SCHARP
Statistical Center for HIV/AIDS Research and Prevention

STATISTICAL ANALYSIS PLAN

Safety, Tolerability and Acceptability of Long-Acting Cabotegravir (CAB LA) for the Prevention of HIV among Adolescent Females – A Sub-study of HPTN 084

HPTN 084-01

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LIST OF ABBREVIATIONS AND ACRONYMS

Term/Abbreviation	Definition
ADaM	Analysis Dataset Model
AEs	Adverse Events
AESI	AEs of Special Interest
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
CAB LA	Long-Acting Cabotegravir
CABG	Coronary Artery Bypass Grafting
CASI	Computer Assisted Self Interview
CBC	Complete Blood Count
CMC	Clinical Management Committee
CPK	Creatine Phosphokinase
CRF	Case Report Forms
CV	Coefficient of Variation
DAIDS	Division of AIDS
EC	Ethics Committee
FDA	(US) Food and Drug Administration
GEE	Generalized Estimating Equations
HBsAg	Hepatitis B Virus Surface Antigen
HBV	Hepatitis B Virus
HDL	HighDensity Lipoprotein
IM	Intramuscular
IoR	Investigator of Record
IRB	Institutional Review Board
ISR	Injection Site Reaction
IUD	Intrauterine Device
IUS	Intrauterine System
LDL	Low Density Lipoprotein
MO	Medical Officer
NIAID	National Institute of Allergy and Infectious Diseases
NICHD	National Institute of Child Health and Human Development
OHRP	Office for Human Research Protections
OLE	Open Label Extension
PTCA	Percutaneous Transluminal Coronary Angioplasty

SD	Standard Deviation
SMC	Safety Monitoring Committee
SPDSMP	Study Progress and Data Safety Monitoring Plan
STI	Sexually Transmitted Infection
Tbili	Total Bilirubin
ULN	Upper Limit of Normal
US	United States
WBC	White Blood Cell
WHO	World Health Organization
βHCG	Beta Human Chorionic Gonadotropin

2. INTRODUCTION

This SAP is intended to describe the final primary and secondary analyses upon completion of HPTN084-01. Sections of the SCHARP SAP template had to be adapted here to reflect the distinct single-arm outcomes, as opposed to the more common multi-arm studies that the template was designed for. Key variable definitions are included in appendix B.

2.1 General Design Considerations

HPTN084-01 is a phase IIB single arm trial designed to establish the minimum safety, tolerability and acceptability data needed to support the use of cabotegravir long-acting injection (CAB LA) in an adolescent population, potentially transforming the field of HIV prevention for young people. The study target population is sexually-active, healthy female adolescents aged below 18 years. The study target is to enroll more than 50 participants with at least 50 participants receiving at least one injection. Participant recruitment will take approximately 12 months.

Study participation includes:

Step 1: a 5-week oral CAB 30mg QD safety lead-in followed by

Step 2: a series of 5 intramuscular (IM) injections of 3 mL (600 mg) cabotegravir administered at 8-week intervals after a 4-week loading dose (injections at weeks 5, 9, 17, 25 & 33). Adherence support strategies (e.g., counseling, reminders, pill cases) will be included to support pill-taking during the first five weeks and to support retention during the injectable phase. A safety visit will follow each injection to ascertain pharmacokinetic-peak safety data, including injection site reactions.

Step 3: A blood draw visit, the +8 Week Visit, will follow the last injection to monitor CAB drug levels, with additional blood collection at the +24, +36, and +48 Week Visits. All participants who have received at least one injection will be followed for 48 weeks after their last injection. Waning levels of cabotegravir (the PK tail) will be covered with locally sourced oral Tenofovir/emtricitabine (Trade name: TDF/FTC, Truvada®) for daily use for 48 weeks. Both clinical and laboratory evaluations will occur during follow-up phase visits, and behavioral and acceptability data will be collected via computer-assisted self-interview (CASI). Total participant commitment for the entire study is up to 87 weeks, or approximately 1.5 years

Alternative to Step 3-Open Label Extension: Participants may be offered the opportunity to join an open label extension (OLE) CAB study at any time following completion of Step 2, if such a study is being implemented in their area at the time.

We anticipate recruitment for the study will take approximately 12 months. Participants who discontinue study product during Step 2 for any reason other than HIV infection or study product related AE occurrence will be transitioned to open label TDF/FTC for 48 weeks.

There are in total three study sites: Ward 21 CRS, Johannesburg, South Africa; Spilhaus CRS, Harare, Zimbabwe; MU-JHU Research Collaboration (MUJHU CARE LTD) CRS, Kampala, Uganda.

Study is sponsored by Division of AIDS (DAIDS), United States (US) National Institute of Allergy and Infectious Diseases (NIAID), Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), US National Institutes of Health (NIH), IND number is 122,744. Protocol Chair is Sybil Hosek, PhD and Protocol Co-chair is Lynda Stranix-Chibanda, MBChB, MMED.

