 1, at Month 3, and Month 8<br>• Summary of HIV care provider/clinical staff other quantitative questionnaires at Month 1, Month 4, and Month 8<br>• Qualitative interviews assessed at Month 8 with HIV care providers/clinical staff, participants and IC/ASA staff |
| To assess the preference of participants on the location to receive CABENUVA | • Summary of preference on the location to receive CABENUVA at Month 1, Month 3, and Month 8 assessed by participant other quantitative questionnaires<br>• Qualitative interviews assessed at Month 8 with participants |
| To assess the advantages to receive or refer participants to receive CABENUVA at the infusion center from participants and HIV care providers/clinical staff | • Summary of advantages of receiving CABENUVA at IC/ASA at Month 1, Month 3, and Month 8 assessed by participant other quantitative questionnaires<br>• Summary of advantage to referring |

| Objectives | Endpoints |
|---|---|
| | participants to the IC/ASA to receive CABENUVA at Month 1, Month 4, and Month 8 assessed by HIV care provider/clinical staff other quantitative questionnaires<br>• Qualitative interviews assessed at Month 8 with participants and HIV care providers/clinical staff |
| To assess the disadvantages about receiving CABENUVA at the infusion center from participants and HIV care providers/clinical staff | • Summary of disadvantages of receiving CABENUVA at ICs/ASAs from participant other quantitative questionnaires at Month 1, Month 3, and Month 8<br>• Summary of disadvantage of referring participants to IC/ASA for CABENUVA injections from HIV care providers/clinical staff other quantitative questionnaires at Month 1, Month 4 and Month 8<br>• Qualitative interviews assessed at Month 8 with participants and HIV care providers/clinical staff |
| To evaluate the acceptability of receiving and referring participants for CABENUVA injections at infusion centers from participants and HIV care providers/clinical staff | • Summary of acceptability of the process of receiving injections at ICs/ASAs from participant other quantitative questionnaires at Month 1, Month 3 and Month 8<br>• Summary of acceptability of the process of referring participants to the infusion center for CABENUVA by HIV care providers/clinical staff other quantitative questionnaires at Month 1, Month 4, and Month 8<br>• Qualitative interviews assessed at Month 8 with participants and HIV care providers |
| To evaluate the usefulness of blueprint intervention by IC/ASA staff and the POT for HIV care providers/clinical staff | • Summary of usefulness of the blueprint intervention by IC/ASA staff other quantitative questionnaires prior to Month 1, at Month 3 and Month 8 |

| **Objectives** | **Endpoints** |
|---|---|
| | • Summary of usefulness of the POT by HIV care providers/clinical staff other quantitative questionnaires at Month 4 and Month 8<br>• Qualitative interviews assessed at Month 8 with HIV care providers/clinical staff and IC/ASA staff |
| To evaluate overall opinion of receiving and administering the injection at an infusion center by IC/ASA staff, participants and HIV care providers/clinical staff | • Summary of the overall opinion of administering the injection at an IC/ASA by IC/ASA staff other quantitative questionnaires prior to Month 1, at Month 3, and Month 8<br>• Summary of overall opinion of receiving CABENUVA at an infusion center by participant other quantitative questionnaires at Month 1, Month 3, and Month 8.<br>• Summary of overall opinion of referring patients to an IC/ASA center for CABENUVA injections by HIV care provider/clinical staff via other quantitative questionnaires at Month 1, Month 4 and Month 8<br>• Qualitative interviews at Month 8 with participants, HIV care providers/clinical staff and IC/ASA staff |
| To evaluate fidelity to treatment and dosing window | • Proportion of injections occurring within target window from target date (± 7 days of target date) through Month 8 |
| *Other / Tertiary* | |
| CCI [redacted] | |

| Objectives | Endpoints |
| --- | --- |
| CCI [redacted] | |

# 4. RESEARCH DESIGN

This study will be conducted in accordance with the protocol and with:

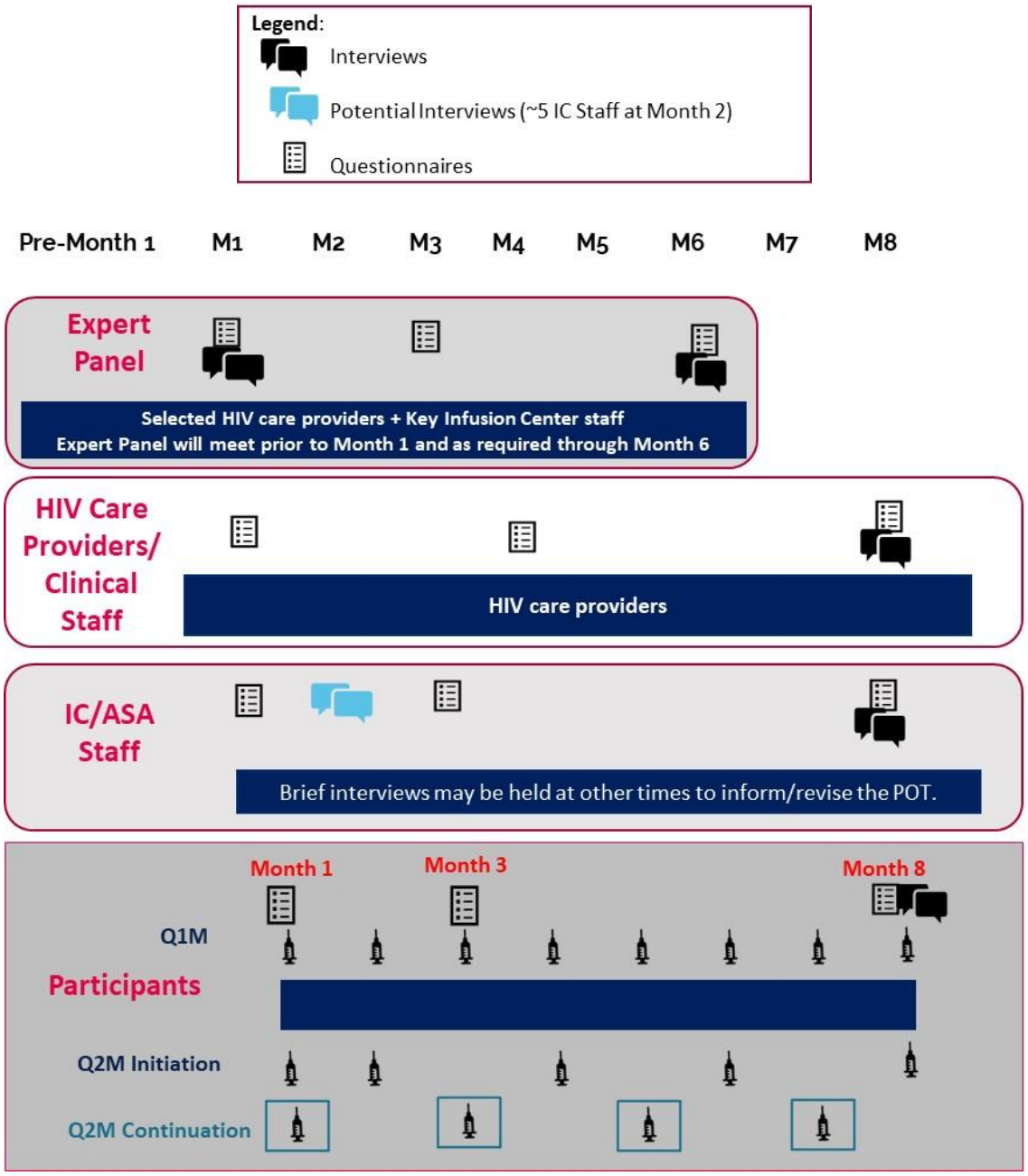
- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

## 4.1. Study Design

This is a Phase 4, single arm, open-label, multi-center study examining the administration of CABENUVA IM in infusion centers in the United States. This study is being conducted following FDA approval and commercial availability of CABENUVA in the U.S.

Eligible and consenting participants will be followed for 8 months to evaluate and scale-up an implementation blueprint for IM administration of CABENUVA for HIV-1 treatment at ICs/ASAs. The total study duration for participants is approximately 8 months from the time of enrollment and receipt of the first study related administration of CABENUVA IM injections at the IC/ASA. For a detailed Schedule of Activities (SoA) refer to Annex 1: Schedule of Activities. CABENUVA dosing adherence information and schematics can be found in the Study Reference Manual (SRM).

**Figure 1 Study Design Schematic**




Expert Panel questionnaires completed prior to the first participants first visit at the Month 1 visit. The Expert Panel will complete their review and optimization of the blueprint in Q4 2022. Thus, the ICs/ASAs initiating between approximately from November 2022 and Q1 2023 will use the optimized version of the blueprint and key IC/ASA staff will be allowed to modify prior to site enrollment, at 3-4 months and at the Month 8 visit.

Questionnaires include the FIM, AIM and other quantitative questionnaires

Participant assessments are completed based on Month regardless of monthly versus every-2-month dosing

Note, Study design may not include all potential patterns of dosing. Talk to the HIV Care Provider or the Medical Monitor if you have any questions on the injection schedule.

## 4.2. Study Population

During the recruitment period, the aim is to recruit no more than 120 participants who have been prescribed CABENUVA by their HIV care provider.

After signing an informed consent, participants will complete Baseline's assessments to confirm participant eligibility. Each participant being screened for study enrolment evaluation will be assigned a participant number at the Baseline visit.

### 4.2.1. Eligibility Criteria

#### 4.2.1.1. Inclusion Criteria

**AGE:**

1 Adults (≥18 years old) at the time of signing the informed consent.

**Type of Participant and Disease Characteristics**

2 HIV-1 infected and have been prescribed CABNEUVA per the USPI. Participants can be enrolled:

- If they have been taking oral VOCABRIA + EDURANT or other ART for approximately 1 month (at least 28 days) prior to Baseline/Month 1, or
- Already taking CABENUVA prior to Baseline/Month 1 and the last injections were within a 1 month ± 7-day window or for every 2-month injections, the timing will vary they are receiving the initiation injections (1 month ± 7-day) or the continuation injections (2 months ± 7 days) per the USPI, or
- Prescribed direct to inject and receive their 1st injection without an oral lead in at the Infusion Center on the last day of any other antiretroviral therapy.

**Informed Consent**

3 Capable of giving signed informed consent as described in Section 7.3 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

**Other**

4 Agreement to receive CABENUVA IM injections at participating infusion center.

#### 4.2.1.2. Exclusion Criteria

Participants may be excluded from the study, **in consultation with the HIV care provider**, based on information from the most current Prescribing Information [CABENUVA USPI] at the time of study enrolment.

1. Contraindications, as per the current Prescribing Information [CABENUVA USPI]
   - Previous hypersensitivity reaction to cabotegravir or rilpivirine.
   - Contraindicated co-administered drugs:

- Anticonvulsants: Carbamazepine, oxcarbazepine, phenobarbital, phenytoin
- Antimycobacterials: Rifabutin, rifampin, rifapentine
- Glucocorticoid (systemic): Dexamethasone (more than a single-dose treatment)
- Herbal product: St John's wort (Hypericum perforatum)

2. New health condition / prohibited medication reported
   - After discussion with the referring HIV care provider a decision was made not to enter participant into the study

3. Other Reason at the discretion of the HIV care provider or IC/ASA staff

## 4.3. Study Groups and Duration

This study will include the following groups: An Expert Panel, HIV care providers, virologically suppressed PLWHIV seeking to start or continue CABENUVA for treatment for HIV-1, and the IC/ASA staff. A CABENUVA POT will be agreed between the HIV care provider and the IC/ASA prior to study participants receiving their first study related injections at the IC/ASA.

Assessments can be found in Annex 1: Schedule of Activities and in the POT.

### 4.3.1. Participants with HIV-1

PLWHIV are allowed in the study if they have been prescribed CABENUVA per the USPI [CABENUVA USPI] and meet all eligibility criteria (Section 4.2.1) at the Baseline/Month 1 visit. Participants meeting all eligibility criteria will sign the informed consent form at the IC/ASA and will enter into the study.

If a participant plans to miss the injections by more than 7 days, in consultation with the HIV care provider, oral VOCABRIA + EDURANT or other ART regimens should be taken daily to replace up to 2 consecutive planned missed monthly injection visits or every 2-month injection visit-doses. Dosing of oral bridging in the event of missed doses will be in accordance with the most recent CABENUVA prescribing information [CABENUVA USPI].

In consultation with the HIV care provider, participants may switch from monthly injections to an every-2-month continuation injection schedule, or from a 2-month continuation injection schedule to a monthly continuation dosing schedule. When switching dosing regimens, follow all instructions as outlined in the most current Prescribing Information [CABENUVA USPI]. The total duration of study participants is approximately 8 months from the time of enrolment. and receipt of the first study related administration of CABENUVA IM injections at the IC/ASA. A participant is considered to have completed the study if he/she has finished all Month 8 assessments.

### 4.3.2. HIV Care Providers

Selected HIV care providers will be included on the Expert Panel. The Expert Panel will meet prior to Baseline/Month 1, and as required over the first 6 months, and per the SoA (Annex 1: Schedule of Activities) to develop the CABENUVA implementation blueprint as described in Section 5.1. The Expert Panel will complete the Month 6 review and revision of the blueprint within 2 to 4 weeks of the last site initiation visits of the additional ICs/ASAs.

Any HIV care provider will be allowed to refer PLWHIV to approximately 35 designated ICs/ASAs. Once an HIV care provider has identified a PLWHIV who would benefit from receiving CABENUVA or is already receiving CABENUVA and the patient agrees to receive the CABENUVA IM injections given at the IC/ASA, the provider will send a referral to the IC/ASA. The IC/ASA will conduct insurance verification. Once insurance verification is approved and reviewed with the patient, the IC/ASA will inform the HIV care provider and the patient will initiate treatment per the CABENUVA USPI.

HIV care providers will manage all medical and clinical aspects of their PLWHIV during the study including management of adverse events. The HIV care provider can request the following procedures to take place at the IC/ASA (i.e., local labs, vital signs) at any time.

- Prior to their HIV care providers first participant first visit (FPFV), providers will work with the IC/ASA to review and complete the POT for their patients. The HIV care provider will be notified that IC/ASA staff, clinical research organization (CRO) staff and/or the Medical Monitor may request additional information, including medical records if required, on CABENUVA-related AEs, AEs leading to withdrawal of CABENUVA and study withdrawals, SAEs, or other assessments (e.g., follow-up on liver chemistry elevations, pregnancies). HIV care providers will be notified of all adverse events and will be requested to provide a causality assessment.
- During the oral lead-in phase (for those initiating CABENUVA for the first time) and for the duration of the study, the HIV care providers will remain responsible for the medical management of their PLWHIV.
- HIV care providers will be notified by the IC/ASA of all planned and any unplanned missed visits. The HIV care provider will determine when to start oral therapy for planned missed doses, or restart CABENUVA according to the most current USPI.
- If the IC/ASA or the HIV care provider cannot contact the participant following missed injections of CABENUVA, this should be documented in the participants medical record, and if an injection is not administered within the allotted window period, such participants will be removed from the study and the clinical management of the participant will remain with the HIV care provider

Some HIV care providers manage their patients in conjunction with other clinic staff members who work with ICs/ASAs and may be better to complete some study assessments. Thus, in Protocol Amendment 4, the completion of study questionnaires

and potential interviews to be completed by the HIV Care Providers could potentially be completed by other clinical staff members.

Up to approximately 20 HIV care providers/clinical staff who refer their PLWHIV to a study IC/ASA, and after the HIV care provider's first patient is enrolled into the study, the HIV care provider/clinical staff may be asked to complete questionnaires per the SoA (Annex 1: Schedule of Activities).

The duration of study participation for each HIV care provider/clinical staff is approximately 8 months after their last PLWHIV has their first visit (LPFV) and received CABENUVA IM injections at a participating IC/ASA.

### 4.3.3. Infusion Center Staff

Key IC/ASA staff members involved in decision making and/or overseeing daily operations at the IC/ASA will participate in the Expert Panel. IC/ASA staff that are not part of the Expert Panel will complete assessments per the SoA (Annex 1) and in the POT. Baseline questionnaires should be completed by IC/ASA staff, prior to the first participant enrolled at their center.

