Janssen Scientific Affairs, LLC

Clinical Protocol

Protocol Title

A Phase 4, Randomized, Active-Controlled, Open-label Study to Evaluate the Safety and Tolerability of Switching to Once-Daily Darunavir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (D/C/F/TAF) Fixed-dose Combination (FDC) Regimen in Virologically-suppressed Human Immunodeficiency Virus Type 1 (HIV-1) Infected Participants Experiencing Rapid Weight Gain with an INI + TAF/FTC ARV Regimen

DEFINE

Short Title

D/C/F/TAF FDC Evaluated as a Fixed Dose Combination Regimen in Participants Switching from an Integrase Inhibitor who have Experienced Rapid Weight Gain

Protocol TMC114FD2HTX4004; Phase 4
AMENDMENT 3
TMC114+JNJ-48763364-AAA+JNJ-35807551-AAA+JNJ-63625328-ZCA (darunavir 800 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir alafenamide 10 mg)

This study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312).

Status: Approved
Date: 29 April 2022
Prepared by: Janssen Scientific Affairs, LLC
EDMS number: EDMS-ERI-178641402, 5.0

GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 3	29-April-2022
Amendment 2	21-May-2021
Amendment 1	24-April-2020
Original Protocol	16-December-2019

Amendment 3 (29 April 2022)

Overall Rationale for the Amendment:- The overall reason for this amendment is to account for new data and investigator feedback indicating 10% weight gain may not occur within 12 months but could occur more gradually over a longer period of time.

Section Number and Name	Description of Change	Brief Rationale
1.1. Synopsis (Overall Design); 1.2 Schema; 4.1. Overall Design; 5.1. Inclusion Criteria #4	Eligible patients need to have a rapid and significant body weight gain which is defined as a ≥10% increase within a 36-month time period prior to screening and after starting an INI-based regimen.	The weight gain criterion has caused confusion as written and is re-worded for clarity to capture the intended population for enrollment
5.1 Inclusion criteria 5.4 Screen failures 10.5 Appendix 5: Contraceptive and Barrier Guidance and Collection of Pregnancy Information	The text was updated to reflect the updated template text as per the latest template dated 21 March 2022, version 15.	To align with the latest protocol template
1.1 Synopsis 4.1 Overall Design	The text was modified (deletion in strikethrough) to: After Week 24, all participants in the Delayed Switch Arm will ~~be given the option to~~ receive the D/C/F/TAF FDC tablet and will be followed for an additional 24 weeks.	The sentence regarding participants randomized to the Delayed Switch Arm switching to D/C/F/TAF FDC at Week 24 was re-worded for clarity

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1. PROTOCOL SUMMARY

1.1. Synopsis

A Phase 4, Randomized, Active-Controlled, Open-label Study to Evaluate the Safety and Tolerability of Switching to Once Daily Darunavir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (D/C/F/TAF) Fixed-dose Combination (FDC) Regimen in Virologically-suppressed Human Immunodeficiency Virus Type 1 (HIV-1) Infected Participants Experiencing Rapid Weight Gain with an INI + TAF/FTC ARV Regimen

Short Title: D/C/F/TAF FDC Evaluated as a Fixed Dose Combination Regimen in Participants Switching from an Integrase Inhibitor who have Experienced Rapid Weight Gain.

Primary Study Intervention

The primary study intervention is the darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) fixed-dose combination (FDC). D/C/F/TAF FDC is a 4-agent tablet for oral once-daily use for the treatment of human immunodeficiency virus (HIV)-1 infection in adults. This tablet contains the protease inhibitor (PI) darunavir (D or DRV) (800 mg), the pharmacokinetic (PK) enhancer cobicistat (COBI or C) (150 mg), the nucleoside reverse transcriptase inhibitor (NRTI) emtricitabine (FTC or F) (200 mg), and the tenofovir (TFV) prodrug tenofovir alafenamide (TAF) (10 mg). The D/C/F/TAF FDC tablet (SYMTUZA®) was approved by the United States (US) Food and Drug Administration as a complete regimen for the treatment of HIV-1 infection in adults who have no prior antiretroviral (ARV) treatment history or who are virologically-suppressed (human immunodeficiency virus type 1 ribonucleic acid [HIV-1 RNA] less than 50 copies per mL) on a stable ARV regimen for at least 6 months and have no known substitutions associated with resistance to DRV or TFV.

Participants will be randomized 1:1 to either remain on their baseline integrase (INI)-based regimen (Delayed Switch) or to switch to a regimen of D/C/F/TAF FDC (Immediate Switch). After 24 weeks participants who were randomized to remain on their INI-based regimen will also be switched to D/C/F/TAF FDC for an additional 24 weeks. All enrolled participants will be assigned randomized treatments in an open-label manner.

- **D/C/F/**TAF **FDC Arm (Immediate Switch):** Switch to a regimen of DRV 800 mg + COBI 150 mg + FTC 200 mg + TAF 10 mg FDC once daily, (n=55) for 48 weeks;
- **Active-Control Arm (Delayed Switch):** Continue current INI + TAF/FTC ARV regimen, (n=55) for 24 weeks. After 24 weeks participants will switch to a regimen of DRV 800 mg + COBI 150 mg + FTC 200 mg + TAF 10 mg FDC once daily for an additional 24 weeks.