2.2 Study Objectives and Endpoints

Primary objectives:

- To evaluate the safety, tolerability and acceptability of CAB LA in healthy, HIV-uninfected female adolescents aged below 18 years

Secondary objectives:

- To examine adherence to and timeliness of injections over time among adolescent participants provided CAB LA and information regarding its safety and efficacy
- To examine patterns of sexual risk behavior over time among adolescent participants provided CAB LA and information regarding its safety and efficacy
- To evaluate the safety of oral CAB during step 1 (oral phase) as well as all study products during the aggregate oral+injectable period for all enrolled participants
- To characterize the pharmacokinetics of CAB LA
- Additional exploratory analyses will be done with the laboratory and clinical data, including resistance mutations

To achieve the primary and secondary objective, the planned primary and secondary endpoints are:

Primary endpoints:

1. Safety endpoint: Proportion of participants experiencing any Grade 2 or higher clinical adverse events (AEs) and laboratory abnormalities from adverse event reporting among participants who receive at least one injection of CAB LA. Laboratory abnormalities include grade 2 or above on tests include (CRF: Chemistry Panel, Fasting Lipid Test Results, Urinalysis, Hematology):
    a. Renal function: Creatinine, Creatinine clearance
    b. Hematology: Hemoglobin, Platelets, WBC, Neutrophils, Lymphocytes
    c. Liver function: Alkaline phosphatase, AST, ALT, Total bilirubin
    d. Electrolytes: Phosphorus, Calcium
    e. Other chemistries: CPK, Glucose, Amylase, Lipase
    f. Urine test: Protein, Glucose
    g. Fasting Lipid Test Results: Total cholesterol, Triglycerides, LDL, HDL

2. Tolerability endpoint: Proportion of participants who receive at least 1 injection and who discontinue receiving injections prior to the full course of injections due to intolerability of injection, frequency of injections or burden of study procedures. Reasons for intolerability may include:
    1. Injection site reaction
    2. Participant refused further participation[1]
    3. Participant lost to follow-up
    4. Participant is unwilling or unable to comply with required study procedures
    5. Participant refused further study product use
    6. Participant unable to adhere to visit schedule

    [1]Excluding cases in which reason for termination is unrelated to intolerability

- Acceptability endpoint: Proportion of participants who complete all scheduled injections and proportion of participants who receive at least one injection who would consider using CAB LA for HIV prevention in the future. This endpoint will be evaluated using CASI questionnaires at the last injection visit (Step 2, week 33) For participants who do not have acceptability data at the Step 2, week 33 visit (either due to a change in when the questionnaire items were administered[2], missed the final injection visit, or discontinue injections early)and continue to step 3, acceptability endpoints are evaluated during the follow up phase (step 3, week +12). The primary acceptability outcome is:
    a. If you wanted to protect yourself from getting HIV, which of the following product(s) would you prefer to use?
        - Prefer not using a product
        - Condoms only
        - Oral PrEP pills only
        - Injectable PrEP only
        - Condoms and oral PrEP pills together
        - Condoms and injectable PrEP together
        - Prefer not to answer

    [2]The CASI survey was updated to include acceptability endpoints at the Step 2, week 33 visit on 01NOV2021 for all sites, since the addition of OLE could have otherwise precluded this endpoint from being captured (for participants who never begin Step 3). At this time, 6 participants had already completed their Step 2, week 33 visit.

Secondary endpoints:

- Plasma CAB pharmacokinetics
- Proportion of participants experiencing Grade 2 or higher clinical AEs and laboratory abnormalities in the oral phase and the aggregate oral and injection phases
- Proportion of injection visits that occurred “on-time”
- Change from enrollment of self-reported sexual behavior (number of sexual partners, increased episodes of vaginal or anal sex without a condom) during the oral and injection phases
- Presence of ART resistance among HIV seroconverters

2.3 Randomization

There is no treatment randomization as this study is a single arm, open label trial.

2.4 Blinding

Participants and site staff will be unblinded throughout the trial.

2.5 Sample Size and Power

The expected sample size available for analysis for this protocol (n=50) is the number of participants agreed upon by the industry sponsor and regulators in order to provide supplementary safety and behavioral data on adolescents in collaboration with the HPTN 083 and HPTN 084 adult trials. The goal of the safety evaluation for this study is to identify safety concerns associated with CAB LA.

Width of 95% confidence interval for estimated proportion as a function of the true proportion, assuming a sample size of 50.	
True proportion	Width of 95% CI
0.1	± 0.083
0.2	± 0.11
0.3	± 0.13
0.4	± 0.14
0.5	± 0.14

Since each of the primary endpoints is a proportion, Width of 95% confidence interval for estimated proportion as a function of the true proportion, assuming a sample size of 50. shows the precision (confidence interval width) that will be obtained for each endpoint with a sample size of 50.

Recognizing that some participants will not reach the first injection visit and/or may not receive any study injections due to personal or clinical concerns, the study will continue to recruit participants until it is clear that at least 50 participants will progress to the injection phase. Experience in the parent study HPTN 084 suggests that only a small proportion of participants will fail to reach the injection stage, and it is expected that approximately 5-7 additional enrollees may be needed in order to reach 50 participants in the injection phase.

3. GENERAL DATA ANALYSIS CONSIDERATIONS

3.1 Analysis Set(s)

Primary and secondary analyses will be carried out among the following populations:

Screened Population: Includes all participants who were screened for potential enrollment.

Injection Population: Includes enrolled female adolescents who receive at least one injection of CAB LA.

Safety Population: Includes enrolled participants who began step 1 (oral phase).

Enrolled Population: Includes all enrolled participants.

Seroconverter Population: Includes all enrolled participants who seroconverted during the study.

TDF/FTC Population: All enrolled participants who were provided TDF/FTC during the study.

3.2 Statistical Analysis Issues

AEs will be tabulated using MedDRA preferred terms. The number and percentage of participants experiencing each specific AE (All AEs, Grade 2 or higher, and SAEs) will be tabulated by severity and by relationship to study product. For the calculations in these tables, each participant's AEs will be counted once as the maximum severity and relationship to study product. AEs leading to temporarily or permanently stopping drug will also be summarized.