Insurance verification will be done by the ICs/ASAs for all referred PLWHIV that are new to CABENUVA. The IC/ASA staff is responsible for promptly informing the PLWHIV and HIV care provider of the outcome of the insurance verification.

- The IC/ASA and the referring HIV care provider will review and individualize the POT for each participant prior to their first injections, if required. The IC/ASA center will explain that medical records may be collected for SAEs or other events for their PLWHIV enrolled at their center.
- At the first study-related injection visit (M1), the IC/ASA staff will obtain the participant's informed consent prior to enrolling in the study. After consent is obtained, the IC/ASA staff will administer CABENUVA IM injections as per the most current approved prescribing information in the CABENUVA USPI.
- The IC/ASA will be responsible for scheduling the monthly or every 2-month injections, reminding participants when they are scheduled to receive their injections, and rescheduling missed injections

The IC/ASA will immediately notify the participant's HIV care provider for any of the following reasons:

- The participant has missed a dose and/or is outside the dosing window (±7 days)
- The IC/ASA cannot contact the participant to reschedule a missed appointment
- The IC/ASA learns of an AE or SAE. The IC/ASA staff will be responsible for reporting all AEs/SAEs (refer to Section 10.3), to the HIV care provider. All events should be kept in the participant source documentation.
- Participant has started a new medication with the potential for drug-drug interactions (DDI) or is a contraindicated medication

**The HIV care provider will manage all medical and clinical follow-up required, including management of adverse events.**

Every injection visit will be recorded as a study visit. Additional participant contacts will not need to be documented as a study visit; however, the results of the viral load or other assessments are to be entered into the electronic Case Report Forms (eCRF).

The IC/ASA staff are responsible for the completion of all eCRF forms. Refer to Section 10.3.10, Table 3 for AE/SAE and pregnancy reporting timelines.

Total duration of study participation for IC/ASA staff is approximately 8 months from the time of enrollment of the last participant at that IC/ASA site.

# 5. IMPLEMENTATION RESEARCH METHODS

## 5.1. Formative Evaluation Procedures

HIV care providers will refer their PLWHIV that are interested in receiving CABENUVA injections at a participating IC/ASA. Participants of the study will be required to receive all their monthly or every 2-month injections at the IC/ASA, unless the injection is given at the HIV care providers office, as part of a routine care visit.

### 5.1.1. Expert Panel

The Expert Panel (approximately 10 members) will convene prior to any participant enrolment and will develop a CABENUVA implementation blueprint and an IC POT for the study. The pre-determined panel will be comprised of key IC/ASA staff members involved in decision making and/or overseeing daily operations at the IC/ASA, selected HIV care providers and VHC. VHC will provide oversight, and participate on the Expert Panel, when appropriate to ensure critical components of the process are addressed and that the blueprint is complying with the protocol, and the delivery of the study objectives and endpoints. IC/ASA Staff and HIV care provider membership of this panel will be chosen after completion of feasibility, and members will be asked to remain on the panel for the duration of the Expert Panel.

Prior to any participant enrollment in the study, the Expert Panel members will participate in a brief baseline qualitative interview and a meeting to design the blueprint, which will provide guidance to any IC/ASA about the overall process and implementation strategies to support CABENUVA initiation and continuation injections and will be used for the development and/or refinement of the POT. Templated analysis will occur for rapid coding both instream during the interviews as well as afterwards, if necessary, to capture additional information. Data from all stakeholder interviews will be summarized for top level key constructs noted across interviews.

At the Expert Panel first meeting, the qualitative interview data will be discussed, elements for the blueprint that will be used to develop the IC/ASA POT will be identified. This blueprint and POT will direct the entire spectrum of users (participants, HIV care providers, IC/ASA staff) on processes including clinical procedures and facilitative communication. This process will follow an evidence-based qualitative improvement process (e.g., identifying potential barriers to implementation, generating a plan to address it, and ultimately testing through implementation) paired with a nominal

group technique. The nominal group technique involves the ability to ask the Expert Panel to rank order different recommendations anonymously then discuss the triaged barriers and create an implementation blueprint to test in each cluster or iteration of the process. At the end of the initial meeting, an implementation blueprint draft will be prepared and will serve as the foundation for the IC/ASA POT for guiding successful implementation.

Additionally, as part of the blueprint and the POT, the Expert Panel will define which labs (i.e, HIV-1 RNA, CD4 cell counts, liver chemistries, or other labs) or other procedures are required, and at what timepoints. The HIV care provider and the IC/ASA can add additional labs to the POT, if required, for the clinical management of their PLWHIV.

After agreement on the initial blueprint, the participating IC/ASA sites and HIV care providers will begin to deploy the implementation blueprint, including the POT, and begin referring appropriate candidates for enrollment for CABENUVA treatment at the participating ICs/ASAs.

The Expert Panel will meet per the SoA (Annex 1: Schedule of Activities) and/or as required over the first 6 months, after the first participant was referred, to refine and optimize the blueprint and POT if needed. The revised blueprint and POT will then guide the care of the referred PLWHIV.

At approximately Month 6, the members of the Expert Panel will complete all assessments per the SoA (Annex 1: Schedule of Activities), or as required, over the first 6 months. The Expert Panel will meet for a final time at Month 6 to analyze key outcomes and to optimize the final blueprint.

As the additional ICs/ASAs are joining the study at the completion of the Expert Panel (approximately November 2022 to Q1 2023), the additional sites may revise the implementation blueprint outside of the Expert Panel. There will be a review of the blueprint and POT pre-study, at 3-4 months into the study to ensure IC/ASA experience, and at the end of study.

### 5.1.2. Implementation Assessments

Implementation outcomes align with the specified aims and Proctor and colleague's [Proctor, 2011] implementation outcome recommendations. Assessments for the Expert Panel, HIV care providers/clinical staff, participants and the IC/ASA staff will be administered as outlined in Table 1 and in Annex 1. Baseline assessments for the Expert Panel and the IC/ASA Staff should be completed prior to the first participant is enrolled. Implementation assessments may also be gathered from IC/ASA staff members who are administering CABENUVA outside of this study.

A baseline analysis and one or more interim analysis will be conducted to provide early evaluation of the implementation science primary and key secondary objectives. The timing of the interim/s will be based on when a sufficient number of IC/ASA staff and/or study participant questionnaires and interviews have been completed.

Per Protocol Amendment 4, HIV care providers/clinical staff will be asked to complete questionnaires and interviews.

**Table 1 Implementation Assessments**

| Outcome | Assessment Level | Measurement | Time point |
|---|---|---|---|
| **Feasibility** | Expert Panel*† | FIM<br>Other quantitative questionnaires<br>Qualitative Interview | Prior to FPFV, M3, M6<br>Prior to FPFV, M3, M6<br><br>Prior to FPFV, M6 |
| | HIV Care Providers/ Clinical Staff | FIM<br>Other quantitative questionnaires<br>Qualitative Interview | M1, M4, M8<br>M1, M4, M8<br><br>M8 |
| | Participants | FIM<br>Other quantitative questionnaires<br>Qualitative Interview | M1, M3, M8<br>M1, M3, M8<br><br>M8 |
| | IC/ASA Staff | FIM<br>Other quantitative questionnaires<br>Qualitative Interview | Prior to M1, M3, M8<br>Prior to M1, M3, M8<br><br>M8 |
| | Cross study | Consent Rate<br>Show Rate<br>Participant Notification<br>Provider Notification<br>Return rate | M1- M8<br>M1- M8<br>M1- M8<br>M1- M8<br>M1- M8 |
| **Acceptability** | Expert Panel*† | AIM<br>Other quantitative questionnaires<br>Qualitative Interview | Prior to FPFV, M3, M6<br>Prior to FPFV. M3, M6<br><br>Prior to FPFV, M6 |
| | HIV Care Providers/ Clinical Staff | AIM<br>Other quantitative questionnaires<br>Qualitative Interview | M1, M4, M8<br>M1, M4, M8<br><br>M8 |
| | Participants | AIM<br>Other quantitative questionnaires<br>Qualitative Interview | M1, M3, M8<br>M1, M3, M8<br><br>M8 |
| | IC Staff | AIM<br>Other quantitative questionnaires<br>Qualitative Interview | Prior to M1, M3, M8<br>Prior to M1, M3, M8<br><br>M8 |
| CCI [redacted] | | | |
| **Fidelity** | Participants | Adherence to Target date (±7 days) | Monthly |
| **Process evaluation** | HIV Care Providers/ Clinical Staff, Participants, IC/ASA Staff | Qualitative Interview | M8 |

| Outcome | Assessment Level | Measurement | Time point |
|---|---|---|---|
| **Perceptions, Facilitators, and Barriers/Concerns,** | HIV Care Providers/ Clinical Staff | Qualitative Interview<br>Other quantitative questionnaires | M8<br>M1, M4, M8 |
| | Participants | Qualitative Interview<br>Other quantitative questionnaires | M8<br>M1, M3, M8 |
| | IC/ASA Staff | Qualitative Interview<br>Other quantitative questionnaires | M8<br>Prior to M1, M3, M8 |
| **Preferences** | Participants | Qualitative Interview<br>Other quantitative questionnaires | M8<br>M1, M3, M8 |
| **Advantages and Disadvantages** | HIV Care Providers/ Clinical Staff | Qualitative Interview<br>Other quantitative questionnaires | M8<br>M1, M4, M8 |
| | Participants | Qualitative Interview<br>Other quantitative questionnaires | M8<br>M1, M3, M8 |
| **Acceptability of receiving and referring patients** | HIV Care Providers/ Clinical Staff | Qualitative Interview<br>Other quantitative questionnaires | M8<br>M1, M4, M8 |
| | Participants | Qualitative Interview<br>Other quantitative questionnaires | M8<br>M1, M3, M8 |
| **Usefulness of the blueprint and POT** | HIV Care Providers/ Clinical Staff | Qualitative Interview<br>Other quantitative questionnaires | M8<br>M4, M8 |
| | IC/ASA Staff | Qualitative Interview<br>Other quantitative questionnaires | M8<br>Prior to M1, M3, M8 |
| **Overall opinion of receiving and administering the injections at an IC** | HIV Care Providers/ Clinical Staff | Qualitative Interview<br>Other quantitative questionnaires | M8<br>M1, M4, M8 |
| | Participants | Qualitative Interview<br>Other quantitative questionnaires | M8<br>M1, M3, M8 |
| | IC/ASA Staff | Qualitative Interview<br>Other quantitative questionnaires | M8<br>Prior to M1, M3, M8 |

**Abbreviations: AIM: Acceptability of Intervention Measure; ASA: Alternate Sites for Administration; FIM: Feasibility of Intervention Measure; FPFV = First participant first visit, IC = Infusion Center; M: Month**
***Expert Panel includes selected HIV Care Providers and Key IC Staff**
**†The Expert Panel will meet as required over the first 6 months to discuss any iterations that are needed to refine and optimize the blueprint.**
**Only HIV care providers/clinical staff that had patients enrolled into the study will be included in assessments post Baseline/Month 1.**

### 5.1.3. Timepoint Definitions for Completion of Questionnaires and Interviews

**Participants:**

- Baseline/Month 1 is defined as the date when a participant signs ICF and completes Baseline/Month 1 protocol procedures prior to receiving the first study related CABENUVA injections at the IC/ASA.
- All additional study visits, including those where questionnaires and/or interviews are administered at Months 3, and 8, will be anchored off of each participants Month 1 visit, so it will reflect the Months on study, regardless of what injection schedule they are on and regardless of whether they have missed any injections and received oral bridging.

**Expert Panel:**

- Panel members will meet prior to Baseline/Month 1 to design the Blueprint and refine the POT
- Baseline/Month 1 is defined as the date when a participant signs ICF and completes protocol procedures and receives the first study related CABENUVA injections at any infusion center
- Month 3 and Month 6 assessments are to be completed after approximately 10 participants (across all ICs/ASAs) have completed their Month 3 and Month 6 study visits at any IC/ASA site

**HIV Care Providers/Clinical Staff:**

- Baseline/Month 1 is defined when the HIV care provider's first patient referred to the IC/ASA is enrolled into the study and receives their first injections of CABENUVA at the IC/ASA. HIV care providers/clinical staff will be asked to complete the Baseline/Month 1 questionnaire within 4 weeks of their first referred patient enrolled.
- Month 4 and Month 8 assessments are to be completed when the HIV care provider's first referred patient completes the Month 4 or Month 8 study visits, respectively
    - Questionnaires and/or interviews can be completed up to 2 weeks before or after the Month 4 or Month 8 study visits

**IC**/ASA **Staff:**

- Baseline/Month 1 questionnaires should be completed prior to enrollment of the first participant at each infusion center
- Month 1 for each IC/ASA is defined when the first participant enrolls into the study at that specific IC/ASA and the participant is administered the first study related injections of CABENUVA

- Month 2 for potential interviews of approximately 5 IC/ASA staff will be defined after at least 1 participant, at their respective IC/ASA site, has completed their Month 2 study visits
- Month 3 and Month 8 will be defined after at least 1 participant, at their respective IC/ASA site, has completed their Month 3 or 8 study visits, respectively
    - Questionnaires and/or interviews can be completed up to 2 weeks before or after the Month 2, Month 3, or Month 8 study visits.

The full SoA can be found in Annex 1: Schedule of Activities.

### 5.1.4. Primary Endpoint

The primary endpoint is participant feasibility at Month 8. The secondary endpoints include the feasibility in HIV care providers/clinical staff and IC/ASA staff, acceptability in all groups (HIV care providers/clinical staff, IC/ASA staff, and participants), as well as fidelity. Other feasibility measures as shown in Table 1 will be informed by Pai and colleagues [Pai, 2017]. In addition to the quantitative feasibility thresholds, we will incorporate data from stakeholder discussions and qualitative data prior to making a final rating of success.

### 5.1.5. Blueprint and Plan of Treatment

The Expert Panel will construct a blueprint that all ICs/ASAs will follow. The blueprint is similar to standard operating procedures and is intended to provide an overview of essential features of implementing CABENUVA as administered via an IC/ASA. This will include procedures and optimal strategies for successful implementation. This may include, but is not limited to:

- Referral process
- Time for Insurance processing/Notification of Patient
- When to order/obtain labs on participants receiving CABENUVA treatment at an IC/ASA?
- Point of service for labs (i.e. at infusion center, at clinic, at an external lab)?
- How often do HIV care providers want their participants to be seen in their clinic while getting CABENUVA at the IC/ASA?
- How is the HIV care provider notified that the participant received a dose or missed a dose?
- Communication plan for AEs, SAEs, and medical management of AEs/SAEs.
- What happens when a participant misses a scheduled dose?
- Scheduling/Rescheduling
- Appointment Reminders

As the Expert Panel will complete their assessments Q4 2022, following this timepoint, key IC/ASA staff members involved in decision making and/or overseeing daily operations at the IC/ASA, will be given the opportunity to review and revise both the blueprint and the POT. The blueprint and POT will be reviewed and/or revised as necessary pre-study, at 3-4 months into the study to ensure experience with participants and at the end of study.

Part of the blueprint will involve a POT, which outlines key information needed to ensure the IC/ASA and HIV care providers have communicated necessary information on new referrals for CABENUVA. A typical process for incorporating a new product into routine care at ICs/ASAs involves development and/or refinement of a POT, which they iterate as needed until the process works seamlessly for communication and engagement between HIV care providers, participants, and IC/ASA staff. The blueprint and POT will be iterated to include any IC/ASA letters or other means of advertisements that contacts HIV care providers in the community to refer their PLWHIV to them. This process will be documented and incorporated into a final blueprint at the end of the study. Once the initial POT is agreed upon, the IC/ASA will begin incremental real word roll-out into their centers that were not previously participating in the study. Documentation will occur around how ICs/ASAs measures success and the impact to further iterate the blueprint or not.