Currently, four INIs are FDA approved (bictegravir, dolutegravir, elvitegravir/cobicistat, and raltegravir) to treat both treatment naïve and certain treatment experienced patients in combination with other antiretroviral agents and have demonstrated favorable efficacy and tolerability profiles in registrational clinical studies. The individual agents bictegravir, dolutegravir, and elvitegravir/cobicistat are available in several co-formulated single tablet regimens including NRTIs. Tenofovir alafenamide is an NRTI approved for treatment of patients living with HIV-1 in combination with other antiretrovirals and is available in several fixed dose combinations or single tablet regimens with FTC.

OBJECTIVES AND ENDPOINTS

Week 24 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the percent change in body weight when switching to D/C/F/TAF FDC (Immediate Switch Arm) compared to continuing the current INI + TAF/FTC ARV regimen (Delayed Switch Arm) in virologically-suppressed (HIV-1 RNA <50 copies/mL) HIV-1 infected participants who have experienced rapid and significant body weight gain	• Percent change from Baseline in body weight at Week 24
Secondary	
Metabolic	
• To assess changes in body weight when switching to D/C/F/TAF FDC (Immediate Switch Arm) compared to continuing the current INI + TAF/FTC ARV regimen (Delayed Switch Arm)	• Change from Baseline in absolute body weight at Week 24 • Proportion of participants with % change in body weight >3% at Week 24 • Proportion of participants with % change in body weight >5% at Week 24 • Change from Baseline in BMI at Week 24
• To assess changes in body composition when switching to D/C/F/TAF FDC (Immediate Switch Arm) compared to continuing the current INI + TAF/FTC ARV regimen (Delayed Switch Arm)	• Change from Baseline in body composition as measured by DEXA scan at Week 24 • Change from Baseline in waist circumference at Week 24
• To assess change in blood pressure when switching to D/C/F/TAF FDC (Immediate Switch Arm) compared to continuing the current INI + TAF/FTC ARV regimen (Delayed Switch Arm)	• Change in SBP and DBP from Baseline at Week 24
• To assess changes in clinical laboratory tests when switching to D/C/F/TAF FDC (Immediate Switch Arm) compared to continuing the current INI + TAF/FTC ARV regimen (Delayed Switch Arm)	• Change from Baseline in fasting lipids at Week 24 • Change from Baseline in fasting glucose at Week 24 • Change from Baseline in HOMA-IR at Week 24 • Change from Baseline in HbA1c at Week 24 • Change from Baseline in leptin and adiponectin at Week 24
• To assess changes in liver biomarkers when switching to D/C/F/TAF FDC (Immediate Switch Arm) compared to continuing the current INI + TAF/FTC ARV regimen (Delayed Switch Arm)	• Change from Baseline in the proportion of participants with advanced fibrosis according to the NAFLD fibrosis score at Week 24 • Change from Baseline in the proportion of participants at high risk of NASH according to the HAIR score at Week 24
• To assess changes in concomitant medications of interest (including anti-hypertensive, anti-hyperglycemic, and lipid lowering agents) when switching to D/C/F/TAF FDC (Immediate Switch	• Proportion of participants having a dose-reduction or complete withdrawal of anti-hypertensive, anti-hyperglycemic, or lipid lowering agents in the Immediate

Objectives	Endpoints
Arm) compared to continuing the current INI + TAF/FTC ARV regimen (Delayed Switch Arm)	Switch Arm or Delayed Switch Arm from Baseline to Week 24 • Proportion of participants initiating an anti-hypertensive, anti-hyperglycemic, or lipid lowering agent in the Immediate Switch Arm or Delayed Switch Arm from Baseline to Week 24
Safety	
• To evaluate the safety of switching to D/C/F/TAF FDC (Immediate Switch Arm) compared to continuing the current INI + TAF/FTC ARV regimen (Delayed Switch Arm)	• Incidence of any Grade AEs (related and not related) through Week 24 • Incidence of Grade 3 and 4 AEs (related and not related) through Week 24 • Incidence of discontinuations due to AEs through Week 24 • Incidence of SAEs (related and not related) through Week 24 • Change from Baseline in clinical laboratory tests through Week 24 • Incidence of Grade 3 and 4 laboratory abnormalities through Week 24
Efficacy	
• To evaluate the virologic outcomes when switching to D/C/F/TAF FDC (Immediate Switch Arm) compared to continuing the current INI + TAF/FTC ARV regimen (Delayed Switch Arm)	• Proportion of participants with confirmed virologic rebound through Week 24 • Proportion of participants with virologic response (HIV-1 RNA<50 copies/mL) at Week 24 according to the FDA snapshot algorithm • Proportion of participants with virologic failure (HIV-1 RNA ≥50 copies/mL) at Week 24 according to the FDA snapshot algorithm • Proportion of participants having virologic response (HIV-1 RNA<200 copies/mL) at Week 24 according to the FDA snapshot algorithm • Proportion of participants having virologic failure (HIV-1 RNA ≥200 copies/mL) at Week 24 according to the FDA snapshot algorithm
• To evaluate immunological changes when switching to D/C/F/TAF FDC (Immediate Switch Arm) compared to continuing the current INI + TAF/FTC ARV regimen (Delayed Switch Arm)	• Change from Baseline in CD4+ cell count at Week 24
Resistance	
• To assess viral resistance in participants with confirmed HIV-1 RNA rebound for participants switching to D/C/F/TAF FDC (Immediate Switch Arm) compared to continuing the current INI + TAF/FTC ARV regimen (Delayed Switch Arm)	• Proportion of participants with pre-baseline PR, RT, and INI resistance-associated mutations (RAMs) based on historical genotypes • Incidence of observed genotypic and phenotypic ARV resistance for