Methods for imputation of missing dates are described in Appendix C.

4. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE

See: Study progress and safety data monitoring plan (SPDSMP) for a detailed description of the study monitoring committee (SMC) and the data safety monitoring board (DSMB) reports for this study.

5. GENERAL ANALYSIS METHODS

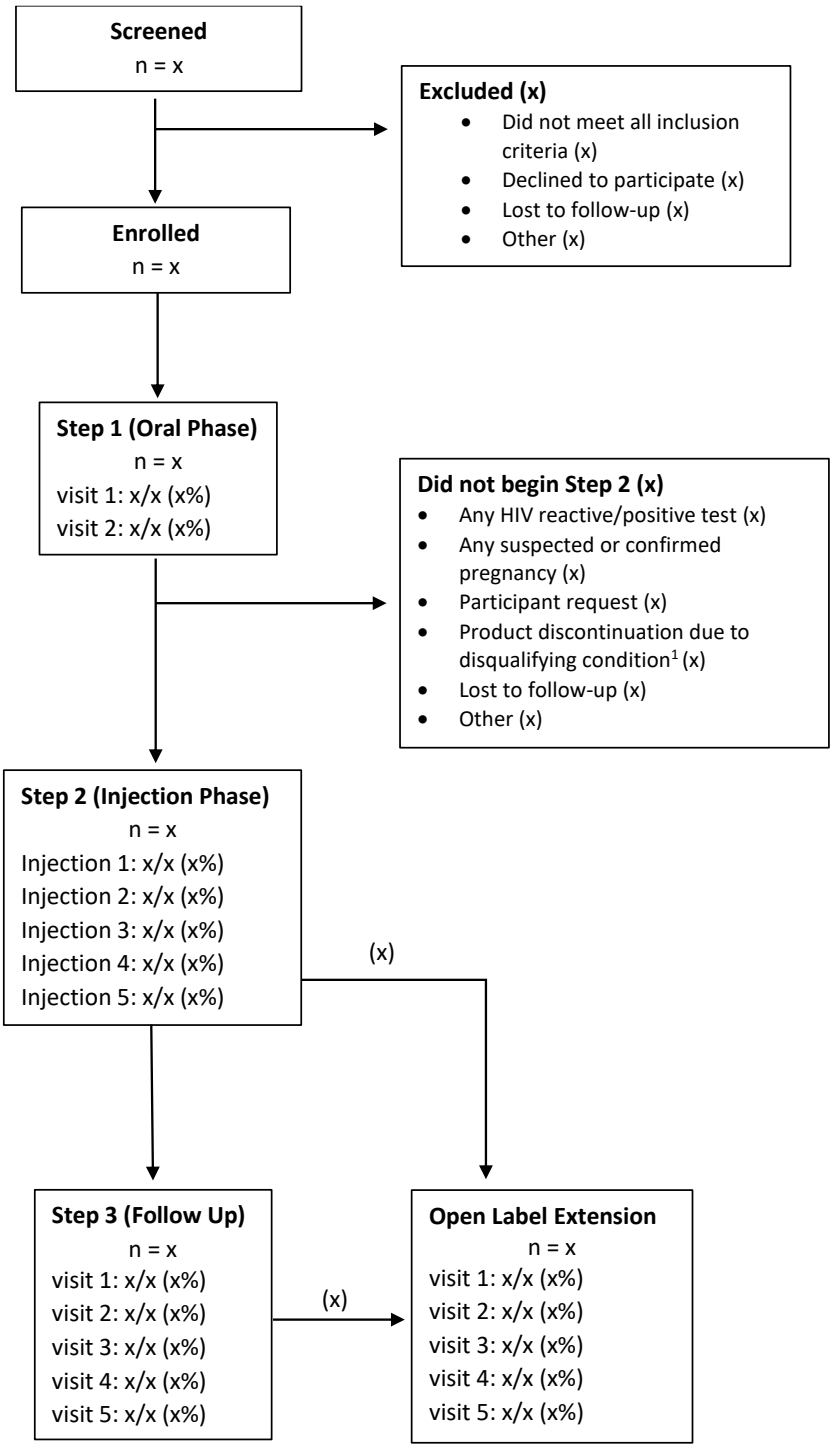
Within the single arm, all primary and secondary outcome proportions with 95% CIs will be calculated.

6. TRIAL PARTICIPANT DISPOSITION

6.1 Disposition of Participants

The study will recruit participants to ensure that at least 50 participants progress to the injection phase, therefore more than 50 participants will be screened and enrolled.

Consort Diagram (numbers to be determined)



[1]Conditions in Step 1 that could disqualify a participant from transitioning to Step 2 are as follows:

- Pill count suggestive of less than 50% adherence at the Week 4 visit
- Missed or delayed Week 4 visit
- Not on effective long-term contraception at the Week 4 visit
- Grade 2 ALT at week 4, or grade 3 and above ALT anytime in step 1
- Grade 3 AE that related to study product anytime in step 1, excluding ALT & CPK
- Grade 4 AE anytime in step 1, excluding ALT & CPK
- At substantial risk of HIV infection and/or qualifies for oral PrEP by local guidelines
- HIV reactive or positive test
- Confirmed pregnancy

Participant enrollment inclusion and exclusion criteria (see study protocol)