POTs are often unique to the IC/ASA, however, the POT developed in this study will be used as a model moving forward for all participating ICs/ASAs. A POT may include, but is not limited to, the following:

- Patient information (e.g., name, height, weight, year of birth)
- Diagnosis
- Pre-medication
- Dose and frequency of treatment
- Insurance information
- Preferred form of communication
- Additional requests from referring physicians

### 5.1.6. Scale-up

The blueprint that was determined to achieve optimal performance through formative evaluation will be used to support successful scale-up of CABENUVA IM injections across all ICs/ASAs. Data collected to capture the scale-up will be collected on additional participants that enroll to receive CABENUVA, as well as HIV care providers that opt into participating in the study, as outlined in Table 1. The blueprint will be used to help other alternate administration facilities set up similar models of care and service delivery.

## 5.2. Scientific Rationale for Study Design and Research Methods

The study design is based on the well-established Quality Enhancement Research Initiative (QUERI) Four Phase Framework for Implementation Projects [QUERI, 2013]. These studies are designed to produce valid evidence on operations and impact in a rigorous manner while allowing for continued refinement of program design. The formulative evidence of this study maps onto Phase 2 in the QUERI framework in which a small clinical trial is conducted to refine and evaluate an implementation program (e.g., the process of referring and engaging PLWHIV choosing to receive CABENUVA IM injections at an infusion center). The scale-up of this study maps onto the QUERI framework Phase 3, which involves regional roll-out of projects. This type of design allows for real world testing while collecting data on real-time refinements of the implementation strategy, measurement of impact on key patient and provider outcomes, while having an opportunity to examine what real world scale-up would look like. The measurement follows gold standard implementation outcome guidelines to ensure valid measurement of the intended effect.

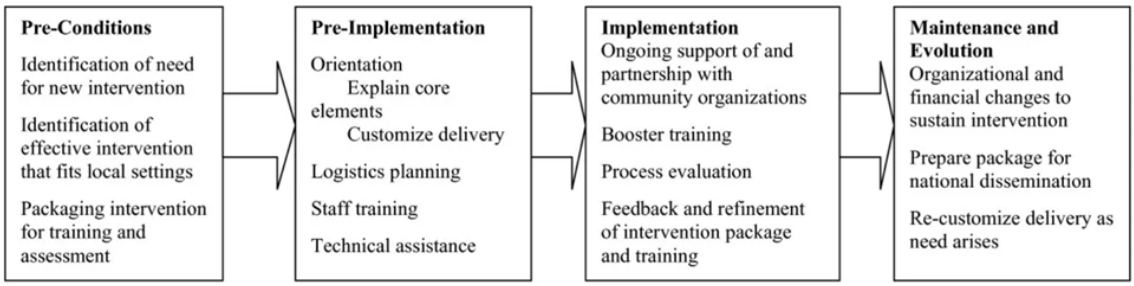
Data from advisory boards has demonstrated a preference for having AIFs to expand access to CABENUVA when it becomes available in routine care. To accommodate the anticipated increased visits in routine care that are associated with the CABENUVA, an expanded capacity for delivery is needed. Shifting to delivering HIV treatment in AIFs is one option to expand uptake of this new treatment. Research shows that just because an effective treatment exists, translation into routine care is slow and often never occurs [Bauer, 2019]. As a result, understanding how to efficiently incorporate AIFs into HIV care, as well as stakeholder views on this option, could serve as a critical step in uptake and sustainment of this novel HIV treatment in the community.

### 5.2.1. Implementation Frameworks

To support the QUERI phased design used in this implementation study, per implementation methodology it is also guided by 3 gold standard frameworks (covering process, determinants and evaluation): Replicating Effective Programs (REP) [Kilbourne, 2007], the Consolidated Framework for Implementation Research (CFIR) [Damschroder, 2009] and the Proctor [Proctor, 2011] outcomes framework.

REP will be used to guide the process of the study. REP is based on the United States Center for Disease Control REP project, which developed systematic and effective strategies to prepare HIV treatments for dissemination [Kilbourne, 2007]. REP provides a conceptual framework on processes needed to prepare effective interventions for use in community settings. The four steps of REP (see Figure 2; pre-conditions, pre implementation, implementation, and maintenance and evolution) ensure key factors are thoroughly addressed that are crucial to implementation of effective interventions in healthcare settings. REP is intended to be flexible and adapted to the context in which implementation is intended to occur with a new effective intervention.

**Figure 2 Replicating Effective Programs**




CFIR will serve as the main determinant's framework guiding examination of factors influencing CABENUVA implementation and the qualitative interviews. This framework provides a menu of constructs that can be used to systematically assess potential barrier and facilitators to implementation. Lastly, the Proctor outcomes will also be used to guide measurement decisions to ensure the appropriate outcomes are measured across the two frameworks [Proctor, 2011]. Notably, acceptability, feasibility, and fidelity will be focused on in the proposed study.

# 6. STATISTICAL CONSIDERATIONS

The statistical analysis plan will be finalized prior to database release, 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 the most important endpoints including primary and key secondary endpoints. The learnings over the first 6 months will will be used to inform the final data analyses.

A baseline analysis will be planned to gain insights on the initial assessment of implementation science data on primary and key secondary objectives. It is expected that this analysis will be performed with baseline questionnaire data needed from participants and IC/ASA staff.

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.

The timing of the interim/s will be based on when a sufficient number of IC/ASA staff and/or 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.

A Statistical Analysis Plan will describe the planned baseline/interim analysis in greater detail individually. There is potential analysis for a small number of interviews ($N \cong 5$) with IC/ASA staff at Month 2 to gain an understanding of what is occurring at ICs/ASAs during early implementation.

All interviews will be audio recorded, professionally transcribed by a third-party vendor, and reviewed for quality assurance purposes. Analyses will be done via qualitative rapid

coding in Excel and targeted at capturing key concepts of interest for assessing the blueprint and POT (including any recommended changes prior to the Month 3 and Month 6 assessments).

## 6.1. Study Size

This study will include up to 120 participants prescribed CABENUVA by their HIV care providers, who will be referred to approximately 35 study infusion centers to receive their injections and will be enrolled. Approximately 20 referring HIV care providers/clinical staff will be selected to complete appropriate questionnaires. Approximately 5 IC/ASA staff at each of the IC/ASA locations will be selected to complete the questionnaires.

Approximately 20 participants will be selected for the Month 8 interview. In addition, approximately 10 referring HIV care providers/clinical staff and 10 IC/ASA staff will be selected to conduct interviews.

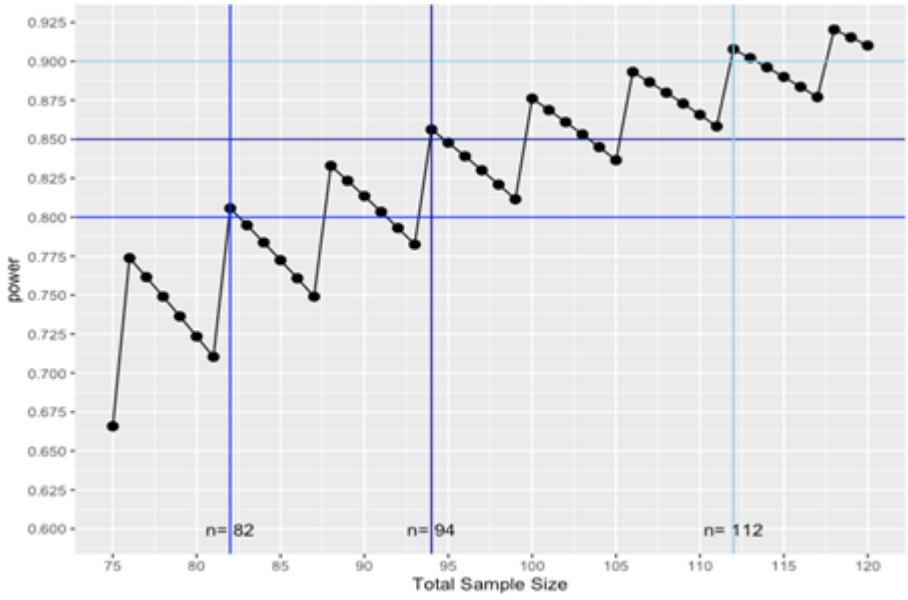
The Expert Panel will review the questionnaire data and real-time feedback from the Infusion Centers to determine if the blueprint and/or the POT will need to be updated. Approximately 10 participants across all ICs/ASAs should have completed the Month 3 assessments prior to the Expert Panel meetings at Month 3 and Month 6.

The Acceptability of Intervention Measure (AIM) and the Feasibility of Intervention Measure (FIM) are employed to evaluate the acceptability and feasibility of our implementation strategy. The AIM and FIM are validated implementation outcome measures [Weiner, 2017a; Weiner, 2017b]. Higher scores for AIM and FIM indicate greater acceptability and feasibility. For these two types of measures, we focus on the proportion of participants that agree or completely agree (a score of 4 or higher) across all items. The following power and sample size discussion is based on the primary endpoint of feasibility score. Suppose that the indicators for feasibility success are set at 80%, then we want to detect a proportion of participants that agree or completely agree (a score of 4 or higher) across all items on FIM, which is 80% or higher. The following analysis shows how sensitive the statistical power is to the number of participants enrolled.

Assuming the true proportion of participants that agree or completely agree on FIM across all items is 90%>80%, Figure 3 shows the relationship between the study power to detect such a proportion and the sample size. In order to have 80% study power, a sample size of 82 participants is needed. If 106 or more participants are enrolled, we would have >85% power to detect such a percentage. To have 90% power, a minimum sample size of 112 participants would be recommended.

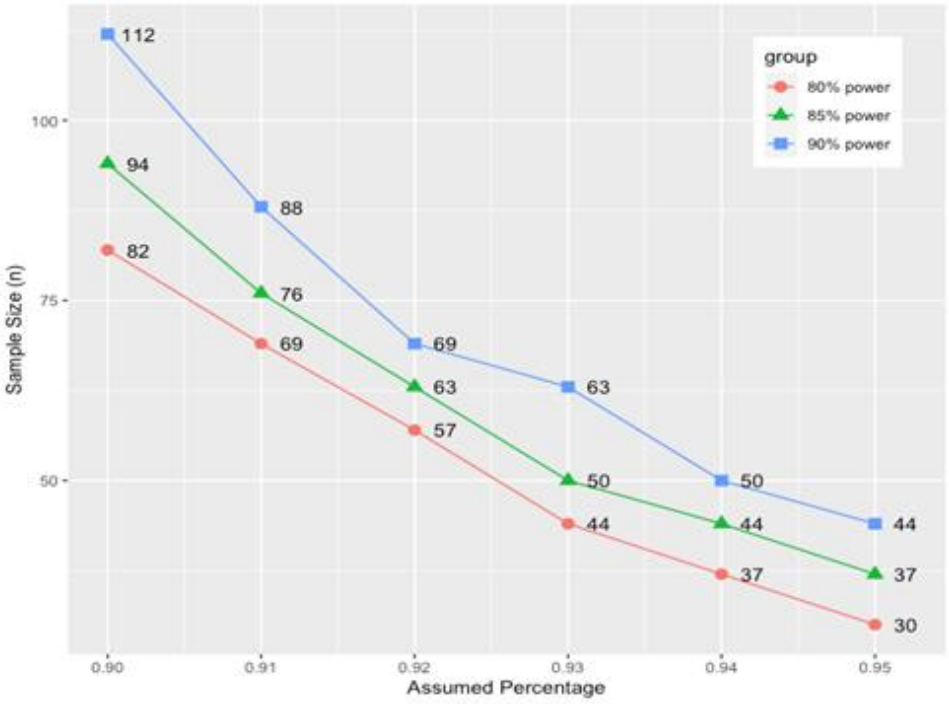
Note: "Enrolled" means a HIV-1 participant agrees to participate in this clinical study, following completion of an informed consent process and provided they meet the baseline eligibility criteria for participation. If required, a legally acceptable representative may provide the participants agreement to participate in the clinical study and sign the ICF.

**Figure 3 Relationship between Study Power and Sample Size**




Further, if we consider a series of possible true percentage, Figure 4 summarizes corresponding minimum sample size needed to achieve three target powers (80%, 85%, 90%). For instance, if the true percentage is a little higher than 90%, which we considered above, say, 93%, then a sample size of 44 participants is required to achieve 80% power. And approximately 50 and 63 participants are needed to have 85% and 90% power respectively.

**Figure 4 Relationship between Minimum Sample Size Required and the Assumed Percentage**



Considering the real-world uptake of CABENUVA is evolving, we might expect some potential low enrollment scenarios at the end of the recruitment period, which could impact the study power significantly due to insufficient sample size available. Under the assumption that the true proportion of participants that agree or completely agree on FIM across all items is 0.90, 0.93 or 0.95, Figure 5 below demonstrates how the study power will vary as the enrollment of participants ranges from 30 to 80. If the true percentage is 0.95, the study power is still relatively high and above 70% for all possible sample size in this range, while the power might be lower than 70% for sample size within 30-42 but keep above 50% for all cases if the true percentage decreased to 0.93. When the true percentage is 0.90, the study power will maintain below the statistically desired 80% as the sample size increases from 30 to 80. In this case, at least 64 participants are needed to achieve 60% or above power.

**Figure 5 Sensitivity of Study Power to Relatively Small Sample Size**

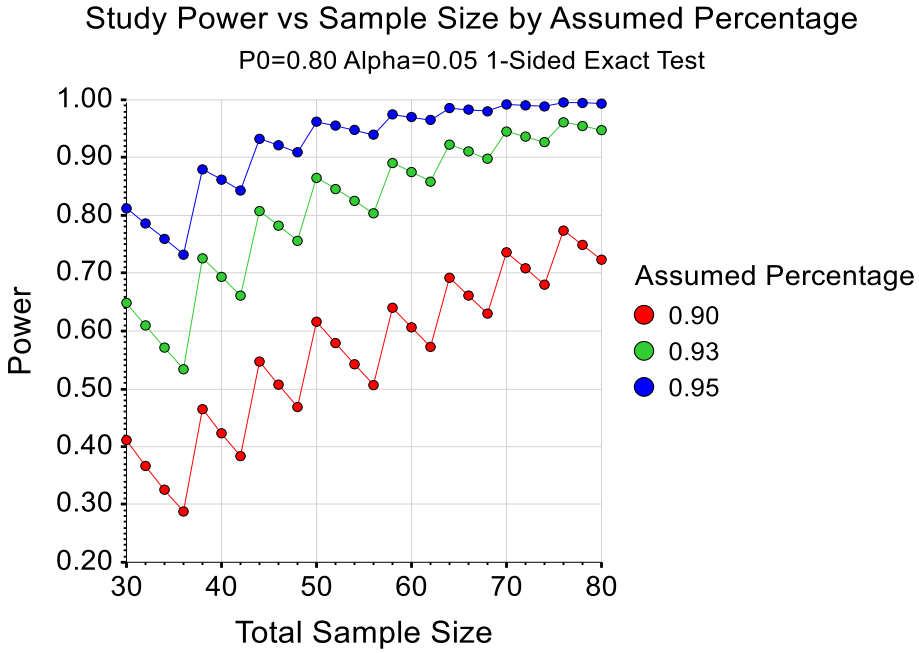



Table 2 below provides more details on the associated study power to some selected sample size in the range 30-80 with the true percentage equal to 0.90.

**Table 2 Relationship between Study Power and Sample Size with Range 30-80**

| True Percentage | Sample Size | Power |
|---|---|---|
| 0.90 | 30 | 0.41 |
| 0.90 | 36 | 0.29 |
| 0.90 | 42 | 0.38 |
| 0.90 | 48 | 0.47 |
| 0.90 | 54 | 0.54 |
| 0.90 | 60 | 0.61 |
| 0.90 | 66 | 0.66 |
| 0.90 | 72 | 0.71 |
| 0.90 | 78 | 0.75 |
| 0.90 | 80 | 0.72 |

## 6.2. Essential Analysis

The primary endpoint in terms of feasibility is the percentage of participants that agree or completely agree (a score of 4 or higher) across all items on the FIM [Weiner, 2017b] at Month 8. For FIM of each study group, the sample percentage and associated 95% confidence interval (CI) will be presented.