Objectives	Endpoints
	participants meeting HIV-1 RNA rebound criteria through Week 24 • Proportion of participants with newly identified post-baseline RAMs and phenotypic resistance, compared to pre-baseline resistance tests when available, upon meeting confirmed virologic rebound through Week 24
PROs	
• To assess changes in the burden of common symptoms associated with HIV treatment or disease for participants switching to D/C/F/TAF FDC (Immediate Switch Arm) compared to continuing the current INI + TAF/FTC ARV regimen (Delayed Switch Arm)	• Change from Baseline in the proportion of participants who have bothersome symptoms (scores of 2, 3 or 4) across all items of the HIV-SI at Week 24 • Change from Baseline in the proportion of participants who have any symptoms (scores of 1, 2, 3 or 4) across all items of the HIV-SI at Week 24 • Association between treatment arm and each bothersome symptom of the HIV-SI adjusting for Baseline variables at Week 24
• To describe responses on the PGIC in participants switching to D/C/F/TAF FDC (Immediate Switch Arm) and in participants continuing the current INI + TAF/FTC ARV regimen (Delayed Switch Arm)	• PGIC at Week 24
Adherence	
• To evaluate adherence in participants switching to D/C/F/TAF FDC (Immediate Switch Arm) compared to continuing the current INI + TAF/FTC ARV regimen (Delayed Switch Arm)	• Adherence rates by participant self-report using 4-day recall at Week 4, 12, and 24
Exploratory	
Exploratory clinical biomarker	
• To assess changes in alpha melanocyte-stimulating hormone when switching to D/C/F/TAF FDC (Immediate Switch Arm) compared to continuing the current INI + TAF/FTC ARV regimen (Delayed Switch Arm)	• Change from Baseline in alpha melanocyte-stimulating hormone at Week 24
Exploratory PROs	
• To assess changes in eating-related concepts (hunger, appetite, cravings, and satiety) for participants switching to D/C/F/TAF FDC (Immediate Switch Arm) compared to continuing the current INI + TAF/FTC ARV regimen (Delayed Switch Arm)	• Change from Baseline in the scores on the DAILY EATS at Week 24

Objectives	Endpoints
• To assess changes in concerns about body shape for participants switching to D/C/F/TAF FDC (Immediate Switch Arm) compared to continuing the current INI + TAF/FTC ARV regimen (Delayed Switch Arm)	• Change from Baseline in the scores on the BSQ-8D at Week 24 • Change from Baseline in the proportion of participants who have no concern (<19), mild concern (19-25), moderate concern (26-33) or marked concern (>33) with their body shape at Week 24

Abbreviations: AE: adverse event, ARV: antiretroviral, BMI: body mass index, BSQ 8D: body shape questionnaire, D/C/F/TAF FDC: Darunavir/Cobicistat/Emtricitabine/Tenofovir Alafenamide Fixed dose Combination, DBP: diastolic blood pressure, DEXA: dual energy X ray absorptiometry, FDA: Food Drug Administration, FTC: emtricitabine, HAIR: hypertension, age, insulin, resistance, HIV 1 RNA: human immunodeficiency virus type 1 ribonucleic acid, HIV SI: HIV Symptom Index, HOMA IR: homeostatic model assessment of insulin resistance, INI: integrase, NAFLD: non alcoholic fatty liver disease, NASH: Nonalcoholic fatty liver disease, PGIC: patient global impression of change, PR: protease, PROs: patient reported outcomes, RT: reverse transcriptase, SAE: serious adverse event, SBP: systolic blood pressure.

Secondary objectives/endpoints at Week 48 are similar to the Week 24 Objectives and Endpoints and thus will be used to assess 1) outcomes for the Immediate Switch Arm at Week 48 and 2) the consistency of effect on outcomes from Baseline to Week 24 in the Immediate Switch Arm versus the Week 24 to Week 48 in the Delayed Switch Arm.

Hypothesis

Based on the primary endpoint, the percent change in body weight at Week 24 from baseline in the Immediate Switch Arm is less than that of the Delayed Switch Arm (INI + TAF/FTC ARV).

OVERALL DESIGN

This is a randomized, 48 week, active-controlled, open-label, prospective, multicenter, Phase 4 study to evaluate the safety and tolerability of switching to D/C/F/TAF FDC compared to continuing the current INI + TAF/FTC ARV regimen in virologically-suppressed HIV-1 infected adult participants who have experienced rapid and significant body weight gain while receiving an INI + TAF/FTC ARV regimen. Approximately, 110 participants will be included in this study. A maximum enrollment of approximately 70% male participants will be utilized to ensure adequate recruitment of female participants. A maximum enrollment of approximately 70% non-black participants will be utilized to ensure adequate recruitment of diverse races.