A. Inclusion Criteria

1) Assigned female at birth
2) At enrollment, below 18 years of age
3) [a]At enrollment, body weight ≥ 35 kg (77 lbs.)
4) Willing to provide written informed assent/consent for the study and/or able to obtain written parental/guardian informed consent
5) Self-reported sexual activity with a male (oral, anal or vaginal) in the past 12 months
6) In general, good health, as evidenced by the following laboratory values:
   a. Non-reactive / negative HIV test results
   b. Absolute neutrophil count > 799 cells/mm3
   c. Platelet count ≥ 100,000 cells/mm3
   d. Hemoglobin > 11g/dL
   e. Calculated creatinine clearance ≥ 60 mL/minute using the modified Schwartz equation
   f. Alanine aminotransferase (ALT) < 2.0 times the upper limit of normal (ULN) (< grade 1) and total bilirubin (Tbili) ≤ 2.5 x ULN
   g. Hepatitis B virus (HBV) surface antigen (HBsAg) negative) and accepts vaccination
   h. HCV Antibody negative
7) Willing to undergo all required study procedures
8) Must have a negative beta human chorionic gonadotropin (βHCG) pregnancy test (sensitivity of ≤ 25 mIU/mL) performed (and results known) on the same day as Enrollment and before initiating study product
9) Must agree to use a reliable form of long acting contraception, during the trial and for 48 weeks after stopping the long acting injectable, or 30 days after stopping oral study product, from the list below:
   a. Intrauterine device (IUD) or intrauterine system (IUS) that meets <1% failure rate as stated in the product label

   b. Hormone-based contraceptive that meets <1% failure rate when used consistently and correctly as stated in the product label (implants or injectables only; this excludes combined oral contraception).

10) [b]If currently on PrEP from a non-study source, willing to stop said PrEP prior to enrollment and agree to switch to oral CAB for the lead-in period and CAB LA injections.

B. Exclusion Criteria[c]

1) Co-enrollment in any other HIV interventional research study or other concurrent studies which may interfere with this study (as provided by self-report or other available documentation)
2) Past or current participation in HIV vaccine trial with exception for participants who can provide documentation of receipt of placebo
3) Exclusively had sex with biological females in lifetime
4) In the last 6 months (at the time of screening):
   a. active or planned use of any substance use which would, in the opinion of the site investigator, interfere with study participation (including herbal remedies)
5) Known history of clinically significant cardiovascular disease, as defined by history/evidence of symptomatic arrhythmia, angina/ischemia, coronary artery bypass grafting (CABG) surgery or percutaneous transluminal coronary angioplasty (PTCA) or any clinically significant cardiac disease
6) Inflammatory skin conditions that compromise the safety of intramuscular (IM) injections
7) Tattoo or other dermatological condition overlying the buttock region that may interfere with interpretation of injection site reactions
8) Current or chronic history of liver disease (e.g., non-alcoholic or alcoholic steatohepatitis) or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome, asymptomatic gallstones, or cholecystectomy)
9) Known history of clinically significant bleeding
10) A history of seizure disorder, per self-report
11) Medical, social or other condition that, in the opinion of the site investigator, would interfere with the conduct of the study or safety of the participant (e.g., provided by self-report, or found upon medical history and examination or in available medical records)
12) Plans to move out of the geographic area within the next 18 months or otherwise unable to participate in study visits, according to the site investigator
13) Pregnant or currently breastfeeding at the time of screening or intends to become pregnant and/or breastfeed while on study

[a] Letter of Amendment (LoA) #1 (03 December 2020): Decreased weight criterion from > 50 kg (110 lbs) to > 35 kg (77 lbs).

[b] LoA #1: Added new inclusion criterion #10.

[c] LoA #1: Removed exclusion criterion “Currently receiving PrEP from a non-study source” has been removed. Three exclusion criteria have been removed, to broaden the sexual risk profile for participants, due to the superiority results from HPTN 084: In the last 6 months (at the time of screening): 1. self-reported unprotected anal or vaginal intercourse with someone known to be HIV infected. 2. self-reported illicit injection drug use of any kind or stimulant use (including inhaled nitrate, cocaine in any form, methamphetamine, or non-physician prescribed pharmaceutical-grade stimulants) 3. self-report of greater than 5 different sexual partners (anal or vaginal), regardless of use of protection or knowledge of HIV status in last 6 months.

6.2 Treatment Exposure

During step 1 (oral phase) staff are required to observe participants take one pill at enrollment, week 2 and week 4. Pill counts will occur at visits for week 2 and 4.

All injections during step 2 (injection phase) will be administered (and therefore directly observed) by study staff. Injections will be considered “on-time” if they occur in the visit window, described in the secondary analyses (section 12).

Blood samples will be collected throughout the study from all participants and assayed for plasma CAB concentrations. PK sample times include pre-dose trough samples at W5, W9, W17, W25, and W33 (final concentration in injection phase) 1-week post injection samples at W6, W10, W18, W26, W34, with a final sample at +8-weeks following the final injection. For participants advancing to Step 3 (and not the OLE), additional follow-up samples will be collected at +24, +36 and +48-weeks following the final injection and at HIV confirmatory visit.

6.3 Protocol Deviations

Protocol deviations will be summarized in regular reports to the SMC, the details of which are available in the SPDSMP**.** Serious protocol deviations may result in participants being terminated from the trial and/or being excluded from analyses. The decision to exclude participant data from the analyses will be made based on independent review.

7. BASELINE DATA

The following data will be described overall, and by site:

Demographics (Table 1):

- Age (continuous – mean, SD, median, min max; categorical (<16, ≥ 16): n (%))
- Gender
- Sexual orientation
- Race
- Weight (continuous – mean, SD, median, min max; categorical (<50 kg, ≥50 kg): n (%))
- BMI
    - Age standardized BMI z-score (continuous – mean, SD, median, min max)
    - Classification as obese, overweight, normal, thinness, severe thinness based on z-score
- Housing security*
    - -Do you have a regular place or home where you stay and store your things? (yes/no)
- Food security*
    - In the past 6 months, how frequently did you worry that your household would not have enough food?