One of the secondary endpoints is the change in FIM scores of participants over time at Month 3, and Month 8. In addition to summary of FIM scores at different timepoints, the shift table for each item of FIM will be given to display the number of participants who completely disagree (scale=1), disagree (scale=2), neither agree or disagree (scale=3), agree (scale=4), completely agree (scale=5) at Baseline/Month 1 and the shift of these quantities at each timepoint that follows.

The feasibility composite score will be further refined based on the standard process outlined in the blueprint. The components that are planned to be evaluated at Month 1 through Month 8 and as part of the composite score are outlined below. The intention is to have a sub-score from the following measures, however, information from the Expert Panel will be used to finalize the proposed composite scores prior to data analysis:

1. FIM Score: Proportion of HIV care providers/clinical staff, participants, and IC/ASA Staff respectively that agree or completely agree (a score of 4 or higher) across all items on the FIM.
    - Numerator: Number of HIV care providers/clinical staff, participants, and IC/ASA Staff respectively that agree or completely agree on FIM (a score of 4 or greater) across all items
    - Denominator: Total number of HIV care providers/clinical staff, participants, and IC/ASA Staff respectively
2. Consent Rate: Proportion of participants that provide consent to participate in the study

- Numerator: Number of participants consented
- Denominator: Number of participants referred to the IC/ASA to receive CABENUVA IM injections

3. Show Rate: Proportion of scheduled injection appointments that are not missed
   a. Numerator: Number of scheduled injection appointments that result in shows
   b. Denominator: Number of confirmed scheduled injection appointments for participants
4. Participant Notification: Proportion of contacts the participant receives from the infusion center for missed appointments out of the standard number they should be contacted
   a. Numerator: Number of documented times that a participant is contacted by infusion center staff regarding a missed appointment
   b. Denominator: Standard number of times that a participant is contacted regarding a missed appointment, according to infusion center policy
5. HIV Care Provider Notification:
   a. 1) Proportion of participants whose information regarding test results are communicated to their HIV Care Provider
      — Numerator: Number of participants whose information was communicated to the appropriate HIV care provider
      — Denominator: Total number of participants in the study
   b. 2) Proportion of all appointments missed that are communicated to the HIV care provider
      — Numerator: Number of missed appointments that are communicated to the appropriate HIV care provider
      — Denominator: Total number of missed appointments
6. Return Rate at Visit N: Proportion of participants that completed any injection at Visit N after the completion of (N-1)th injection visit
   a. Numerator: Number of participants who returned to the infusion center and completed an injection at Visit N
   b. Denominator: Number of participants who completed an injection at the infusion center at the previous visit (N-1)
   — This definition is for any scheduled post-baseline visit. When N=1, the previous visit (N-1) is the baseline visit.

The estimates of these quantitative measures will be given and corresponding 95% CIs will also be presented.

The feasibility composite score will be informed by the Expert Panel process to ensure it matches the critical variables identified by all members of the panel. Summary details of feasibility composite score will be included in the statistical analysis plan.

To evaluate the effect of contextual factors on the variability of responses to implementation science measurements. subgroup analysis will be undertaken at specified assessment timepoints, which include, but not limited to, demographic, baseline characteristics, prior clinical experience, initiation method (oral lead in or direct to injection or receiving continuation dose), the number of injections received prior to enrollment and injection option (monthly or every 2-months) for participants, provider type, site type and setting (urban, suburban, rural) for IC/ASA staff, and affiliation for HIV care providers.

## 6.3. Secondary Analysis

A key secondary outcome is Acceptability:

AIM Score: Proportion of HIV care providers/clinical staff, participants, and IC/ASA Staff respectively that agree or completely agree (a score of 4 or higher) across all items on the Acceptability of Intervention Measure (AIM). The score will be calculated approximately at Month 1, Month 4 and Month 8 for HIV care providers/clinical staff, and at prior to Month 1/Month 1, Month 3, and Month 8 for participants and IC/ASA Staff.

- Numerators: Numbers of HIV care providers/clinical staff, participants, and IC/ASA Staff respectively that agree or completely agree (a score of 4 or higher) on AIM across all items
- Denominators: Total numbers of HIV care providers/clinical staff, participants, and I/ASA C Staff respectively

Other secondary outcomes to be evaluated include:

- Fidelity: Proportion of injections occurring within target window from target date (±7 days of target date)
- Feasibility, acceptability and the process of CABENUVA administration at infusion centers from the Expert Panel
- Perceptions, facilitators, and barriers/concerns by HIV care providers/clinical staff, participants, and IC/ASA staff
- Preference of participants on the location to receive CABENUVA
- Advantages to receive or refer participants to receive CABENUVA at the infusion center from participants and HIV care providers/clinical staff
- Disadvantages about receiving CABENUVA at the infusion center from participants and HIV care providers/clinical staff
- Acceptability of receiving and referring participants for CABENUVA injections at infusion centers from participants and HIV care providers/clinical staff
- Usefulness of blueprint intervention by IC/ASA staff and the POT for HIV care providers/clinical staff
- Overall opinion of receiving and administering the injection at an infusion center by IC/ASA staff, participants and HIV care providers/clinical staff

Estimates and associated 95% CI of the quantitative measures above will be presented. Qualitative interview data will be summarized by a third party and reported as part of the overall study results (clinical study report (CSR)). Details of these analyses will be described in a separate analysis plan provided by the CRO partner under GSK's oversight.

## 6.4. Other/Tertiary Endpoints

CCI

[redacted]

CCI [redacted]

## 6.5. Limitations of the Research Methods

This is a single-arm study for gathering information on the feasibility and acceptability of utilizing an IC/ASA to administer CABENUVA in the US. As such there are geographic limitations. The study is deliberately non-stratified to reduce limitations on recruitment.

Thus, this approach may result in some characteristics under- or overrepresented within the participants and limited diversity in terms of demographics or introduction of confounding factors.

# 7. PROTECTION OF HUMAN SUBJECTS

## 7.1. Ethical Approval and Participant Consent

The protocol, protocol amendments, ICF, and other relevant documents (e.g., advertisements) must be submitted to an Institutional Review Board (IRB) and reviewed and approved by the IRB before the study is initiated.

Any amendments to the protocol will require IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The IC/ASA will be responsible for the following:

- Providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB
- Notifying the IRB of SAEs or other significant safety findings as required by IRB procedures
- Providing oversight of the conduct of the study at the ICs/ASAs and adherence to requirements of 21 CFR, ICH guidelines, the IRB, and all other applicable local regulations

## 7.2. Participant Confidentiality

Participants will be assigned a unique identifier. 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 their 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 their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

All IC/ASA study staff will ensure protection of participant personal data and will not include participant names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws.

## 7.3. Informed Consent Process

The IC/ASA will explain the nature of the study to the participant or their 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.
- 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 IC/ASA authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF during their participation in the study.
- A copy of the ICF must be provided to the participant or their legally authorized representative.

ViiV Healthcare (alone or working with others) may use participant's coded study data and other information to carry out this study; understand the results of this study; learn more about CABENUVA or about the study disease; and publish the results of these research efforts.

## 7.4. Quality Control / Study Monitoring

In accordance with applicable regulations including GCP, study monitors will contact the ICs/ASAs prior to the start of the study to review with the IC/ASA staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and VHC 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. The study monitors will monitor the study and IC/ASA 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 IC/ASA staff and the head of the IC/ASA (where applicable) agrees to allow the monitor direct access to all relevant documents.

# 8. CABENUVA AND CONCOMITANT THERAPY

The protocol only requires that the participant is initiating or continuing CABENUVA IM injections, dosed in accordance with the approved label [CABENUVA USPI, EDURANT USPI, VOCABRIA USPI]; no CABENUVA is provided by VHC. No dose reductions, modifications, or changes in the frequency of any components of CABENUVA will be allowed during the study beyond what is allowed within the approved CABENUVA label

The IC/ASA will refer to the most recent CABENUVA USPI, for the preparation and administration of CABENUVA [CABENUVA USPI].

## 8.1. Missed CANENUVA Injections

Adherence to the CABENUVA monthly or every 2-monthly injection dosing schedule is required. If a participant misses a scheduled injection visit, the referring HIV care provider must be notified. The HIV care provider is responsible for all medical management decision for participants after a missed dose, as described in the most recent USPI [CABENUVA USPI]. The IC/ASA staff should also notify the Medical Monitor of missed injections; however, the Medical Monitor is not responsible for decisions regarding medical management of missed injections.

Any changes in a participant's ART must be recorded in the eCRF. This includes oral dosing of VOCABRIA and EDURANT or other ART regimens to ensure anti-viral coverage during a planned or unplanned missed visit.

Participants receiving CABENUVA are anticipated to be at risk for development of virologic resistance if ART is interrupted. The time period during which participants are at risk for development of virologic resistance may be determined by the period between when drug levels fall below therapeutic values and when they fall below levels which exert selective pressure on HIV. This time period will vary by ART agent and is dependent upon effective concentration, inhibitory concentration, and half-life. Plasma concentrations of both drugs (cabotegravir, rilpivirine) may be measurable for more than one year following IM injections.

## 8.2. Treatment of an Overdose

At the IC/ASA, an SOP will be developed for the management of treatment overdose following prescribing label information [CABENUVA USPI]. For this study, any dose of CABENUVA greater than listed in the prescribing information will be considered an overdose. All overdoses and any treatment for the overdosage should be recorded in the eCRF.

There is no known specific treatment for overdose with cabotegravir or rilpivirine. If overdose occurs, contact the PPD Medical Monitor immediately while monitoring the participant and apply standard supportive treatment as required, including monitoring of vital signs as well as observation of the clinical status of the patient, and record in the participants source documentation. Consider the prolonged exposure to cabotegravir and rilpivirine (components of CABENUVA) following injections when assessing treatment needs and recovery.

In the event of an overdose, the IC/ASA should:

1. **Contact both the HIV care provider and the PPD Medical Monitor immediately**.
2. Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.
3. Document any signs or symptoms the IC/ASA assess as related to the overdose in the eCRF

Decisions regarding dose interruptions or modifications will be made by the HIV care provider and may consult with the Medical Monitor based on the clinical evaluation of the participant.

### 8.3. Concomitant Therapy

HIV care providers and IC/ASA staff will monitor concomitant medications, referring to the most recent USPI [CABENUVA USPI], paying special attention to the contraindicated medications and medications with a potential for drug-drug interactions.

The IC/ASA will note all new concomitant medications and send to the HIV care provider. The IC/ASA should consult with the HIV care provider if any new contraindicated or concomitant medications with the potential for drug interactions are noted prior to administering CABENUVA. Contraindicated or concomitant medications with the potential for drug interactions must be recorded in the eCRF at each visit. The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

## 9. DISCONTINUATION OF CABENUVA AND PARTICIPANT DISCONTINUATIONS

### 9.1. Discontinuation of CABENUVA

It may be necessary for a participant to permanently discontinue CABENUVA. If CABENUVA is permanently discontinued, the participant will not remain in the study. See the SoA (Annex 1: Schedule of Activities) and the POT for data to be collected at the time of discontinuation of CABENUVA. All study and CABENUVA discontinuations will be captured in the eCRF.

A participant may have to discontinue CABENUVA due to moderate to severe (as clinically determined by the IC/ASA and/or HIV care provider) COVID-19 infection

(suspect, probable, or confirmed using the most recent version of the World Health Organization (WHO) case definition [WHO, 2020].

All study and CABENUVA discontinuations will be recorded.

## 9.2. Temporary Discontinuation

The referring HIV care providers will determine if a temporary discontinuation is appropriate for their PLWHIV, per the most recent USPI for CABENUVA [CABENUVA USPI]. The IC/ASA will capture temporary discontinuations and restart information in the eCRF. If the participant does not restart CABENUVA they will no longer be eligible to continue the study.

**If the referring HIV care provider determines a temporary discontinuation of CABENUVA is appropriate, he/she is responsible for all medical management decisions regarding ART coverage during this time.** The IC/ASA staff should also notify the Medical Monitor of temporary discontinuations; however, the Medical Monitor is not responsible for decisions regarding medical management of missed injections.

Any changes in a participant's ART must be recorded in the eCRF. This includes oral dosing of VOCABRIA and EDURANT or other ART regimens to ensure anti-viral coverage during a planned or unplanned missed visit.

## 9.3. Participant Discontinuation / Withdrawal from the Study

A participant may discontinue CABENUVA and withdraw from the study at any time at their own request or may be withdrawn at any time at the discretion of the IC/ASA or HIV care providers for safety (i.e., AE, SAE), behavioural, or compliance reasons (i.e., protocol deviation).

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA (Annex 1: Schedule of Activities) and the POT. The SoA includes the data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

## 9.4. Lost to Follow-up

A participant will be considered lost to follow-up if they fail to return for one or more scheduled visits and is unable to be contacted by the IC/ASA or the HIV care provider.

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

- The IC/ASA must immediately contact the HIV care provider if a participant has missed a visit.

- The IC/ASA must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue receiving monthly or every 2-monthly injections at the IC/ASA.
- Before a participant is deemed lost to follow up, the IC/ASA and HIV care provider must make every effort to regain contact with the participant. These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, they will be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up".

# 10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS AND SAFETY ASSESSMENTS

Planned time points for all safety assessments are provided in the SoA, Annex 1 and in the POT. Definitions of AEs, SAEs and CV events can be found in Annex 3.

All AEs, SAEs and clinical laboratory abnormalities should be graded using the Division of AIDS (DAIDS) table for grading the severity of adult and pediatric adverse events [DAIDS, 2017].

## 10.1. Clinical safety laboratory assessments

All Baseline/Month 1 lab assessments should be drawn prior to the 1st study injections. If labs will be taken off-site from the IC/ASA, then the study participant should sign the ICF and receive a requisition for a blood draw at another location (i.e., Quest, Labcorp). Labs should be drawn 7-10 days prior to the Baseline/Month 1 visit. Confirmation that labs were drawn prior to the 1st study injections are mandatory, relevant labs should be added to the eCRF. If a potential participant has had labs drawn with 10 days of the Month 1/Baseline visit, and the HCP is willing to share that data, this data can then be used and added to the eCRF.

Local laboratory assessments for this study will be performed as per the blueprint and the POT at local laboratories. All laboratory reports will be shared with the HIV care provider. See the SRM for additional information.

- The HIV care provider will determine if any laboratory tests have values considered clinically significantly abnormal and will be responsible for the participant clinical management. The IC/ASA and HIV care provider will agree if follow-up labs are to be collected at the IC/ASA. The PPD Medical Monitor should be informed of abnormal laboratory tests considered clinically significant.
- The IC/ASA should document this review and record any HIV care provider determination of clinically significant changes occurring during the study as an AE/SAE. The PPD Medical Monitor should be informed. The laboratory reports must be filed with the source documents.
- If any laboratory test results require a change in participant management or are considered clinically significant by the HIV care provider, then the results must

be recorded in the eCRF as appropriate (e.g., abnormal lab results that are considered an SAE, CABENUVA related or required CABENUVA to be discontinued).

- If laboratory values from non-protocol specified laboratory tests performed at the HIV care provider's local laboratory require a change in participant management or are considered clinically significant by the provider then the results must be recorded in the eCRF as appropriate (e.g., abnormal lab results that are considered an SAE, CABENUVA-related AE, requires CABENUVA to be discontinued, or COVID-19 related).

It is expected that at a minimum, HIV-1 RNA and liver chemistries will be analyzed. Other lab assessments will be determined by the Expert Panel (e.g., absolute CD4 cell counts) and the POT between the HIV care provider and the IC/ASA.

- Liver chemistries should include:
    - Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)
    - Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)
    - Alkaline Phosphatase
    - Total and direct Bilirubin

Additional tests may be performed at any time during the study as determined necessary by the HIV care provider.

## 10.2. Liver Chemistry Monitoring

The HIV care provider and the Medical Monitor must be contacted at onset of liver chemistry elevations to discuss participant safety. Liver event documents (i.e., "Liver Event eCRF" and updates, "Liver Imaging eCRF" and/or "Liver Biopsy eCRF", as applicable) should be completed as soon as possible. See the SRM for more information on liver events. Safety contact information can be found in Annex 4.