Eligible participants are to:

- have documented HIV-1 infection currently treated with a stable ARV regimen consisting of an INI combined with TAF/FTC for ≥6 consecutive months preceding the screening visit.
- BMI of ≥18 kg/m^2 at the time of starting an INI + TAF/FTC ARV regimen.
- have a rapid and significant weight gain, defined as a ≥10% increase in body weight within a 36-month time period prior to screening and while on the current INI + TAF/FTC ARV regimen.
- be virologically suppressed, with at least 1 plasma HIV-1 RNA measurement <50 copies/mL occurring between 12 and 2 months prior to screening while being on the stable INI + TAF/FTC ARV regimen and having HIV-1 RNA<50 copies/mL at the screening visit.
- Not have had previous failure on DRV treatment or known documented history of ≥1 DRV resistance-associated mutations (RAMs).

The study will consist of 3 phases: Screening (approximately 30 days [up to a maximum of 6 weeks]), Open-Label Treatment (48 weeks), and Follow-up (for any participant who has an ongoing adverse event (AE) or serious adverse event (SAE) at the time of his/her last study visit).

After obtaining the informed consent form (ICF) from the participant, selection criteria will be reviewed to confirm the participant's eligibility. At baseline (Day 1), participants who meet all eligibility criteria will be randomized in a 1:1 ratio to 1 of the following 2 treatment arms in an open-label manner. Randomization will be stratified by sex (Male or Female) and race (Black/African American or Non-Black/African American) at Baseline.

- **D/C/F/TAF FDC Arm (Immediate Switch):** Switch to a regimen of DRV 800 mg + COBI 150 mg + FTC 200 mg + TAF 10 mg FDC once daily, (n=55) for 48 weeks;
- **Active-Control Arm (Delayed Switch):** Continue current INI + TAF/FTC ARV regimen, (n=55) for 24 weeks. After 24 weeks participants will switch to a regimen of DRV 800 mg + COBI 150 mg + FTC 200 mg + TAF 10 mg FDC once daily for an additional 24 weeks.

Participants randomized to the Immediate Switch Arm must start D/C/F/TAF FDC within 24 hours of the Baseline visit and will continue to receive D/C/F/TAF treatment for a total of 48 weeks. Participants randomized to the Delayed Switch arm, will continue their current INI + TAF/FTC ARV regimen for 24 weeks. After Week 24, all participants in the Delayed Switch Arm will receive the D/C/F/TAF FDC tablet and will be followed for an additional 24 weeks.

Participants will return for study visits at Weeks 4, 12, 24, 36, and 48. Additionally, participants randomized to the Delayed Switch Arm will have a study visit at Week 28 (ie, 4 weeks after switching from the INI + TAF/FTC ARV regimen to D/C/F/TAF FDC). Key metabolic assessments include body weight measurement, body composition assessed via dual-energy x-ray absorptiometry (DEXA) scan, waist circumference measurements, vital sign measurements, select clinical laboratory tests (including fasting lipids, fasting glucose, homeostatic model assessment of insulin resistance [HOMA-IR], HbA1c, leptin, adiponectin), and liver biomarkers. Key efficacy assessments include HIV-1 viral load, $CD4^+/CD8^+$ cell count, and HIV-1 genotype/phenotype resistance testing if necessary. Key safety assessments will include AEs, physical examinations, standard clinical laboratory tests, and pregnancy testing. Concomitant medications will be recorded. Self-reported adherence will be assessed using 4-day recall, and reasons for non-adherence will be monitored. Patient Reported Outcomes (PRO) (Body Shape Questionnaire [BSQ-8D], DAILY EATS, HIV-Symptom Index [HIV-SI], and patient global impression of change [PGIC] including PGIC-S) will be completed.

HIV-1 genotypic and phenotypic resistance testing (using PhenoSense GT® Plus Integrase) will be performed for participants with confirmed virologic rebound (2 consecutive HIV-1 RNA values ≥200 copies/mL at a scheduled or unscheduled visit) and a HIV-1 RNA >400 copies/mL at the time of confirmed rebound or at later timepoints; the confirmatory testing should be conducted 2 to 4 weeks after the initial HIV-1 RNA value ≥200 copies/mL. If genotypic/phenotypic resistance to study intervention is determined, study intervention may be discontinued, and the participant will be referred for continued medical care outside of the study if the decision is made to discontinue study intervention.

Plasma concentrations of DRV and COBI may be determined in participants experiencing virologic rebound using stored blood samples collected throughout the study, if deemed necessary. Plasma concentrations of INIs for the Delayed Switch Arm may be determined in participants experiencing virologic rebound using stored blood samples collected throughout the study, if deemed necessary.

The end of the study is defined as completion of the last data collection visit for the last participants participating in the study. For the purpose of the primary analysis, a participant will be considered to have completed the study if data collection as required per protocol through the complete course of 24 weeks of ART has been completed. The primary analysis of this study will be performed once all participants have completed the Week 24 visit or discontinued earlier. At the end of the study, participants will resume routine clinical care with the care provider who will determine their future care.

A follow-up visit is required for any participant who has an ongoing AE or SAE after completion of the last study-related visit (unless consent is withdrawn).