Sexual behavior/HIV prevention (Table 2):

- Sexual behaviors*:
  During the past month the participant had:
    - a primary partner
    - a primary partner who is reported to be HIV positive or unknown
    - transactional sex with a man
    - number of male sex partners
    - number of male sex partners who are reported to be HIV positive
    - number of episodes of vaginal sex (median (Q1, Q3))
    - number of episodes of vaginal sex without condom (median (Q1, Q3))
    - number of episodes of anal sex
    - number of episodes of anal sex without condom
- Sexually transmitted infections (STIs):
    - Syphilis
    - Gonorrhea
    - Chlamydia

- HIV risk perception*:
    - How much do you personally feel at risk of getting infected with HIV?

Mental health (Table 3):

- Depression indices[1]
    - CES-D-10* (continuous – mean, SD, median, min max; categorical (≤10: not depressed, >10: depressed): n (%))
    - PHQ9 (continuous – mean, SD, median, min max; categorical (none-minimal, mild, moderate, moderately severe, severe): n (%))
- Intimate partner violence (IPV)*
    - In the past 6 months, have any of your partners punched, slapped, kicked, bit you, or caused you any type of physical harm?
    - In the past 6 months, have any of your partners insulted, ignored or humiliated you, yelled at you, or made you feel ashamed or bad about yourself?
    - In the past 6 months, have any of your partners forced you to have sex or perform any sexual act, or touched you sexually in any way that you did not want?
    - In the past 6 months, have any of your partners made you feel afraid, unsafe or in danger?
- Primary care post traumatic stress disorder screening questionnaire (PC-PTSD-4)* (continuous – mean, SD, median, min max; categorical (≤2: no PTSD, >2: potential PTSD): n (%))
- alcohol/substance use*
    - How often do you have a drink containing alcohol?
    - How often do you have six or more drinks on one occasion?
    - In the past month, did you have a drink containing alcohol just before or during sex?
    - In the past month, how often have you used each of the following substances?
        - Cannabis (Also called marijuana, pot, grass, dakka, dagga or hash)
        - Amphetamine-type stimulants (For example Tik/Crystal Meth, ecstasy, speed, or diet pills)
        - Prescription drugs for non-prescription purposes (For example codeine (including cough syrup), efavirenz, valium)

[1]Internal consistency of Depression Index summaries *(addendum to Table 3)*:

1. Tabular cross-frequency of the categories for CES-D-10/PHQ9
2. Scatterplot of the values of either index, with color-coding based on whether they agree on qualitative risk of depression

*CASI questionnaire variables

8. PRIMARY ANALYSES

For each of the three primary endpoints the number and proportion of participants will be computed along with corresponding exact 95% confidence intervals where applicable. Endpoint descriptions are available in section 2.2.

8.1 Safety endpoint analysis

Population: Injection population
Analysis description: Number and percent of participants experiencing any Grade 2 or higher clinical adverse events (AEs) or laboratory abnormalities (reported as adverse events) from the first injection visit to 8 weeks after the last Step 2 injection visit or week 41, whichever comes first.

8.2 Tolerability endpoint analysis

Population: Injection population
Analysis description: Number and percent of participants who receive at least 1 injection and who discontinue receiving injections prior to the full course of injections due to intolerability of injection or burden of study procedures. Reasons for intolerability may include:

1. Injection site reaction
2. Burden of study procedure
    i. Participant refused further participation
    ii. Participant is unwilling or unable to comply with required study procedures
    iii. Participant refused further study product use
    iv. Participant unable to adhere to visit schedule

8.3 Acceptability endpoint analysis

8.3.1 Completion of scheduled injections

Population: Injection population and Enrolled population
Analysis description: Number and percent of participants who complete all scheduled injections[1]

[1]Definition of completing all scheduled injections for participants who are confirmed pregnant, confirmed HIV seroconverted, or discontinue product due to the following reasons:

- Death
- Early study closure
- HBV infection

During Step 1:
Enrolled population: completed all 0 of 0 scheduled injections
Injection population: not applicable, did not receive injection

During Step 2:
both enrolled and injection: completed all injections whose target window closed prior to pregnancy/seroconversion/product discontinuation date

8.3.2 Preferred method for HIV prevention

Population: Injection population
Analysis description: Number and percent of participants who choose 'injectable PrEP' or 'condoms and injectable PrEP' when asked the question "If you wanted to protect yourself from getting HIV, which of the following product(s) would you prefer to use?"

9. SAFETY ANALYSES

See section 8.1 above. In addition to the primary safety outcomes (grade 2 or higher), AEs and laboratory data will be summarized in the closed DSMB report (described in the SPDSMP).

9.1 Adverse Events and Deaths

Adverse events of special interest (AESI) will be summarized in the Clinical Study Report. Planned AESI summaries for the CSR are described in Appendix A.

9.2 Laboratory Evaluations

Population: Safety population
Description: Laboratory findings for CBC (hemoglobin, platelets, WBC, neutrophils, lymphocytes), chemistries (urea, creatinine, CPK, glucose, calcium, phosphorous, amylase, lipase), liver function (AST, ALT, total bilirubin, alkaline phosphatase) and fasting lipid profile (total cholesterol, triglycerides, HDL, LDL) will be reported by grade, as defined in the "Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events". The proportion of laboratory findings qualifying as Grade 2 or above will be presented. Baseline laboratory values will be summarized by site using: median, 1st and 3rd quartiles, and min and max. Change from baseline in laboratory values will be summarized at follow up visits using: median, and 1st and 3rd quartile. Summaries involving values and changes from baseline at scheduled visit time points will consider values from scheduled visits only, and in the case of missing values, results will not be carried forward from interim (unscheduled) visits. For summaries and analyses involving changes in laboratory values over time or maximum change from baseline (e.g. shift tables), values from interim (unscheduled) visits will also be considered.