The decision whether to discontinue CABENUVA for abnormal liver tests should be made by HIV care provider. The POT between the IC/ASA and the HIV care provider will include the monitoring of liver chemistries and communications between the IC/ASA, HIV care provider, and the PPD Medical Monitor. The PPD Medical Monitor may request additional information regarding the results of and/or the monitoring of liver chemistries. Additional information can be found in Section 10.1 and in the SRM.

## 10.3. Adverse Events (AEs), Pregnancy Exposure and Incident Reporting

Clinical safety data will be collected as outlined in the eCRF. The complete definitions of adverse events (AE) or serious adverse events (SAEs) can be found in Annex 3. For AEs, only those that are considered related to CABENUVA, or that caused the

participant to discontinue the study are required to be reported to PPD PVG (See Section 10.3.1). All AEs will be reported to the HIV care provider.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative (LAR)) be collected and stored in the participants source documentation.

The IC/ASA staff 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 CABENUVA or that cause the participant to discontinue CABENUVA from the time of the informed consent to participants withdrawal or completions of the study.

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 10.3.10.

Please call the PPD safety hotline located in Annex 4 for AE/SAE assistance (i.e., is this event an SAE?) and for eCRF entry assistance.

### 10.3.1. Specific Adverse Events to be Documented in this Study

Please refer to the most current USPIs for CABENUVA, VOCABRIA and EDURANT for additional safety information [CABENUVA USPI; EDURANT USPI, VOCABRIA USPI].

AEs and SAEs that are required to be recorded as defined in the eCRF include:

- AEs/Adverse drug reactions* (ADRs) reported at the Baseline/Month 1 visit that are considered related to oral VOCABRIA or EDURANT or from the time of the last injections
- AEs/ADRs considered related to CABENUVA
- All AEs, whether considered related or not, that cause the participant to discontinue CABENUVA
- All SAEs whether related to CABENUVA or not
- All CV events listed in Annex 3
- COVID-19 related adverse events

*An adverse drug reaction (ADR) is defined as a noxious and unintended response to a medication related to any doses where there is at least a reasonable possibility, or the relationship cannot be ruled out, that it is related to CABENUVA.

Non serious AEs that are considered not related to CABENUVA or do not lead to withdrawal, should be documented in the source documents but will not be documented in the eCRF, as this information has been extensively collected in treatment clinical trials, no further information is needed to characterize these events.

### 10.3.2. Time Period and Frequency for Collecting AE and SAE Information

The IC/ASA staff are obliged to collect and report AE information from the time of informed consent to the participants withdrawal or completion from the study.

AEs that begin during the oral lead-in and are considered related to VOCABRIA or EDURANT will be recorded as a VOCABRIA or EDURANT-related AE after obtaining the informed consent.

For participants that are already receiving CABENUVA injections prior to enrolling in the study, any CABENUVA related AEs reported after their last injections will be recorded after obtaining the informed consent.

- All other events that begin before the administration of CABENUVA IM injections but after obtaining informed consent will be recorded as Medical History/Current Medical Conditions not as AEs.

All SAEs will be recorded and reported to PPD PVG immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.3.10, Table 3. The IC/ASA will submit any updated SAE data to PPD PVG (Annex 4)within 24 hours of it being available.

The IC/ASA should send all participant reported AEs/SAEs to the HIV care provider and request a causality assessment. The HIV care provider is responsible to the medical management of any AE/SAEs.

The IC/ASA is not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the IC/ASA 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 IC/ASA staff must promptly notify PPD PVG.

### 10.3.3. Methods of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about any adverse event occurrence.

### 10.3.4. Follow-up of AEs and SAEs

After the initial AE/SAE report, the HIV care provider and/or the IC/ASA 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 (as defined in Section 9.4). Further information on follow-up procedures is given in the SRM.

### 10.3.5. Regulatory Reporting Requirements for SAEs

The definition of SAEs can be found in Annex 3.

**Prompt notification by the IC/ASA staff to PPD of SAEs is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of VOCABRIA, EDURANT and/or CABENUVA are met.** All SAEs need to be reported and recorded to PPD within 24 hours of IC/ASA awareness of the event. The primary mechanism for reporting SAEs to PPD will be the eCRF, which will send an automated, electronic safety alert to PPD. If the electronic system is unavailable, the IC/ASA will use the paper SAE form and fax it to PPD.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of VOCABRIA, EDURANT and/or CABENUVA. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRBs), ICs/ASAs and the referring HIV care providers.

The IC/ASA which receives a safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the required study documents and will notify the IRB, if appropriate according to local requirements.

Safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to participating HIV care providers as necessary.

### 10.3.6. Adverse Event Follow-up with the HIV Care Provider

The IC/ASA should send all AEs and SAEs to the HIV care provider for follow-up medical management and to confirm or determine relatedness to CABENUVA.

### 10.3.7. Causality Assessments

The causality assessment to CABENUVA is one of the criteria used when determining regulatory reporting requirements.

Please refer to the most recent USPIs for CABENUVA, VOCABRIA and EDURANT for additional safety information [CABENUVA USPI; EDURANT USPI; VOCABRIA USPI].

- For each AE/SAE, the IC/ASA physician **must** document in the medical notes that he/she has reviewed the AE/SAE reported and has provided an initial assessment of causality. All AE/SAEs, along with the initial assessment of causality to CABENUVA, should be sent to the referring HIV care provider.
- There may be situations in which an SAE has occurred, and the IC/ASA physician has minimal information to include in the initial report to PPD PVG. However, **it is very important that the IC/ASA physician always make an assessment of causality for every event before the initial transmission of the SAE data to PPD PVG.**
- The HIV care provider is expected to provide a causality assessment. The HIV care provider's assessment will determine the final causality to CABENUVA.

- **When a causal relationship is determined by the HIV care provider to be related to CABENUVA, this must be recorded as a treatment related AE or SAE as soon as possible.** The PPD Medical Monitor should be informed of these events.
- If the HIV care provider does not provide a causality, it will remain as the IC/ASA physician's initial determination.
- In the case that the IC/ASA physician determines a non-serious AE that hasn't resulted in discontinuation or withdrawal is not related to CABENUVA, the AE would not be entered into the eCRF. However, if the referring HIV care provider determines that the non-serious AE is related to CABENUVA, the IC/ASA staff will enter the AE into the eCRF.
- The IC/ASA staff may change causality as confirmed by the referring HIV care provider or when additional follow-up information is available, in which case an SAE follow-up report is sent to PPD (via the automated eCRF email) with the updated causality assessment included.

### 10.3.8. Serious Post-Injection Reactions

Per the current CABENVUA USPI [CABENUVA USPI], participants should be observed briefly (approximately 10 minutes) after the injection. Serious post-injection reactions include dyspnea, agitation, abdominal cramping, flushing, sweating, oral numbness, and changes in blood pressure). These events may have been associated with inadvertent (partial) intravenous administration. For more information, please refer to the most recent CABENUVA USPI. These events should be considered as a serious adverse event and reported to PPD PVG as described in Section 10.3.10.

If a participant experiences a serious post-injection reaction, monitor and treat as clinically indicated. In case of a serious post-injection reaction after administration of CABENUVA, an ECG may be obtained if medically required. The ECG should be included in the participants source documents.

The HIV care provider will determine whether the participant should continue to receive CABENUVA and remain in the study. The Medical Monitor should be made aware of these events.

### 10.3.9. Injection Site Reactions

Injection site reactions (ISRs) are considered drug related as they are related to the administration of CABENUVA. ISRs may include redness, itching, pain or swelling or discomfort at the site of the reaction. All ISRs must be recorded in the eCRF.

As ISRs have been well characterized throughout the development program of CABENUVA and are considered common adverse drug reactions for CABENUVA, therefore only serious ISRs and ISRs leading to discontinuation are required to be reported to PPD PVG as described in Section 10.3.10.

### 10.3.10. Reporting of AEs and Timelines

If the eCRF is down at the time of notification of these events, complete the applicable AE/SAE paper forms or other safety event eCRF and fax the completed forms to PPD PVG. All SAEs should be reported to PPD PVG immediately and under no circumstance should this exceed 24 hours. Please see Annex 4 for safety contact information the SRM for additional information on the follow-up of safety events.

AE or SAE information must include relationship to CABENUVA. Specific events requiring safety follow-up are:

- SAEs reported at the Baseline/Month 1 visit that are considered related to oral VOCABRIA or EDURANT or from the last injection
- All SAEs (Annex 3) whether related to CABENUVA or not

The non-serious AEs listed below will require reporting within 3 days to PPD PVG and will use the same automated safety alerts within the eCRF.

- AEs/Adverse drug reactions (ADRs) (Annex 3) reported at the Baseline/Month 1 visit that are considered related to oral VOCABRIA or EDURANT or from the last injection
- AEs/ADRs considered related to CABENUVA
    - **Note:** non-serious injection site reactions do not have to be reported to PPD
- All AEs, whether considered related or not, that cause the participant to discontinue CABENUVA (including ISRs)
- Cardiovascular AEs considered related to CABENUVA

Safety reporting timeline requirements for AE and SAE is summarized in Table 3.

**Table 3 Reporting of Serious Adverse Events and Other Events**

| | Initial Reports | | Follow-up Information on a Previous Report | |
|---|---|---|---|---|
| **Type of Event** | **Time Frame** | **Documents** | **Time Frame** | **Documents** |
| All SAEs | 24 hours | "SAE eCRF" | 24 hours | Update "SAE eCRF" |
| Cardiovascular (CV)[a] or death event | Initial and follow-up reports to be completed when the CV event or death is reported[b] | 'AE/SAE eCRF' and "CV events" and/or "death" eCRF | Initial and follow-up reports to be completed when the CV event or death is reported[b] | 'Updated AE/SAE eCRF' and Update "CV events" and/or "death" eCRF |
| Pregnancy | 24 hours | "Pregnancy Notification Form" and SAE (if required) | Within 24 hours of IC/ASA staff awareness of pregnancy outcome | "Pregnancy Follow-up Form" and SAE (if required) |
| Non serious ADRs[c] | 3 days | eCRF | 3 days | eCRF |
| AEs leading to withdrawal | 3 days | eCRF | 3 days | eCRF |

a. CV events are noted in Annex 3.
b. Additional details and time frames for reporting supplementary information for cardiovascular and death events are provided in Section 10.3.12.
c. See Section 10.3.1 for additional information of what AE/ADRs need to be collected.

## 10.3.11. Pregnancy

Pregnancy status at enrolment should be confirmed in all participants of child-bearing potential (POCBP) by asking their pregnancy status and/or when was the last menses period (LMP). If a participant states they are pregnant, or the LMP was >4 weeks, call the HIV care provider to confirm if CABENUVA should be administered. This confirmation from the HIV care provider should be stored in the participants source documentation.

Pregnancy testing will be managed by the HIV care provider. For POCBP, IC/ASA staff should verbally ask about pregnancy status at each visit by asking when was the LMP. If the LMP was >4 weeks, call the HIV care provider before injecting CABENUVA.

**If a pregnancy is reported, the IC/ASA will work with the HIV care provider to record pregnancy information on the appropriate form and submit it to PPD within 24 hours of learning of the pregnancy and should follow the procedure outlined in SRM.**

Whilst pregnancies are not part of the study nor documented within eCRF, **they will however be reported to the sponsor within 24 hours of awareness**. All pregnancies will be followed up until outcome (including premature terminations and complications) for both mother and child.

The IC/ASA staff will be provided with necessary "pregnancy notification" and "pregnancy follow up" forms and supported by clinical monitor and/or GSK/ViiV medical team in complying with regular pregnancy reporting procedures. Pregnancies

will also be reported to the Antiretroviral Pregnancy Registry (APR) by GSK global safety. The IC/ASA staff should not report to APR, to avoid duplication.

- Any participant who becomes pregnant while participating in the study will be assessed by their HIV care provider whether to continue or discontinue CABENUVA and whether to remain in the study. Pregnancy information will be collected from Day 1 and followed for 52 weeks, including any post-study SAEs possibly related to CABENUVA should be reported promptly.

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 SAEs.

Any SAE occurring in association with a pregnancy should be brought to the IC/ASA attention after the participant has completed the study and considered by the HIV care provider as possibly related to CABENUVA, must be promptly reported to ViiV/GSK.

- ViiV/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 antiretroviral (ARV) products. Additional information and a list of participating manufacturers/licensees are available from http://apregistry.com/index.htm.

Prior to the enrolment of pregnant participants or the continuation of CABENUVA following pregnancy, the following must occur:

- HIV care provider confirms CABENUVA can be continued and this documentation is stored in the participants source documents.
- The IC/ASA, along with the HIV care provider, agrees to monitor the outcome of the pregnancy and the status of the participant and her offspring.

### 10.3.12. Cardiovascular and Death Events

All deaths will be reported and recorded as SAEs. In addition, all deaths will be required to have the eCRF death forms completed by the IC/ASA. These sections include questions regarding the death (including sudden cardiac death and non-cardiovascular death).

The Death eCRF 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.

For any CV events detailed in ANNEX 3, whether or not they are considered SAEs, specific CV sections of the eCRF will be required to be completed. These sections include questions regarding the CV event (including sudden cardiac death).

The CV CRFs are presented as queries in response to reporting of certain CV Medical Dictionary for Regulatory Activities (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.

### 10.3.13. Medical Device Deficiency

The vial adaptor, syringe, and needles provided commercially in the study are classed as medical devices by the FDA. If a medical device deficiency or incident is noted during the study, please follow the instructions found in the CABENUVA packaging for reporting the incident.

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# ANNEX 1: SCHEDULE OF ACTIVITIES

| Procedure[1] | Baseline/ Month 1[2] | Treatment Period (Months) | | | | | | | E.D.[3] | Notes |
|---|---|---|---|---|---|---|---|---|---|---|
| | | 2 | 3 | 4 | 5 | 6 | 7 | 8 | | |
| 1. The timing and number of planned study assessments may be altered during the study based on newly available data.<br>2. The following sequence of events must be followed for participants at the Baseline/Month 1 visit: 1) Informed consent form (ICF) Consent 2) Confirm Inclusion and Exclusion criteria 3) complete questionnaires and assessments, 4) Receive first study related intramuscular (IM) injections at the IC/ASA. Baseline is defined as the Month 1 visit.<br>3. E.D = early discontinuation/ withdrawal: This visit should only be conducted if the participant discontinues from the study, and the discontinuation/withdrawal reason should be recorded.<br>**NOTE**: Carefully follow the Instructions for Use when preparing and administering CABENUVA IM to avoid accidental intravenous administration | | | | | | | | | | |
| **Clinical and Other Assessments** | | | | | | | | | | |
| Informed consent | X | | | | | | | | | Written informed consent must be obtained from each potentially eligible participant by IC/ASA personnel prior to the initiation of any Baseline procedures as outlined in this protocol. |
| Inclusion and exclusion criteria | X | | | | | | | | | Inclusion/exclusion criteria will be fully assessed at the Baseline/Month 1 Visit. |
| Demography | X | | | | | | | | | |
| Pregnancy Status | X | X | X | X | X | X | X | X | X | Ask POCBP at each visit if they are pregnant and ask for the date of their LMP. See Section 10.3.11 for additional information.<br>For participants on every 2 monthly injections, pregnancy status should be confirmed only at IC/ASA visits |