NUMBER OF PARTICIPANTS

The planned sample size is 110 participants (55 participants per treatment arm). This sample size should provide 80% power to detect a treatment effect size of 0.54 at the significance level of 0.05, 2-sided. An interim analysis (IA) is planned when approximately 60% of the initial planned 110 participants have completed the Week 12 visit and approximately 30% of participants have completed the Week 24 visit to re-estimate the sample size to ensure adequate power for the hypothesis testing. All cumulative data will be used for the interim analysis. Details for the sample size re-estimation (SSR), threshold for the conditional power, and protection of overall significance level will be provided in the statistical analysis plan (SAP) for the IA and monitoring. The planned maximum total sample size after SSR is 150 participants.

INTERVENTION ARMS AND DURATION

Description of Intervention

Eligible participants will be randomized in a 1:1 ratio to the Immediate Switch Arm (switch to D/C/F/TAF FDC) or the Delayed Switch Arm (maintain current INI + TAF/FTC ARV regimen).

- Immediate Switch Arm: D/C/F/TAF FDC (DRV 800 mg + COBI 150 mg + FTC 200 mg + TAF 10 mg FDC) once daily for 48 weeks.
- Delayed Switch Arm: continue current INI + TAF/FTC ARV regimen for 24 weeks. After 24 weeks participants will switch to a regimen of D/C/F/TAF (DRV 800 mg + COBI 150 mg + FTC 200 mg + TAF 10 mg) FDC once daily for an additional 24 weeks.

The D/C/F/TAF FDC tablet must be taken orally with food and with approximately 240 mL (8 ounces) of water. The tablet should be swallowed whole; alternatively, for participants who are unable to swallow the tablet whole, D/C/F/TAF FDC may be split into 2 pieces using a tablet-cutter, and the entire dose should be consumed immediately after splitting. Participants should not attempt to dissolve the tablet in water.

If participants notice that they have missed a D/C/F/TAF FDC intake and it is still within 12 hours of their regular dosing time, they should take the D/C/F/TAF FDC immediately with food. Participants can then continue their usual dosing schedule. If participants notice that they have missed a dose more than 12 hours after the time it is usually taken, they should be instructed not to take it and simply resume the usual dosing schedule. Participants should not take a double dose to make up for a missed dose.

Instructions regarding how to take D/C/F/TAF FDC tablet, what to do if a dose is missed and how to store the D/C/F/TAF FDC tablet will be provided on the wallet (study) card.

For the Delayed Switch Arm, all components of the INI + TAF/FTC ARV regimen should be dosed and administered using the dosing schedule specified in the ARV agent's Prescribing Information.

ASSESSMENTS

Metabolic Assessments

The primary evaluation will be body weight measurements. Participants should be weighed on a calibrated scale wearing underwear and a gown; they will be instructed to take off their shoes and to empty their bladders before being weighed. The scale should be calibrated according to the manufacturer's specifications and at the frequency recommended by the manufacturer before the first participant is weighed. Calibration must be documented in the calibration log.

Systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse rate (supine after at least 5 minutes rest) will be recorded in a quiet setting without distractions, with a completely automated technique. Manual techniques will be used only if an automated device is not available. Body Mass Index (BMI) will be calculated using body weight method described for primary end point and height. Height will be measured at screening using a wall-mounted stadiometer or one mounted on a balance beam scale, whichever is most appropriate for the individual participant. Participants should be wearing socks or barefoot and should not be wearing shoes. Body composition will be assessed via DEXA scans. Waist circumference will be measured with the participant standing, wearing underwear, with or without a gown. The measurement will be performed at a level midway between the superior aspect of the iliac crests and the lower lateral margin of the ribs. The measurement need not be at the level of the umbilicus. The measuring tape will be kept horizontal. Fasting clinical laboratory tests will assess changes in the lipids, calculated HOMA-IR, HbA1c, leptin, adiponectin, and alpha melanocyte-stimulating hormone. Non-alcoholic fatty liver disease (NAFLD) Fibrosis and hypertension, age, insulin, resistance (HAIR) scores will be calculated based on receipt of central laboratory assessments and clinical status of the participant. If a participant has not fasted prior to the visit, the visit may proceed, but participant must return within 72 hours in a fasted state to have a blood draw for the metabolic assessments.

Efficacy Assessments

Blood samples for determination of plasma HIV-1 RNA viral load and immunologic parameters and for HIV-1 genotypic/phenotypic resistance testing (PhenoSense GT® Plus Integrase) will be taken at the time points specified in the Schedule of Assessments (SoA).

Plasma viral load will be measured using a validated assay at a central laboratory (ie, Roche COBAS AmpliPrep/COBAS TaqMan HIV-1 Test, Version 2.0.) The assay linear range is 20 to 10,000,000 copies/mL with a lower limit of quantification (LLOQ) of 20 copies/mL and a limit of detection (LOD) of 20 copies/mL). Immunologic change will be determined by changes in CD4+ cell count (absolute and %). Changes in viral load, changes in CD4+ cell counts (either decreases or increases) or detected resistance will be part of the efficacy analysis and should not be reported as AEs or SAEs.

Participants will be considered to have virologic rebound if they have 2 consecutive HIV-1 RNA values ≥200 copies/mL at a scheduled or unscheduled visit after maintaining HIV-1 RNA <50 copies/mL; confirmatory testing should be conducted 2 to 4 weeks after the initial HIV-1 RNA value ≥200 copies/mL. For participants with confirmed virologic rebound, HIV-1 genotypic and phenotypic resistance testing (PhenoSense GT® Plus Integrase) will be performed on the confirmed rebound sample, if HIV 1 RNA ≥400 copies/mL or on a following visit with HIV-1 RNA ≥400 copies/mL. Genotype/phenotype testing at other time points may be requested if deemed necessary by the sponsor.