9.3 Other Safety Measures

10. IMMUNOGENICITY ANALYSES

NA

11. PHARMACOKINETIC ANALYSES

Plasma will be collected during Steps 1 and 2 for pharmacologic assessment of CAB concentrations. Plasma and DBS will also be collected for participants entering Step 3. If a study participant seroconverts during Step 3, pharmacologic analysis of plasma will be performed to assess PrEP adherence; plasma TFV and intraerythrocytic TFV-DP collected as DBS will be used to interpret TDF/FTC adherence during Step 3. Analysis details are provided in the current version of the Pharmacokinetics Analysis Plan.

12. SECONDARY ANALYSES

For binary secondary endpoints, the number and proportion of endpoints will be computed along with corresponding 95% exact confidence intervals where applicable. Endpoint descriptions are available in section 2.2. Note: Some secondary analyses will not be included in the Clinical Study Report, and the Clinical Study Report will not generally provide 95% confidence intervals for secondary analyses.

12.1 Plasma CAB pharmacokinetics

Analysis details are provided in the current version of the Pharmacokinetics Analysis Plan.

12.2 Proportion of participants experiencing Grade 2 or higher clinical AEs and laboratory abnormalities in the oral phase and over the aggregate oral and injection phase

Population: Safety population
Analysis description: Number and percent of participants experiencing any Grade 2 or higher clinical adverse events (AEs) or laboratory abnormalities from:

1. enrollment to week 5 (oral phase (step 1), including interim visits).
2. enrollment to 8 weeks following the last injection received (aggregate over oral+injection phases (step 1-step 2) including interim visits)

12.3 Proportion of participants receiving 1 or more injections experiencing Grade 2 or higher clinical AEs and laboratory abnormalities from initial injection to 36 weeks later

Population: Injection population
Analysis description: Number and percent of participants experiencing any Grade 2 or higher clinical adverse events (AEs) or laboratory abnormalities from the first injection visit to approximately 36 weeks later regardless of whether participants received all 5 injections. For participants receiving all 5 injections, the end date is 8 weeks following the week 33 injection visit. For participants discontinuing study product early and moving on to Step 3, the end date is 36 weeks after the initial injection. Participants who terminate early are included in the analysis and censored at the date of termination.

12.4 Proportion of injection visits that occurred "on-time"

Population: Injection population
Analysis description: Number and percent of injection visits (up to 5 per participant) that occur "on-time"[1], using the number of injections given as the denominator. This will be presented along with the total number and percent of injections given, among all intended injections (i.e. 5 injections per participant).

[1]The target injection date is defined by the W5 visit i.e. for the initial injection, the target injection date is 0 days (same day), and is +28, +84, +140, +196 days from the W5 visit for injections 2-5, respectively. The target visit window for injection visits for the week 5 injection is 0 to 3 days after the W5 visit (if the injection could not be done on the same day as the W5 visit), for all other injection visits (W9, W17, W25, W33) the target window is +/- 3 days from the target injection date. Injection dates happening within the target window are considered "on-time".

12.5 Change from enrollment of self-reported sexual behavior (number of sexual partners, increased episodes of vaginal or anal sex without a condom) during the study period

Note: This secondary analysis will not be included in the Clinical Study Report.

Population: Enrolled population
Analysis description: We will use generalized estimating equations (GEE) with robust variance to model change in self-reported sexual behavior from enrollment (W0) to follow up visits (W4, W5, W9, W17, W25, W33, W+12, W+24, W+36, W+48), with an indicator variable for all on-study visits (i.e. enrollment visit = 0) to measure change in the outcome behavior. We will model count outcomes (number of sexual partners, number of episodes of vaginal sex without a condom) using a poisson model and binary outcomes (any episodes of anal sex without a condom) using a logistic model.

12.6 Evaluate rates of HIV drug resistance among participants who acquire HIV infection during the study

Population: Seroconverter population
Analysis description: Data from steps 1, 2, and 3 will be included. The number of cases of drug resistance will be summarized. All cases of drug resistance among incident HIV infections will be described.

13. AD HOC ANALYSIS

13.1 Change from enrollment of age-standardized BMI z-score during the oral and injection phases

Population: Injection population[1]

Analysis description: We will test a null hypothesis that there is no change in age-standardized BMI z-score, using the one-sample Wilcoxon signed-rank test applied to participant-level difference in BMI z-score as measured at the enrollment and W33 visits. In addition we will estimate the mean change in BMI z-score from baseline and 95% confidence interval.

We will include summary descriptions of change in age-standardized BMI z-scores from enrollment (W0) to follow up visits (W4, W5, W9, W17, W25, W33), including tabular summaries of actual and change (relative to enrollment) values at each visit (mean, SD, median, min max) as well as the number and percent falling into standardized categorizations for the following groups: obesity (z-score >2SD), overweight (1SD< z-score ≤2SD), normal (-2SD< z-score ≤1SD), thinness (-2SD< z-score ≤-3SD), severe thinness (z-score <-3SD). We will present graphical summaries of change in BMI z-scores at each visit using a line plot of median change values, including vertical bars at each visit representing interquartile ranges (including a text annotation of the P-value for change in BMI above the W33 visit). A second graph will include a stacked bar chart at each timepoint, with number and percent in each standardized BMI category defined above.