| **Procedure**[1] | **Baseline/ Month 1**[2] | **Treatment Period (Months)** | | | | | | | **E.D.**[3] | **Notes** |
|---|---|---|---|---|---|---|---|---|---|---|
| | | **2** | **3** | **4** | **5** | **6** | **7** | **8** | | |
| Height and weight | X | X | X | X | X | X | X | X | X | Height will only be collected at Baseline.<br>BMI will be calculated within the eCRF.<br>If possible, the same scale should be used consistently throughout the study and participants should be asked to remove any excess clothing (i.e., coats and shoes).<br>For participants on every 2 monthly injections, weight would be collected only at IC/ASA visits |
| Vital signs: blood pressure, heart rate | X | Vital signs will be measured according to the POT with the HIV care provider. All vital signs collected must be stored in the participants source documentation at the IC/ASA. | | | | | | | | Vital signs are to be measured after resting in a semi-supine position for at least 5 minutes.<br>For participants on every 2 monthly injections, vital signs would be collected only at IC/ASA visits |
| Laboratory assessments (HIV1-RNA, liver chemistries, other labs per POT) | X | | | | | | | X | X | The Baseline/Month 1 labs should be collected prior to the first study injection (at the Baseline/Month 1 visit. See Section 10.1 for additional information<br>The HIV care provider is responsible for monitoring and any follow-up of elevated HIV-1 RNA and liver chemistries in their PLWHIV and to let the IC/ASA know if there are any changes to the monthly or every 2-month injections. The HIV care provider can request that the IC/ASA draw labs at any time or they can perform local labs as required. |
| | | Additional Lab assessments may be obtained per blueprint and the POT with the HIV care provider. All lab reports must be stored in the participants source documentation at the IC/ASA.<br>Fasting is not required unless otherwise required for a specific lab test. | | | | | | | | |
| **Study Treatment: All injections will be administered according to the CABENUVA USPI.** | | | | | | | | | | |
| **CABENUVA IM Injections initiated at IC/ASA,** post oral lead-in (1st injections of CABENUVA at the IC/ASA) | | | | | | | | | | The final oral doses of VOCABRIA + EDURANT, or other ART, should be taken on the same day when injections with CABENUVA are started.<br>Questionnaires and procedures should be conducted prior to the injections. |

| Procedure[1] | Baseline/ Month 1[2] | Treatment Period (Months) | | | | | | | E.D.[3] | Notes |
|---|---|---|---|---|---|---|---|---|---|---|
| | | 2 | 3 | 4 | 5 | 6 | 7 | 8 | | |
| Monthly Dosing (post oral lead-in) | X | X | X | X | X | X | X | X | | IM dosing is expected to occur on the same date of the month as determined by Dose 1 - Treatment Target Date. Dosing window is (+ or -) a 7-day window |
| Every 2-month Dosing | X | X | | X | | X | | X | | Dosing window for every 2-months is +/ - 7-days. |
| **CABENUVA IM Continuation injections:** for those already receiving CABENUVA injections, and who are to get their subsequent injections at the IC/ASA<br>**Note:** To avoid having participants whose last injections are at Month 7 return to the IC/ASA at Month 8, the end of study assessments (Month 8) will be completed at Month 7. Questionnaires and potential interviews will be completed at Month 8 | | | | | | | | | | Questionnaires and interviews should be conducted prior to the injections. |
| Monthly Dosing | X | X | X | X | X | X | X | X | | The first study related CABENUVA injections at the IC/ASA should be started within 1 month (±7-day) after the last injections.<br>For participants switching from an every-2-month continuation injection schedule to a monthly continuation dosing schedule, follow the dosing instructions in the most recent USPI for CABENUVA, pl. |
| Every 2-month dosing (participants already receiving every 2-month dosing) | X | | X | | X | | X | | | Dosing window for every 2-month dosing is ± 7-days.<br>For participants switching from a monthly continuation injection schedule to an every-2-month continuation injection dosing schedule follow the dosing instructions in the most recent USPI for CABENUVA., |

| Procedure[1] | Baseline/ Month 1[2] | Treatment Period (Months) | | | | | | | E.D.[3] | Notes |
|---|---|---|---|---|---|---|---|---|---|---|
| | | 2 | 3 | 4 | 5 | 6 | 7 | 8 | | |
| Concomitant medication review | X | ▯==========▯ | | | | | | | X | The IC/ASA will note all new concomitant medications and send to the HIV care provider. Contraindicated medications and concomitant medications with a potential for a DDI per CABENUVA USPI will be recorded. |
| Adverse Event (AE) Review | X | ▯==========▯ | | | | | | | X | See Section 10 for more information on the DAIDS grading scale, Section 10.3.7 for guidelines on assessment of causality, and Section 10.3.10 for AE reporting requirements<br>Refer to the Annex 3 for definitions of AEs. |
| Serious AEs (SAEs) | X | ▯==========▯ | | | | | | | X | See Section 10 for more information on the DAIDS grading scale, Section 10.3.7 for guidelines on assessment of causality, and Section 10.3.10 for SAE reporting requirements.<br>Refer to the Annex 3 for definitions of SAEs |
| **Questionnaires and Interviews: Questionnaires and Interviews should be completed before receiving CABENUVA IM injections** | | | | | | | | | | |
| **Participants**<br>Baseline/Month 1 is defined as the date when a participant signs ICF and completes Baseline/Month 1 protocol procedures prior to receiving the first study related CABENUVA injections at the IC/ASA<br>All additional study visits, including those where questionnaires and/or interviews are administered at Months 3 and 8 will be anchored off of each participants Month 1 visit, so it will reflect the Months on study, regardless of what dosing regimen the participant is on (e.g., monthly or every 2 monthly) and regardless of whether they have missed any injections and received oral bridging. | | | | | | | | | | |

| Procedure[1] | Baseline/ Month 1[2] | Treatment Period (Months) | | | | | | | E.D.[3] | Notes |
|---|---|---|---|---|---|---|---|---|---|---|
| | | 2 | 3 | 4 | 5 | 6 | 7 | 8 | | |
| Participant Questionnaires | X | | X | | | | | X | X | At Month 1, Questionnaires should be completed after signing the ICF and before receiving CABENUVA IM injections or within 14 days following the Month 1 visit.<br>Questionnaires should be completed before receiving CABENUVA IM injections or ± 14 days following the last visit. |
| Participant Interviews | | | | | | | | X | X | Interviews will be completed at the participants last study Visit: Month 8 or early withdrawal visit. Interviews can be completed 2 weeks before or 2 weeks following the last visit.<br>Interviews should be completed before receiving CABENUVA IM injections if interviews are completed the day the injections are administered. |
| **Expert Panel**: will consist of key IC/ASA staff members involved in decision making and/or oversee daily operations at the IC/ASA, selected HIV care providers that may refer PLWHIV, and ViiV Healthcare (VHC). Panel members will meet prior to Baseline/Month 1 to design the Blueprint (Section 5.1.1)<br>Baseline/Month 1 is defined as the date when a participant signs ICF, completes protocol procedures and receives the first study related CABENUVA injections at any infusion center.<br>Month 3 and Month 6 assessments are to be completed after approximately 10 participants (across all ICs/ASA) have completed their Month 3 and Month 6 study visits at any IC/ASA site | | | | | | | | | | |
| Expert Panel Questionnaires | X (Prior to Month 1) | | X | | | X | | | | FIM, AIM (FIM and AIM also completed prior to FPFV at the Baseline/Month 1 visit)<br>Meetings will be held as required over the first 6 months to discuss any iterations that are needed to refine and optimize the blueprint. |

| Procedure[1] | Baseline/ Month 1[2] | Treatment Period (Months) | | | | | | | E.D.[3] | Notes |
|---|---|---|---|---|---|---|---|---|---|---|
| | | 2 | 3 | 4 | 5 | 6 | 7 | 8 | | |
| Expert Panel Interviews | X (Prior to Month 1) | | | | | X | | | | FIM, AIM (FIM and AIM also completed prior to FPFV at the Baseline/Month 1 visit)<br>Meetings will be held as required over the first 6 months to discuss any iterations that are needed to refine and optimize the blueprint. |
| **HIV Care Providers/Clinical Staff**<br>Baseline/Month 1 is defined when the HIV care provider's first patient referred to the IC/ASA is enrolled into the study and receives their first study related injections of CABENUVA. HIV care providers/clinical staff will be asked to complete the Baseline/Month 1 questionnaire within 4 weeks of their first referred patient enrolled.<br>Month 4 and Month 8 assessments are to be completed when the HIV care provider's first referred patient completes the Month 4 or Month 8 study visits, respectively. Questionnaires and/or interviews can be completed up to 2 weeks before or after the Month 4 or Month 8 study visits | | | | | | | | | | |
| HIV Care Providers/ Clinical Staff Questionnaires | X (Within 4 weeks) | | | X | | | | X | | HIV care providers/clinical staff should complete questionnaires within 4 weeks following their first patient's enrolment into the study. |
| HIV Care Providers/ Clinical Staff Interviews | | | | | | | | X | | Only HIV care providers/clinical staff that had patients enrolled into the study will be included in assessments post Baseline/Month 1. |
| **Infusion Center Staff: Baseline questionnaires should be completed prior to the first participant enrolled**<br>Baseline/Month 1 questionnaires should be completed prior to enrolment of the first participant at each infusion center.<br>Month 1 for each IC/ASA is defined when the first participant enrolls into the study at that specific IC/ASA and the participant is administered the first study related injections of CABENUVA.<br>Month 2 for potential interviews of approximately 5 IC/ASA staff will be defined after at least 1 participant, at their respective IC/ASA site, has completed their Month 2 study visits<br>Month 3 and Month 8 will be defined after at least 1 participant, at their respective IC/ASA site, has completed their Month 3, or 8 study visits, respectively. Questionnaires and/or interviews can be completed up to 2 weeks before or after to the Month 3 or Month 8 study visits. | | | | | | | | | | |

| Procedure[1] | Baseline/ Month 1[2] | Treatment Period (Months) | | | | | | | E.D.[3] | Notes |
|---|---|---|---|---|---|---|---|---|---|---|
| | | 2 | 3 | 4 | 5 | 6 | 7 | 8 | | |
| IC Staff Questionnaires | X (Prior to Month 1) | | X | | | | | X | | Month 1/Baseline questionnaires should be completed prior to the first participant enrolled at that IC/ASA.<br>Questionnaires at other months should be completed within ± 14 days of the scheduled month. |
| IC Staff Interviews | | X | | | | | | X | | Month 1/Baseline questionnaires should be completed prior to the first participant enrolled at that IC/ASA.<br>Questionnaires at other months should be completed within ± 14 days of the scheduled month. |

# ANNEX 2. LIST OF STAND-ALONE DOCUMENTS

Study Blueprint

Plan of Treatment (PoT)

Study Reference Manual (SRM)

# Annex 3: AE and SAE Definitions

## Annex 3.1 Definition of an Adverse Event

| **AE Definition** |
|---|
| • An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of CABENUVA, whether or not considered related to the CABENUVA.<br>• 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 CABENUVA. |
| **Definition of Unsolicited and Solicited AE** |
| • An unsolicited AE is an AE that was not solicited and that is communicated by a participant or their legally authorized representative (LAR) who has signed the informed consent. Unsolicited AEs include serious and nonserious AEs. Only AEs that are considered related to CABENUVA or lead to discontinuation of CABENUVA will be recorded.<br>• Potential unsolicited AEs may be medically attended (i.e., symptoms or illnesses requiring hospitalization, emergency room visit, or visit to/by a healthcare provider). The participants or their LAR(s) will be instructed to contact the HIV care provider and/or the IC/ASA staff as soon as possible to report medically attended event(s), as well as any events that, although not medically attended, are of concern to the participant or LAR. Detailed information about reported unsolicited medically attended AEs will be collected by qualified IC/ASA site personnel, communicated to the HIV care provider, documented in the participant's source documentation, and recorded in the participant's records if related to CABENUVA or leads to discontinuation.<br>• Unsolicited AEs that are not medically attended nor perceived as a concern by participant or their LAR(s) will be collected during the visit with the participants or their LAR(s) and by review of available medical records at the next visit. Any unsolicited CABENUVA-related AEs reported during a visit must be documented in the participant's source documentation, communicated to the HIV care provider, and recorded in the eCRF by the IC/ASA if the event is considered related to CABENUVA or leads to discontinuation. |
| **Events <u>Meeting</u> the AE Definitions** |
| • Any abnormal laboratory test results that are collected (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., electrocardiogram (ECG), radiological scans, vital signs measurements) considered clinically significant and CABENUVA related in the medical and scientific judgment of the HIV care provider and/or IC/ASA physician. |

| **AE Definition** |
|---|
| • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. If the IC/ASA staff are alerted to this, these events should be recorded.<br>• New conditions detected or diagnosed after CABENUVA administration at the IC/ASA that are considered CABENUVA related or lead to the discontinuation of CABENUVA even though it may have been present before the start of the study.<br>• Signs, symptoms, or the clinical sequelae of a suspected CABENUVA interaction.<br>• Signs, symptoms, or the clinical sequelae of a suspected overdose of CABENUVA or a contraindicated or concomitant medication with the potential drug-drug interactions. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.<br>• The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE. "Lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE. |
| **Events <u>NOT</u> Meeting the AE Definition** |
| • Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the HIV care provider to be more severe than expected for the participant's condition.<br>• The disease being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.<br>• Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.<br>• Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).<br>• 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. |

## Annex 3.2 Definition of an SAE

| **An SAE is defined as any serious AE that meets one of the following criteria:** |
|---|
| • **Results in death** |
| • **Is life-threatening**<br>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 that hypothetically might have caused death if it had been more severe. |

**An SAE is defined as any serious AE that meets one of the following criteria:**

- **Requires inpatient hospitalization or prolongation of existing hospitalization**
  - In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) to the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting.
  - Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfils 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) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- **Is a congenital anomaly/birth defect**
- **Other situations:**
  - Possible Hy's Law case: alanine aminotransferase ≥ 3 x upper limit of normal (ULN) AND total bilirubin ≥ 2 x ULN (>35% direct bilirubin) or international normalized ratio (INR) > 1.5 must be reported as SAE
  - Medical or scientific judgment should be exercised by the HIV care providers and/or the IC/ASA physician in deciding whether SAE reporting is appropriate in other situations, such as significant medical events that 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 for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

## Annex 3.3 Definition of a Cardiovascular Event

| **Cardiovascular Events (CV) Definition:** |
|---|
| IC/ASA staff will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs:<br>• Myocardial infarction/unstable angina<br>• Congestive heart failure<br>• Arrhythmias<br>• Valvulopathy<br>• Pulmonary hypertension<br>• Cerebrovascular events/stroke and transient ischemic attack<br>• Peripheral arterial thromboembolism<br>• Deep venous thrombosis/pulmonary embolism<br>• Revascularization |

## Annex 3.4 Recording and Follow-up of AEs and SAEs

| **AE and SAE Recording** |
|---|
| • When a CABENUVA-related AE, AE leading to withdrawal, or any SAE occurs, it is the responsibility of the HIV care provider to review all documentation (e.g., hospital progress notes, laboratory and diagnostics reports) related to the event.<br>• The IC/ASA will then record all relevant AE/SAE (VOCABRIA or EDURANT related AEs, CABENUVA-related AEs, AEs leading to withdrawal, all SAEs) information.<br>• 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.).<br>• It is **not** acceptable for the IC/ASA or HIV care provider to send photocopies of the participant's medical records to the Medical Monitor or the Sponsor in lieu of completion of the eCRF required forms.<br>• There may be instances when copies of medical records for certain cases are requested. 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.<br>• The IC/ASA staff, working with the HIV care provider, will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be |

| **AE and SAE Recording** |
|---|
| documented as the AE/SAE and recorded in the eCRF if it is a VOCABRIA-, EDURANT, or CABENUVA-related AE, an AE leading to withdrawal, or an SAE. |
| **Assessment of Intensity** |
| All AEs and SAEs reported during the study should be evaluated by the IC/ASA physician, working with the HIV care provider, and if an AE/SAE is determined as a CABENUVA related AE, leads to discontinuation, or is an SAE, it will be graded in the eCRF.<br><br>The IC/ASA staff will capture the SAE causality in the participant's source notes in a timely manner, and the IC/ASA staff or an appropriately delegated team member will enter the causality into the eCRF. CRAs will monitor the participant source documentation to confirm that SAE causality is being documented in a timely manner.<br><br>• Mild: An event that is easily tolerated by the participant, causes minimal discomfort, and does not interfere with everyday activities.<br><br>• Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities.<br><br>• 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. |
| **Assessment of Causality** |
| • The IC/ASA physician, working with the HIV care provider, is obligated to assess the relationship between CABENUVA and each occurrence of each AE and SAE reported. Prior to a participant enrolling in the study, if an AE or SAE should be reported and if it is related to oral VOCABRIA or EDURANT, it should be documented in the eCRF.<br><br>• A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than that a relationship cannot be ruled out.<br><br>• The IC/ASA physician, working with the HIV care provider, will use clinical judgment to determine the relationship.<br><br>• Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to CABENUVA administration, will be considered and investigated.<br><br>• The HIV care provider and/or IC/ASA physician will also consult the USPIs for CABENUVA, VOCABRIA, and EDURANT in their assessment<br><br>• For each AE and SAE, the IC/ASA physician **must** document in the medical notes that they have reviewed the AE/SAE and have provided an assessment of causality and have retrieved all required source documentation as available. |

| **AE and SAE Recording** |
|---|
| • There may be situations in which an SAE has occurred, and the IC/ASA has minimal information to include in the initial report to ViiV Healthcare (VHC). However, **it is very important that the IC/ASA physician, working with the HIV care provider, always makes an assessment of causality for every event before the initial transmission of the SAE data to VHC.**<br>• The HIV care provider may change their opinion of causality in light of follow-up information, and the IC/ASA should send an SAE follow-up report with the updated causality assessment.<br>• The causality assessment is one of the criteria used when determining regulatory reporting requirements. |
| **Follow-up of AE and SAE** |
| • The HIV care provider will medically and clinically manage the follow-up of each AE and SAE. If this follow-up information is shared with the IC/ASA, this should be recorded. Information regarding the causality of the AE or SAE can be updated based on these investigations by the HIV care provider.<br>• If a participant dies during participation in the study, the IC/ASA will provide VHC with a copy of any postmortem findings including histopathology, if this is available to them.<br>• New or updated information will be recorded.<br>• The IC/ASA will submit any updated SAE data to VHC within 24 hours of receipt of the information. |