Adherence

Treatment adherence for the study will be assessed at all study visits by participant self-report using a 4-day recall.

Safety Assessments

Safety will be evaluated throughout the study from the time a signed and date ICF is obtained until completion of the participant's last study-related activity. The study will include following evaluations of safety:

- AEs;
- Clinical laboratory tests (biochemistry, hematology, urinalysis, urine chemistry);
- Vital signs measurements;
- Physical examination (complete or symptom directed).

Patient Reported Outcomes:

Patient reported outcomes, including the BSQ-8D, DAILY EATS, HIV-SI, and PGIC (including PGIC-S) will be completed.

Pharmacokinetic Assessments

Plasma samples may be used to evaluate the concentration of DRV and COBI in participants experiencing confirmed virologic rebound using stored blood samples collected throughout the study at the discretion of the sponsor. Plasma concentrations of INIs for the Delayed Switch arm may be determined in participants experiencing confirmed virologic rebound using stored blood samples collected throughout the study, if deemed necessary by the sponsor.

STATISTICAL METHODS

Statistical Hypothesis

The statistical hypothesis is the following:

H_0: Dt -Dc=0 vs. H_1: Dt -Dc $\neq$ 0.

Where H_0 is the null hypothesis, H_1 is the alternative hypothesis; Dt=%body weight change from baseline at Week 24 for treatment D/C/F/TAF, Dc for the Delayed Switch arm.

The statistical hypothesis will be tested using repeated measures longitudinal method (linear mixed-effects model) at 0.05 significance level, 2-sided.

For all participants who receive at least 1 dose of study intervention descriptive statistics will be provided. Participant information will be analyzed based on the Intent-to-treat (ITT) population, unless otherwise specified.

Primary Endpoint Analysis: The primary endpoint analysis will be based on the ITT population. It will be evaluated using linear mixed-effects model with participant as random effect adjusted by baseline BMI and stratification factors in a longitudinal data with repeated measures (percent body weight change measured at multiple visits).

Secondary Endpoint Analyses:

Metabolic Analyses: For the metabolic endpoints of change from baseline, the same statistical model as described for the primary endpoint will be used for analysis. Other secondary metabolic endpoints will be analyzed using descriptive statistics.

Resistance/Efficacy Analyses: HIV-1 genotypes, and phenotypes if applicable, will be analyzed from samples of participants with virologic rebound and with HIV-1 RNA ≥400 copies/mL.

Virologic suppression (HIV-1 RNA<50 copies/mL) and failure (HIV-1 RNA ≥50 copies/mL) using the Food and Drug Administration (FDA) Snapshot algorithm in the ITT will also be analyzed as a secondary endpoint at Weeks 24 and 48.

The proportion of participants experiencing virologic rebound through Weeks 24 and 48 will be tabulated using descriptive statistics along with the 95% confidence intervals (CIs). The Wilson (Score) method for the CI will be used. The changes from screening/baseline in $CD4^+$ cell count at Weeks 24 and 48 will be summarized using descriptive statistics.

The number of identified protease (PR) mutations (including International Acquired Immunodeficiency Virus (AIDS) Society [IAS]-USA primary and secondary PI resistance-associated mutations [RAMs], reverse transcriptase (RT) mutations (including International AIDS Society-United States of America [IAS-USA] nucleoside/nucleotide RT inhibitor [N[t]RTI] RAMs, IAS-USA non-nucleoside RT inhibitor [non-N[t]RTI] RAMs), and integrase (INI) mutations (including International AIDS Society [IAS]-USA INI-RAMs and IAS-USA primary INI mutations), as well as specific mutations associated with resistance to DRV, FTC, and TAF, will be tabulated based on the observed virologic rebound through the study period. Retrospectively, fold change (FC) in 50% effective concentration (EC_{50}) of ARVs may be analyzed and tabulated dependent on the number of virologic rebound and phenotypes available through the study period.

Adherence Analyses: Treatment adherence based on participant self-report, using a 4-day recall will be summarized by means of descriptive statistics and frequency tabulations for both D/C/F/TAF FDC and the INI + TAF/FTC ARV regimen.

Adherence rates will be reported according to the proportion of participants missing 0, 1, 2, 3 or 4 doses using participant self-report 4-day recall at Weeks 4, 12, 24, 36, and 48.

Safety Analyses: For all safety endpoints, descriptive statistics will be used to summarize the endpoints.

The verbatim terms used in the case report form (CRF) by investigators to identify AEs will be categorized according to system organ class and graded according to Division of Acquired Immunodeficiency Syndrome (DAIDS).

Summaries, listings, datasets, or participant narratives may be provided, as appropriate, for those participants who die, who discontinue study intervention due to an AE, or who experience a severe or a SAE.

Laboratory data will be summarized by treatment arm and type of laboratory test. Reference ranges and markedly abnormal results (specified in the SAP) will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte and for changes from Screening/Baseline at each scheduled time point. Laboratory abnormalities will be categorized according to analyte and graded according to DAIDS.