[1]For participants who become pregnant, excludes participant-visits occurring after confirmed pregnancy date. Missed injections will be summarized or included as a footnote.

14. CHANGE HISTORY

Version		Affected Section(s)	Activity Description
Number	Effective Date		
1.0	22/02/2021	All sections	Creation of SAP v 1.0

2.0	Date of last signature	2, 3, 6, 7-9, 11, 12	Revisions based on new alternative to Step 3 (OLE CAB study). Added study populations and definitions. Updated consort diagram, primary and secondary outcomes/analyses, including addition of secondary outcome 12.6. Revisions/edits based on feedback from SCHARP external partners at GSK/PXL/Viiv.
3.0	Date of last signature	2, 6, 7, 8.3.1, 11, 12.1, 12.5, 13, 16, 17	Minor revisions throughout. Updates to consort diagram, acceptability endpoint definition, and reference to PK analysis plan. Additional details to account for changes to schedule of visits and data collection, due to new OLE. Added sections: 13 (ad hoc analysis), appendices B and C (variable definitions and imputation of missing data).

15. APPENDIX A – Adverse Events of Special Interest

Adverse events of special interest (AESI) have been determined for CAB based on pre-clinical and clinical experience, along with information for the integrase inhibitor class of HIV medications safety profile. These are adverse events for which more detailed summaries of event characteristics are of interest.
The identification and classification of AESI will be based on MedDRA preferred terms as specified in the ADRG (Analysis Data Reviewers Guide). The current MedDRA version used for the preferred terms in the ADRG is v24.1. Preferred terms will be updated in the ADRG if a new version becomes available before the database lock.
Table 1 below shows the adverse events of special interest identified and reasons for including.

Table 1 Adverse Events of Special Interest (Clinical Study Report only)

AESI	Product Implicated	Reason for Including as AESI
Hepatic Safety Profile: Assessment of risk of hepatoxicity	CAB	Clinical, Class, Regulatory Interest,
Hypersensitivity Reactions (HSR)	CAB	Class, Regulatory Interest,
Rash	CAB	Class, Regulatory Interest
Neuropsychiatric Events • Suicidal Ideation/Behaviour • Depression • Bipolar Disorder • Psychosis • Mood Disorders • Anxiety • Sleep Disorders	CAB	Clinical, Class, Regulatory Interest,
Injection Site Reactions (ISR)	CAB	Clinical, Regulatory Interest
Seizures and Seizure-like events	CAB	Clinical, Regulatory Interest
Weight Gain	CAB	Clinical, Class, Regulatory Interest
Rhabdomyolysis	CAB	Clinical, Class, Regulatory Interest
Pancreatitis	CAB	Clinical, Therapeutic Area, Regulatory Interest
Impact on Creatinine	CAB	Regulatory Interest, Therapeutic Area
Safety in Pregnancy	CAB	Regulatory Interest, Class

Hyperglycaemia/new onset diabetes mellitus	CAB	Observation from 083, Class

Common ISR adverse events are defined by MedDRA preferred terms including injection site pain, injection site induration, injection site nodules and preferred terms of any other ISR exceeding the threshold as specified in the ADRG. ISRs are summarized and listed regardless of IP relationship.
Separate outputs will be created for each one of the AESIs described in Table 3 to explore the data in more detail. Outputs will summarize Adverse events that occurred during Step 1 and/or Step 2 of the study.
Event Characteristics: The characteristics of all event occurrences during the post-baseline period will be summarized, which looks at event characteristics (serious, drug-related, leading to withdrawal, or Grade 3/4, fatal), number of events per participant, outcome, maximum grade or intensity and action taken.
Time to First Event (TTFE): A tabular summary of time of onset and duration of first event will be produced.
Duration of Events: The total duration of time a subject experience the adverse events in question will also be summarized.
In addition, Pyrexia Plus includes PT: (Chills – 10008531, Feeling of Body Temperature Change - 10061458, Feeling Hot - 10016334, Body Temperature Increased - 10005911, Pyrexia - 10037660, Influenza Like Illness - 10022004, Fever – 10016558) will be summarized in relation to timing of previous injection.
No formal statistical comparison planned for AESI.

16. APPENDIX B – Variable Definitions

1. CES-D-10 (score/categories)

Create a score based on 10 items below (in CASI questionnaire):

In the list below, please indicate how often you have felt this way during the past week by ticking the appropriate box for each question:

1. I was bothered by things that usually don't bother me.
2. I had trouble keeping my mind on what I was doing.
3. I felt depressed.
4. I felt that everything I did was an effort.
5. I felt hopeful about the future.
6. I felt fearful or afraid.
7. My sleep was restless.
8. I was happy.
9. I felt lonely.
10. I could not "get going", I did not feel motivated.

Scoring:

	Rarely or none of the time (less than 1 day)	Some or a little of the time (1-2 days)	Occasionally or a moderate amount of time (3-4 days)	All of the time (5-7 days)
Questions 5 & 8	3	2	1	0
All other questions	0	1	2	3

The total score is calculated by finding the sum of 10 items. Score as 'missing' if 1 or more items are missing/prefer not to answer. Any score ≥10 is considered depressed.

2. PHQ-9 (score/categories)

Create a score based on values from 9 questions (Not at all = 0, Several days = 1, More than half the days = 2, Nearly every day = 3):

Over the last 2 weeks, how often have you been bothered by the following problems?