## Annex 3.5 Reporting of SAEs to ViiV/GSK

| **SAE Reporting to ViiV/GSK via Electronic Data Collection Tool** |
|---|
| • The primary mechanism for reporting SAEs to PPD and to VHC will be the electronic data collection tool.<br>• If the electronic system is unavailable, then the IC/ASA will use the paper SAE data collection tool to **report the event within 24 hours.**<br>• The IC/ASA will enter the SAE data into the electronic system as soon as it becomes available.<br>• The IC/ASA physician or a medically qualified sub-physician, working with the HIV care provider, must show evidence within the source documents of the review and verification of the relationship of each SAE to CABENUVA, VOCABRIA, or EDURANT.<br>• After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. |

| **SAE Reporting to ViiV/GSK via Electronic Data Collection Tool** |
|---|
| • If an IC/ASA 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 offline, then the IC/ASA can report this information on a paper SAE form (see table below) or to the Medical Monitor by telephone.<br>• Contacts for SAE reporting can be found in SRM. |
| **SAE Reporting to ViiV/GSK via Paper Data Collection Tool** |
| • The IC/ASA staff will complete, scan, and upload the applicable AE/SAE or other safety event CRF to SharePoint and will then email Evidera/PPD and wilsafety@ppd.com to inform them that an AE/SAE or other safety event has occurred and that the applicable form has been uploaded to the specific SharePoint folder. AE or SAE information must include the relationship to CABENUVA, and the IC/ASA will contact the participant's HIV care provider urgently to discuss this assessment.<br>• Evidera/PPD project managers (PMs) and the PPD Pharmacovigilance (PVG) team will receive automatic notifications when CRFs are uploaded and will review all AE/SAE and other safety event CRFs within one business day.<br>• Evidera/PPD PMs will contact the PPD PVG team to ensure that they have received the notification.<br>• The PPD PVG team will inform the GSK/ViiV medical monitor(s), safety team, and applicable team members of the event via email and will provide the necessary documentation within 24 hours of awareness. The GSK/ViiV medical monitors will be given access to the SharePoint site. The safety documents will be viewable through SharePoint and will not need to be downloaded. |

# Annex 4: Contact Information for Reporting of AEs and SAEs and Pregnancies

**Study contacts**

Available 24/24 hours and 7/7 days

**PPD Clinical Safety and Pharmacovigilance (PPD PVG)**

SAE Hotline for North America

Phone 1-800-201-8725

Fax: 1-888-488-9697

Email: WIL Safety (SM) wilsafety@ppd.com

Additional contacts can be found in the SRM.

# Annex 5: Protocol Amendments

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

## Annex 5.1 Protocol Amendment 05 (14 November 2022

The primary and only purpose of this amendment is to update the Sponsor address on the Title Page

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Title Page | Updated Sponsor Address | Location Moved |
| Annex 5.1 | Moved the Table of Changes from Protocol Amendment 04 to Annex 5.1 | Moved according to the Protocol template |

## Annex 5.2 Protocol Amendment 04 (6 October 2022)

The primary and only purpose of this amendment is to update the Sponsor address on the Title Page

The primary purpose of this amendment is to support the additional Infusion Centers

The primary purpose of this amendment is to support the additional Infusion Centers being added to the study to broaden the geographical area within the US and to scale-up the implementation blueprint. The additional ICs will be initiated between approximately November 2022 – 1st Quarter 2023. Other changes include deletion of Exclusion Criteria 4 in Section 4.2.1 to allow participants into the study regardless of how many prior (pre-study) injections of CABENUVA they have received at the IC site and to remove the recruitment period of 12 months as the recruitment period for some sites may be longer than or less than 12 months.

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Global Change to Sections listed below | Added other clinical staff to also be allowed to complete questionnaires and interviews, represented as HIV Care Provider/clinical staff | Some HIV care providers manage their patients in conjunction with other clinic staff members who, work with ICs and may be better to complete some study assessments |
| • Global change to Section 1 Abstract, Section 2.1 Background, Section 2.2 Rationale, Section 3. Objectives and Endpoints, Section 4.1. Study Design, Section 4.3.2 HIV Care Providers, Section 5.1.2 Implementation Assessments, Section 5.1.3 Timepoint Definitions, Section 5.1.4 Primary Endpoint, Section 6. Statistical Considerations, | | |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Section 6.1 Study Size, Section 6.2 Essential Analysis, Section 6.3 Secondary Analysis, Annex 1 Schedule of Activities | | |
| Global Change to Sections listed below | Expert Panel expected completion is expected in late 2022 | Clarification for the additional ICs, how the optimized blueprint and POT will be revised outside the Expert Panel |
| • Global change to Section 1 Abstract; Section 2.2 Rationale, Section 4.1 Study Design, Section 4.3.2 HIV Care Providers, Section 5.1.1 Expert Panel, Section 5.1.5 Blueprint and Plan of Treatment | | |
| Through-out | Minor editorial and document formatting revisions | Minor and therefore have not been summarized |
| Section 1 Abstract | Moved the Study Design section up within the abstract<br>Added text regarding the additional ICs<br>Removed all text regarding a 12-month recruitment period | Revised order for readability in light of the changes made<br>Increased the approximate number of IC sites to include the additional ICs<br>The recruitment period for some sites may be longer than or less than 12 months |
| Section 4.1 Study Design | Modified schema | In the Participants design removed one set of the questionnaire/ interview symbols for clarity<br>Added footnote to explain how the blueprint will be revised outside of the Expert Panel |
| Section 4.2 Study Population | Removed all text regarding a 12-month recruitment period | The recruitment period for some sites may be longer than or less than 12 months |
| Section 4.2.1.2 Exclusion Criteria | Removed Exclusion Criteria 4 | To allow participants into the study regardless of how many prior (pre-study) injections of CABENUVA they have received at the IC |
| Section 4.3.2 HIV Care Providers | Revision to number of IC sites | Increased the approximate number of IC sites to include the additional ICs |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Section 4.3.3 Infusion Center Staff | Minor text changes | Clarification of text |
| Section 5.1.1 Expert Panel | Added text regarding the additional ICs entering the study | New information |
| Section 5.1.2 Implementation Assessments<br>Section 6 Statistical Considerations | Added baseline analysis | To gain insights on the initial assessment of implementation science data on primary and key secondary objectives |
| Section 6.1 Study Size | Revision to number of IC sites<br><br>Removed all text regarding a 12-month recruitment period | Increased the approximate number of IC sites to include the additional ICs<br>The recruitment period for some sites may be longer than or less than 12 months |
| Annex 1 Schedule of Activities | Corrected several errors in text and in the Month of assessment | Clarifications |
| Annex 5 Protocol Amendments | Moved Protocol Amendment 3 Table of Changes to Annex 5 | |

## Annex 5.3 Protocol Amendment 03 (20July2022)

### Overall Rationale for Amendment 3

The primary purposes of this amendment are to update Inclusion Criteria 2 in Section 4.2.1 so that it matches the prescribing information in the CABENUVA USPI and to clarify the Schedule of Activities for those participants whose last study injections of CABENUVA at the Infusion Center falls on Month 7.

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Section 1 Abstract; Global change | Change "first study administration of CABENUVA at the Infusion Center (IC)" to "first study related administration of CABENUVA at the IC" | Revised to align with the new Exclusion Criteria 4, excluding participants who have received more than 3 injections of CABENUVA at the IC |
| Section 4.1 Study Design; Global Change | Remove the location of the ICs | Removed as the study may recruit additional sites |
| Section 4.1 Study Design | Revision for clarify | Added timeline for participants entering the study already on every 2-month dosing |
| Section 4.2.1.1 Inclusion Criteria | Revised Inclusion Criteria 2 | Revised Inclusion Criteria to align with the CABENUBA USPI |
| Section 4.2.1.2 Exclusion Criteria | Added new exclusion for those that have received more than 3 non-study CABENUVA injections at an IC | Ensure that all participants have a similar starting point when answering questionnaires at Baseline. |
| Section 4.3.1 Participants with HIV-1 | Revision of text | Modified the first paragraph and removed the next 2 paragraphs as they repeated the text in the new paragraph and in Inclusion Criteria 2 |
| Section 4.3.1 Participants with HIV-1; global change | Removed strikethrough text:<br>A participant is considered to have completed the study if he/she has finished all Month 8 assessments ~~and receive their last injections of CABENUVA at the IC~~ | Clarification, as study participants can continue to receive CABENUVA at the IC after the Month 8 assessments |
| Section 4.3.2 HIV Care Providers and Section 6.1 Study Size | Revision to number of IC sites | Increased the approximate number of ICs as the study may increase the number of IC site |
| Section 4.3.2 HIV Care Providers | Removed strikethrough text:<br>Once insurance verification is approved and reviewed with the patient, the IC will inform the HIV care provider | Revised to ensure compliance with the CABENUVA USPI |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| | and the patient will initiate treatment ~~with the oral lead-in of VOCABRIA + EDURANT~~ per the CABENUVA USPI | |
| Section 4.3.3 Infusion Center Staff | Removed strikethrough text: ~~Completed questionnaires will not be collected in the eCRF~~ | Removed as study is moving to new system for collecting case report forms, and this will include IC staff questionnaires. |
| Section 5.1 Formative Evaluation Procedures | Text revised | Repetitious text was deleted |
| Section 5.1.1 Expert Panel | Text revised | Changed maintenance injections to continuation injections per the USPI |
| Section 5.1.2 Implement Assessments | Revised text to align with changes in Section 6 | Wording on when an interim analysis may be conducted was revised for flexibility |
| Section 5.1.3 Timepoint Definitions for Completion of the Questionnaires and Interviews | Deleted the Month 6 assessment | IC questionnaire Month 6 questionnaire assessment was removed as this was revised in Protocol Amendment 2 |
| Section 6 Statistical Considerations | Revised text | Flexibility was added on the number and when an interim analysis may be conducted |
| Section 6.2 Essential Analysis | Revised text | Additional sub-groups were included to align with the revised Inclusion and Exclusion criteria, initiation methods and the number of injections received prior to enrolment |
| Section 8 CABENUVA and Concomitant Therapy | Revised text<br><br>Deleted sentence | Text was clarified to ensure that all participants were receiving CABENUVA per the USPI<br>Sentence removed regarding the collection points for questionnaires |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Annex 1 Schedule of Activities | Update to include information on participants whose last study injections fall at Month 7 and not at Month 8<br><br>Deleted specific instructions for changing injection schedule in a participant | To avoid having participants whose last injections are at Month 7 return to the IC at Month 8, the end of study assessments (Month 8) will be completed at Month 7. Questionnaires will be completed at Month 8<br>Text revised to ensure the HIV care provider and IC Staff follow the CABENUVA USPI |
| Through-out | Minor editorial and document formatting revisions | Minor and therefore have not been summarized |

## Annex 5.4 Protocol Amendment 02 (16 March 2022)

### Overall Rationale for Amendment 02

The primary purposes of this amendment were to add changes so that the protocol reflects the most recent USPI. The main change was to add in every 2-month dosing. Additionally, the objectives and endpoints for the study were reassessed and modified.

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Through-out: | Removed the 2021year of the CABENUVA USPI<br><br>Added text to reflect the addition of every 2-month dosing regimen | Year removed to ensure protocol reflects most current USPI.<br><br>Every 2-month dosing was recently approved by the FDA; therefore, the protocol will allow enrolment of participants on monthly or every 2 month dosing. |
| Section 3 Objectives and Endpoints | CCI [redacted]<br><br>Primary, secondary and tertiary were modified<br>FIM changed from Month 12 to Month 8 | The real-world strategies for CABENUVA uptake have shifted mid-study which is causing a shift in study approach to recruitment. This will be challenging to track and likely be a confounding variable for these endpoints. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| | **A**ll 12-month endpoints changed to 8 months. For participants, all assessments changed to reflect that the data will be collected at 1,3 and 8 months. For IC staff; 1, 3, 8 and for HIV Care providers, 1, 4 and 8. No changes to expert panel assessments. | |
| Section 4.1 Study Design | Schema and study length updated | Updated version includes participants on every 2-Month dosing regimen. Additionally, updated the timing of assessments and the length of time each participant is in the study was updated to reflect the reduction in timeline from 12 months to 8 months. |
| Section 4.2.1.2 Study Population | Sentence changes to read, "Participants may be excluded from the study, in consultation with the HIV care provider, based on information from the most current Prescribing Information | Sentence restructured for clarity. |
| Section 4.3.1 Participants with HIV-1 | Added text to include every 2-month dosing and added a paragraph around switching to another dosing regimen (monthly or every 2-monthly) | Updates to include every 2-Month dosing. |
| Section 5.1. Formative Evaluation Process | Added changes to reflect every 2-month dosing regimen and revised some sentences for clarification. | Updates to include every 2-Month dosing. |
| Section 5.1.1 Expert Panel | Sentences restructured for clarity. | Clarification |
| Section 5.1.2 Table 1; | FIM Changed from Month 12 to Month 8 throughout the document. | CABENUVA uptake in the real world has changed since the initial protocol was developed. The |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| | All 12-month endpoints changed to 8 months throughout the document.<br>For participants throughout the document, all assessments changed to reflect that the data will be collected at 1,3 and 8 months;<br>For IC staff; throughout the document, Month 1, 3, 8 and for HIV Care providers, 1, 4 and 8. No change to expert panel assessments.<br>Table 1 timepoints were updated. M6 changed to M4. M12 changed to M8.<br>Preferences, advantages, disadvantages, acceptability of receiving and referring patients updated to include MM1, MM4, MM8 | duration of the study was changed to limit the recruitment period to 12 months and the treatment period to 8 months. Monthly assessments have been modified to capture timepoints in the study that align with these shortened time periods.<br>The real-world strategies for CABENUVA uptake have shifted mid-study which is causing a shift in study approach to recruitment. This will be challenging to track and likely be a confounding variable for these endpoints |
| Section 5.1.4 Primary Endpoint | Per the revision in Section 3, CCI [redacted] | Alignment with Section 3 |
| Section 6.1 Sample Size | Update to text, figures and tables to reflect a potential lower sample size | CABENUVA uptake is not as fast as anticipated, which has resulted in slower than anticipated recruitment |
| Section 6.3 Secondary Analysis | Per the revision in Section 3, CCI [redacted] to Section 6.4 | Alignment with Section 3 |
| Section 8.1 Missed CABENUVA Injections | Added text to reflect every 2-month dosing regimen | Updated to include every 2-Month dosing |
| Section 9.4 Lost to Follow-up | Added text to reflect every 2-month dosing regimen | Updated to include every 2-Month dosing |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Annex 1 Schedule of Activities | Added additional text to reflect every 2-month regimen and added Questionnaire completion windows for each dosing regimen | Updated to include every 2-Month dosing |
| Annex 5 | Protocol Amendment 1 revisions table moved | Compliance with current protocol template |
| Through-out | Minor editorial and document formatting revisions | Minor and therefore have not been summarized |

## Annex 5.5 Protocol Amendment 01 (19 November 2021)

### Overall Rationale for Amendment 1

The primary purposes of this amendment were to add additional secondary endpoints and revising safety Section 10 for ease of reading and to enhance the understanding of what adverse events (AEs) and serious adverse events (SAEs) are required to be recorded in the electronic case report form (eCRF) and what safety events are required to be reported to meet regulatory reporting requirements.