Descriptive statistics of vital signs including temperature, pulse/heart rate, body weight, and blood pressure (systolic and diastolic) [(supine)] values and changes from baseline will be summarized at each scheduled time point. The percentage of participants with values beyond clinically important limits will be summarized. Vital signs abnormalities will be categorized according to parameter and graded according to DAIDS.

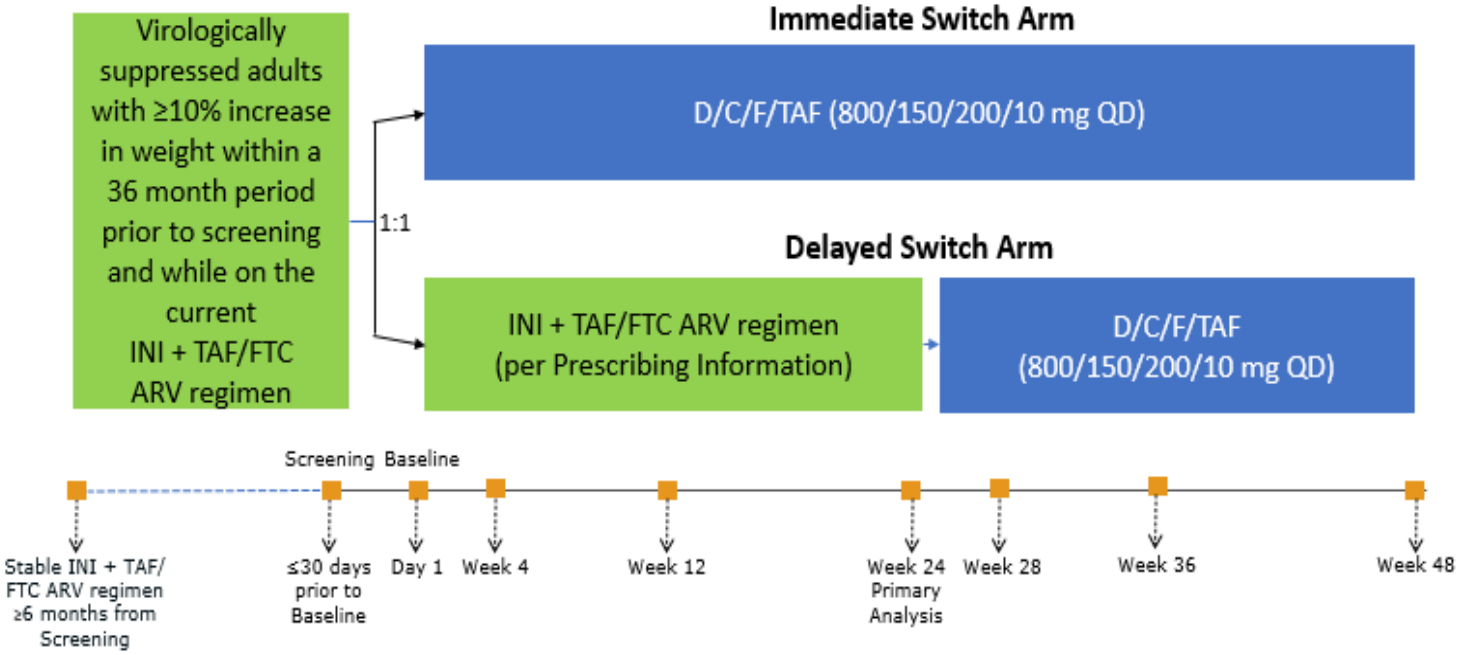
Physical examination findings will be summarized at each scheduled time point. Descriptive statistics will be calculated at baseline and for observed values and changes from baseline at each scheduled time point. Frequency tabulations of the abnormalities will be made.

Patient-reported Outcomes Analyses: Descriptive statistics for absolute values will be calculated for each PRO measure including BSQ-8D, HIV-SI, DAILY EATS, and PGIC and at each timepoint. In addition, changes from baseline in the proportion of participants who have bothersome symptoms (scores of 2, 3 or 4) across all items of the HIV-SI at Weeks 24 and 48, changes from baseline in the proportion of participants who have any symptoms (scores of 1, 2, 3 or 4) across all items of the HIV-SI at Weeks 24 and 48, and changes from baseline in the scores on the BSQ-8D and proportion of participants who have no concern (<19), mild concern (19-25), moderate concern (26-33) or marked concern (>33) with their body shape at Weeks 24 and 48 and changes from baseline in the scores on the DAILY EATS at Weeks 24 and 48 will be summarized. Association between treatment arm and each bothersome symptoms of the HIV-SI adjusting for baseline variables at Weeks 24 will be calculated. To understand meaningful change in scores on PRO measures, PGIC-S will be used as an anchor to assess meaningful change scores for the DAILY EATS in participants living with HIV.

Interim Analysis: An IA will be performed when approximately 60% of the initial 110 planned participants have completed the Week 12 Visit and approximately 30% of participants have completed the Week 24 Visit. At that time, an unblinded SSR will be performed to ensure adequate power for the hypothesis testing for the primary endpoint. More detail will be included in the IA statistical analysis plan (SAP).