1. Little interest or pleasure in doing things
2. Feeling down, depressed, or hopeless
3. Trouble falling or staying asleep, or sleeping too much
4. Feeling tired or having little energy
5. Poor appetite or overeating
6. Feeling bad about yourself - or that you are a failure or have let yourself or your family down",
7. Trouble concentrating on things, such as reading the newspaper or watching television",
8. Moving or speaking so slowly that other people could have noticed. Or the opposite - being so fidgety or restless that you have been moving around a lot more than usual
9. Thoughts that you would be better off dead, or of hurting yourself

PHQ-9 score obtained by adding score for each question (total points). Score as 'missing' if 1 or more items are missing. Then categories of depression severity are created from the total score according to: 0-4: None-minimal, 5-9: Mild, 10-14: Moderate, 15-19: Moderately Severe 20 – 27: Severe.

3. PC-PTSD-4 (score/categories)

Create a score based on values from 4 questions (yes = 1, no = 0):

In your life, have you ever had any experience that was so frightening, horrible, or upsetting that, in the past month, you:

1. Have had nightmares about it or thought about it when you did not want to?
2. Tried hard not to think about it or went out of your way to avoid situations that reminded you of it?
3. Were constantly on guard, watchful, or easily frightened?
4. Felt empty, numb or detached from others, activities, or your surroundings?

If missing or prefer not to answer any questions, then code score as missing. For non-missing scores, a score of 0-2 fails to indicate PTSD, and ≥ 3 indicates the potential for PTSD, which can be determined by a clinical interview.

4. Age-standardized BMI z-score

Based on World Health Organization (WHO) tool:

(1) https://www.who.int/tools/growth-reference-data-for-5to19-years/indicators/bmi-for-age.

With instructions for calculations (see section "**Computation of centiles and z-scores**", link to pdf: "**instructions in English**"):

(2) https://cdn.who.int/media/docs/default-source/child-growth/growth-reference-5-19-years/computation.pdf?sfvrsn=c2ff6a95_4

Age-specific values of necessary parameters *L(t)*, *M(t)*, and *S(t)* can be downloaded from the website (1) (see section: "**Expanded tables for constructing national health cards**" link to dataset "**z-scores: girls**")

Categorical BMI classification based on age-standardized BMI z-score as follows:

- Obesity: >+2
- Overweight: >+1 and ≤+2
- Normal: >-2 and ≤+1
- Thinness: >-3 and ≤-2
- Severe thinness: ≤-3

17. APPENDIX C – Imputation of missing dates

Missing Start and Stop Dates for Prior and Concomitant Medication, and Medical History

The Assumption is to consider the most conservative judgment when imputing.

Start date:
When imputing a start date ensure that the new imputed date is sensible i.e. is prior to the end date and the general rules are:

1. If start date is completely missing, start date will not be imputed
2. If year and month are present and day is missing, set day to the 1st day of month.
3. If year and day are present and month is missing, then set month to January.
4. If year is present and month and day are missing, set month and day to January 1st.

Stop date:

1. If end date is completely missing, end date will not be imputed
2. If year and month are present and day is missing, set day to the last day of month.
3. If year and day are present and month is missing, set month to December
4. If year is present and month and day are missing, set month and day to December 31st.

Missing Start and Stop Dates for Adverse Events (including ISRs)

The Assumption is to consider the most conservative judgment when imputing.

Start date:

1. If start date is completely missing, start date is set to date of first dose.
2. If (year is present, and month and day are missing) or (year and day are present, and month is missing):
    a. If year = year of first dose, then set month and day to month and day of first dose.
    b. If year < year of first dose, then set month and day to December 31st.
    c. If year > year of first dose, then set month and day to January 1st.
3. If month and year are present and day is missing:
    a. If year = year of first dose and
        i. If month = month of first dose, then set day to day of first dose date.
        ii. If month < month of first dose, then set day to last day of month.
        iii. If month > month of first dose, then set day to 1st day of month.
    b. If year < year of first dose, then set day to last day of month.
    c. If year > year of first dose, then set day to 1st day of month.

Stop date:
If the outcome of the AE was ongoing or unknown, then the rules outlined below will not be applied.

1. If stop date is completely missing, stop date is set to date of study discontinuation.
2. If (year is present, and month and day are missing) or (year and day are present, and month is missing):
    a. If year = year of study discontinuation, then set month and day to month and day of study discontinuation.
    b. If year < year of study discontinuation, then set month and day to December 31st.
    c. If year > year of study discontinuation, then set month and day to December 31st.
3. If month and year are present and day is missing:
    a. If year = year of study discontinuation and
        i. If month = month of study discontinuation, then set day to day of study discontinuation date
        ii. If month < month of study discontinuation, then set day to last day of month.
        iii. If month > month of study discontinuation, then set day to last day of month.
    b. If year < year of study discontinuation, then set day to last day of month.
    c. If year > year of study discontinuation, then set day to last day of month.

Missing Start and Stop Dates for Protocol Deviations

The Assumption is to consider the most conservative judgment when imputing.

Start date:
When imputing a start date ensure that the new imputed date is sensible i.e. is prior to the end date and the general rules are:

1. If start date is completely missing, start date will not be imputed
2. If (year is present, and month and day are missing) or (year and day are present, and month is missing), set month and day to January 1st.

3. If year and month are present and day is missing, set day to the 1st day of month.

Stop date:
1. If end date is completely missing, end date will not be imputed
2. If (year is present, and month and day are missing) or (year and day are present, and month is missing), set month and day to December 31st.
3. If year and month are present and day is missing, set day to the last day of month.