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Section 1 Abstract | Removed the words "with HIV" from participants<br>New secondary objectives added<br>New text added to define the other quantitative questionnaires<br>New text added to include sub-group analysis including participants, human immunodeficiency virus (HIV) care providers and infusion center (IC) Staff | Consistency of the use of "participant" thought-out the protocol<br>Change was made in the abstract to reflect the changes in Section 3 Objectives and Endpoints<br>Clarification of other questionnaires in addition to the Feasibility of Intervention Measure (FIM) and Acceptability of Intervention Measure (AIM)<br>New text and type of analysis added |
| Section 2.1 Background | Defined HCPs as healthcare providers | Clarification |
| Section 2.3 Benefit/Risk Assessment | Clarification that the United States Prescribing Information (USPI) contains both the expected benefits and the risks of CABENUVA | New section added |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Section 3 Objectives and Endpoints | Additional secondary objectives and endpoints were added. For clarity with the additional secondary objectives, most objectives and endpoints were re-written and combined.<br>The tertiary objective "To evaluate feasibility of CABENUVA administration at infusion centers from participants with HIV-1" was moved to a secondary objective.<br>The tertiary objective "To further evaluate trends in feasibility of CABENUVA administration at infusion centers (via score from HIV care providers, participants, and IC staff)" was incorporated into a secondary endpoint CCI [redacted]<br>The tertiary endpoint for semi-structured interviews (SSIs) was moved and modified to a secondary endpoint. CCI [redacted] | Objectives and endpoints added to reflect data which will impact feasibility and acceptability. Clarifying text was added regarding the other quantitative questionnaires and the qualitative interview.<br>Removed the mention of injection site reaction (ISRs) and post-injection reactions as those are already being captured under CABENUVA related events |
| Section 4.1 Study Design | Revised Schema to incorporate potential interviews with IC staff at Month 2 and added 2 footnotes<br>The number of participants changed from 106 to 120. | Updated based on change in this amendment and clarifications provided within the footnotes<br>Correction on the sample size |
| Section 4.2 Study Population | Text removed: This number will be given sequentially in chronological order of participant presentation according to a numeric roster provided by GlaxoSmithKline (GSK). | Text removed as there is no randomization in this study |
| Section 4.2.1.1 Inclusion Criteria | Clarification that "within one month" is defined as 28 days | Clarification to align with the USPI |
| Section 4.2.1.2 Exclusion Criteria | Added 3 exclusion criteria based on information from the CABENUVA USPI: Contraindications, new health condition/prohibited medications and Other reasons | Added to aid the IC staff in making exclusionary decisions |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Section 4.3.2 HIV Care Providers | Change in number of IC sites from 23 to 24<br>Text added to include participants who are already receiving CABENUVA<br>Additional clarification that the HIV care provider will manage all adverse events (AEs) and will be requested to make AE/serious adverse event (SAE) causality assessments<br>Text added through-out this section regarding the oral lead-in and for missed injections during the study | An additional IC location was added<br>Clarification of study populations<br>Clarifications on the expected HIV care provider oversight of AE/SAEs<br>Clarifications |
| Section 4.3.3 Infusion Center Staff | Updated text to align with changes made in Section 10<br>Removed 2 bullets on serious post injection reactions and ISRs as these are captured under AEs related to CABENUVA<br>Added a reference to Section 10.3.10 Reporting of AEs and Timelines | Revised to align with the updated information in Section 10<br>Removal of redundant text<br>Removed specific references to Section 10 to reduce potential inconsistencies between sections<br>Alignment with the revised safety Section 10 |
| Section 5.1.2 Implementation Assessments | Implementation Assessments table updated to reflect changes made in Objectives and Endpoints. | Alignment with Section 3 |
| Section 5.1.3 Timepoint Definitions for Completion of Questionnaires and Interviews | Added text to define when the potential Month 2 interviews would be conducted with IC staff | Added text to align with the potential Month 2 interviews |
| Section 5.1.5 Blueprint and Plan of Treatment | Added text to specify medical management of AEs and SAEs | Clarification |
| Section 5.1.6 Scale-Up | Added text that the blueprint will be used to help other alternate administration facilities set up similar models of care and service delivery. | Clarification of the use for the study blueprint |
| Section 6 Statistical Considerations | Text modified to state that the statistical analysis plan will be finalized prior to database release (DBR) and not prior to FPFV<br>Text added to clarify the time of interim analysis (Month 3 and/or Month 6) and the number of | Clarification on when the statistical analysis plan will be finalized<br>Clarification of planned interim analysis and a reduction from 50 – 60 participants to at least 25 participants |

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| | participants (~25) at which these will occur.<br>Text added to explain the possibility of a small number of interviews with IC staff at Month 2<br>Added text about interview procedures and how the interview analysis will take place | Additional interviews added to gain an understanding of what is occurring at ICs during early implementation.<br><br>Clarification on interview process |
| Section 6.1 Study Size | Updated the number of ICs from 23 to 24<br>Text added to clarify the number of HIV care providers, IC staff and participants completing interviews | Update<br><br>Clarification |
| Section 6.2 Essential analysis | Due to moving some of the tertiary/other endpoints regarding FIM to secondary, text was updated to reflect this in several places.<br>New text was added on the evaluation of the contextual factors on the variability of responses | Updated text<br><br>New text |
| Section 6.3 Secondary Analysis | Added the additional secondary outcomes<br>Added how the qualitative interview data will be summarized and details of this analysis will be included within a separate analysis plan | New text |
| Section 6.4 Other/Tertiary Endpoints | CCI [redacted] | Other/Tertiary endpoints updated to reflect changes made in Objectives and Endpoints<br><br>Clarification |
| Section 7.1 Ethical Approval and Participant Consent | Subject changed to Participant in the header | Update |
| Section 7.4 Quality Control / Study Monitoring | The IC Investigator has been changed to IC staff. | Updated for clarity |
| Section 8.2 Treatment of an Overdose | Added the Medical Monitor must be contacted, and that signs and symptoms related to the overdose be recorded in the electronic case report form (eCRF) | Clarification |
| Section 10 Management and Reporting of Adverse | Section 10 was revised, edited and sections were added or moved to | Revisions to the safety section: New and revised sections added for additional |

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| Events and Safety Assessments | improve the information flow throughout this section<br>Added within the Section Header text that this section also has information for safety assessments and reporting requirements<br>Added text that the definitions of AEs, SAEs and cardiovascular (CV) events were added to Annex 3 AE and SAE Definitions<br>Added text that the grading of all AEs, SAEs and lab abnormalities should be graded by Division of acquired immune deficiency syndrome (DAIDS) | clarifications and to ensure understanding of the information<br>Clarification<br>New Annex<br>New grading information included |
| Original Protocol Section 10 Management and Reporting of Adverse Events to new Section 10.3.4 Follow-up of AEs and SAEs | Text from original protocol Section 10 was moved to new Section 10.3.4 to ensure the follow-up of AEs and SAEs is clear | Revisions to the safety sections |
| Original Protocol Section 10.1 Safety Assessments and Section 10.2.3 Reporting of AEs and timelines and moved to new Section 10.3.2 Time Period and Frequency for Collecting AE and SAE Information | Heading name and number revised<br>Added Pharmaceutical Product Development Inc (PPD) Pharmacovigilance (PVG) to collect all SAEs<br>Text added for the HIV care provider to provide causality for safety events<br>Clarified reporting AE/SAEs after study conclusions | Revisions to the safety sections<br>Clarified where all SAEs will be reported<br>Clarification of HIV care provider responsibilities<br>Clarification of safety reporting |
| Original Protocol Section 10.1.1 moved to new Section 10.1 Clinical safety laboratory assessments | Heading number change<br>New text added regarding causality assessment for lab abnormalities<br>Added text to clarify how abnormal labs should be recorded in the eCRF. | Revisions to safety section and Clarifications<br>New text added |
| Original Protocol Section 10.1.2 moved to new Section 10.2 Liver Chemistry Monitoring | Heading number change<br>Added text for the completion of liver event eCRF pages<br>Added a reference to Annex 4 for PPD safety contact information | Revisions to safety section<br>New text added<br>New Annex added |
| Original Protocol Section 10.2 moved to new Section 10.3 Adverse Events | Deleted the definition of AEs as now included within new Annex 3<br>Text from original Protocol Section 10.2.1 Definition of Adverse | Revisions to safety section |

| Section # and Name | Description of Change | Brief Rationale |
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| (AEs), Pregnancy Exposure and Incident Reports | Events was added and revised in new Section 10.3 (collection and storage of AEs in source documentation and detecting, documenting and reporting events)<br>Removed text on causality and moved and revised this text in new Section 10.3.7 Causality Assessments<br>Added a reference to Annex 4 for PPD safety contact information | New Annex 4 reference |
| Original Protocol Section 10.2.1 Definition of Adverse Events moved to Section 10.3 Adverse Events (AEs), Pregnancy Exposure and Incident Reports, Section 10.3.6 Adverse Event Follow-up with the HIV Care Provider and Annex 3 AE and SAE Definitions | Text from original Protocol Section 10.2.1 added and revised into new Section 10.3 (collection and storage of safety events in source documentation and detecting, documenting and reporting events)<br>Sentence was moved to Section 10.3.6 to ensure the appropriate follow-up by the IC staff to the HIV care providers<br>Removed the text about defining AEs as this was moved and revised in Annex 3 | Revisions to safety sections<br>New Annex 3 added |
| Original Protocol Section 10.2.2 Adverse Events to be Documented in this Study moved to new Section 10.3.1 Specific Adverse Events to be Documented in this study | Heading number change and text revised to include the word "Specific"<br>Added all CV events and COVID-19 related AEs are to be documented<br>Added a paragraph regarding non serious AEs that are considered not related to CABENUVA or do not lead to withdrawal, these AEs should be documented and stored in the source documentation but will not be documented in the eCRF, as this information has been extensively collected in treatment clinical trials, no further information is needed to characterize these events.<br>Deleted paragraph regarding AE/SAE follow-up as duplicative with other safety sections | Revisions to safety sections<br>New text added<br>Revisions to safety sections |
| Original Protocol Section 10.2.2.1 Adverse Drug | Section deleted and the definition of adverse drug reactions (ADRs) was added to Section 10.3.1 | Revisions to safety sections |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Reaction moved to new Section 10.3.1 Specific Adverse Events to be Documented in this Study | | |
| Original Protocol Section 10.2.2.2 moved to Section 10.3.8 Serious Post-Injection Reactions | Heading number change<br>Added text for serious post-injection reactions reporting requirement to PPD PVG | Revisions to the safety sections<br>Clarification of reporting requirements |
| Original Protocol Section 10.2.2.3 moved to Section 10.3.9 Injection site reactions | Heading number change<br>Text added for safety reporting requirements | Revisions to the safety sections<br>Clarification that all ISRs should be recorded in the eCRF, however only serious ISRs or those leading to withdrawal need to be reported to PPD PVG |
| Original Protocol Section 10.2.2.4 Serious Adverse Events moved to Section 10.3.5 Regulatory Reporting Requirements for SAEs and Annex 3 AE and SAE definitions | New Section added and contains text from original Protocol 10.2.2.4<br>Removed the text about defining SAEs as this was moved and revised in Annex 3 | Revisions to safety sections<br><br>New Annex 3 added |
| Original Protocol Section 10.2.3 Reporting of AEs and timelines moved to Section 10.3.2 Time Period and Frequency for Collecting AE and SAE Information and Section 10.3.10 Reporting of AEs and Timelines | Heading number and name change<br>One sentence was moved to Section 10.3.2 (obligations of the IC staff to collect and report AEs)<br>New text and a table were added to Section 10.3.10 regarding the specific safety events and the timelines for reporting these events to PPD PVG | Revisions to the safety sections<br><br>New text to clarify reporting requirements |
| Original Protocol Section 10.2.4 Pregnancy moved to Section 10.3.11 Pregnancy | Heading number change<br>Added text that participants of child-bearing potential (POCBP) should be asked their pregnancy status at each visit and date of last menses period (LMP)<br>Removed text regarding the pregnancy specific addendum | Revisions to the Safety sections<br>Clarification and added text to the schedule of activities (SOA) to further support<br><br>The protocol is being conducted in accordance to the currently approved USPI, which does not contraindicate or have a warning and precaution against the use of CABENUVA during pregnancy. It is a HIV care providers |

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| | | decision, after considering whether the expected benefit justifies the potential risk to the fetus to prescribe or have a patient remain on CABENUVA while pregnant. |
| | Added text that pregnancies will be followed and will include the reporting of any post-study SAEs | Clarification of reporting requirements |
| | Deleted text that the Sponsor needs to provide written approval | Not required in this study |
| Original Protocol Section 10.2.5 Death Events moved to new Section 10.3.12 Cardiovascular and Death Events | Heading name and number change | Revisions to the Safety sections |
| | Text added that all deaths will be recorded and reported as a SAE | Clarification |
| | Added new text about cardiovascular events and the recording and reporting requirements | New text added |
| | Added reference to Annex 3 AE and SAE Definitions | New Annex added |
| Section 10.3.3 Methods of Detecting AEs and SAEs | New Section on how to reduce bias with the collection of AEs and SAEs | Revisions to the safety sections |
| Section 10.3.7 Causality Assessments | New Section added to clarify the requirement for the relatedness of any safety event to CABENUVA | Revisions to the safety sections |
| Section 10.3.13 Medical Devise Deficiency | New Section added for the Food and Drug Administration (FDA) regulatory reporting requirements for a medical device incident | Added the FDA spontaneous incident reporting requirement |
| Section 11 References | New reference added | Added reference for the DAIDS grading scale that was added to Section 10 Management and Reporting of Adverse Events and Safety Assessments |
| Annex 1 Schedule of Activities | Added a check for pregnancy status at each monthly visit | New text added |
| | Additional labs at the Month 12 visit have been added | Updated |
| | Added that fasting is not required unless otherwise required for a specific lab test | Clarification |
| | If the early discontinuation (ED) visit is not at a scheduled study visit, participants would not receive CABENUVA injections. If the ED visit is at a scheduled study visit, injections would be captured there | Clarification by removing the X for injections at the ED visit |

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| | AEs and SAEs comments: added links to the relevant Safety sections<br>Removed the row for the collection of ISRs or post-injection reactions as these are included within AEs or SAEs.<br>Added the potential Month 2 IC staff interviews and defined the timepoint this could be completed | Revised to ensure consistency in information<br>Deleted row for clarification on the collection of AEs related to CABENUVA<br>Month 2 potential interviews added |
| Annex 2. List of Stand-Alone documents | Added Study Blueprint<br>Study Specific Pharmacovigilance Plan (sPVP) is removed. | Blueprint is shared with the IC '<br>sPVP Document was no longer required since this is an interventional study |
| Annex 3 AE and SAE Definitions | New Annex added | Moved the AE and SAE definitions from the SRM into the protocol and added in the CV definitions |
| Annex 4: Contact Information for Reporting of AEs and SAEs and Pregnancies | New Annex Added | Added PPD PVG and Safety contact information |
| Through-out | Minor editorial and document formatting revisions | Minor and therefore have not been summarized |

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| Reason for signing: Approved | Name: PPD<br>Role: Approver<br>Date of signature: 29-Mar-2023 08:39:17 GMT+0000 |

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