1.2. Schema

Figure 1: Schematic Overview of the Study



Abbreviations: ARV = antiretroviral; C = cobicistat; D = darunavir; F or FTC = Emtricitabine; INI = integrase inhibitor; QD = once a day; TAF = Tenofovir Alafenamide

1.3. Schedule of Activities (SoA)

Phase	Screening[a]	Baseline Day 1[b]	48-Weeks Treatment Phase[c]						ESID[e]	30-Day FU[f]	Remarks
Visit			Week 4	Week 12	Week 24	Week 28[d]	Week 36	Week 48			
Study Procedures											
Screening/Administrative											
Informed consent	X										Must be obtained before the first study related activity.
Medical history	X										
Height	X										Measured using a wall mounted stadiometer or one mounted on a balance beam scale, whichever is most appropriate for the individual participant. Participants should be wearing socks or barefoot and should not be wearing shoes.
HBV and HCV testing	X										
Serum pregnancy test	X										Females of childbearing potential only; at central laboratory
FSH test	X										FSH test for female participants who have stopped menstruating for at least 2 years but do not have documentation of ovarian failure.
Inclusion/exclusion criteria	X	X									If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of D/C/F/TAF FDC is given such that he/she no longer meets all eligibility criteria, then the participant should be excluded.
Study Intervention											
Randomization		X									Randomization should be performed on the same day as the baseline visit, provided that all screening procedures have been completed and participant eligibility has been confirmed.
D/C/F/TAF Dispensation/Accountability		X	X	X	X		X	X	X		Immediate Switch Arm
D/C/F/TAF Dispensation/Accountability					X	X	X	X	X		Delayed Switch Arm

Phase	Screening[a]	Baseline Day 1[b]	48-Weeks Treatment Phase[c]						ESID[e]	30-Day FU[f]	Remarks
Visit			Week 4	Week 12	Week 24	Week 28[d]	Week 36	Week 48			
Study Procedures											
Adherence		X	X	X	X	X	X	X	X		Treatment adherence will be assessed by participant self report using a 4 day recall during study visit.
Safety Evaluations											
Vital signs	X	X	X	X	X	X	X	X	X	X	BP, pulse rate (supine after at least 5 minutes rest)
Body weight	X	X	X	X	X	X	X	X	X	X	Attention should be given to weigh the participant on the same scale through the duration of the study. Participants should be weighed wearing underwear and a gown; participants will be instructed to take off their shoes and to empty their bladders before being weighed. Note: if disrobing for weighing is logistically impossible, the participant must be dressed as lightly as possible, with consistency from visit to visit
Waist Circumference Measurement	X	X	X	X	X	X	X	X	X		Measured with the participant standing, wearing underwear, with or without a gown. The measurement will be performed at a level midway between the superior aspect of the iliac crests and the lower lateral margin of the ribs. The measurement need not be at the level of the umbilicus. The measuring tape will be kept horizontal.
Body Composition via DEXA scan		X			X			X	X		Performed between screening and baseline (+2 weeks), at Weeks 24, 48, and the ESID visit (±10 days) (only to be performed at ESID if the last scan is more than 12 weeks from the date of the ESID visit and the ESID visit takes place before Week 48). A rescan for technical reasons at all scheduled time points is allowed within 2 weeks.
Complete physical examination	X	X						X	X		
Symptom-directed physical examination			X	X	X	X	X			X	May be conducted at all other scheduled/unscheduled study visits based on reported safety or tolerability issues.
Concomitant medications	X	X	X	X	X	X	X	X	X	X	

Phase / Visit	Screening[a]	Baseline Day 1[b]	48-Weeks Treatment Phase[c]						ESID[e]	30-Day FU[f]	Remarks
			Week 4	Week 12	Week 24	Week 28[d]	Week 36	Week 48			
Study Procedures											
Adverse events (AEs)	X	X	X	X	X	X	X	X	X	X	In the setting of a suspected renal AE, serum creatinine and urine chemistry will be assessed (creatinine, sodium, phosphate, glucose, protein, albumin).
Fasting Clinical Laboratory Tests											
Chemistry profile	X	X	X	X	X	X	X	X	X	X	
Metabolic profile		X			X			X	X		If a participant has not fasted prior to the visit, the visit may proceed, but participant must return within 72 hours in a fasted state to have a blood draw.
Leptin and Adiponectin		X			X			X	X		
Alpha Melanocyte-Stimulating Hormone		X			X			X	X		
Hematology profile	X	X	X	X	X	X	X	X	X	X	
eGFRcr	X	X	X	X	X	X	X	X	X	X	eGFRcr by Cockcroft Gault
Urinalysis	X	X	X	X	X	X	X	X	X	X	Dipstick. If dipstick results are abnormal, the sediment will be examined microscopically.
Urine Pregnancy test		X	X	X	X	X	X	X	X	X	Females of childbearing potential only. Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator, to establish the absence of pregnancy throughout the study.
Efficacy Evaluations											
Plasma HIV-1 RNA	X	X	X	X	X	X	X	X	X	X	If the HIV 1 RNA value is ≥50 copies/mL a retest should be collected at a scheduled or unscheduled visit, 2 to 4 weeks after availability of the results (except for screening and baseline results). Leftover blood samples from the HIV 1 RNA determinations could be used for protocol related testing (virology, safety, PK analysis) at additional time points.
$CD4^+$ cell count	X	X			X			X	X	X	

Phase / Visit	Screening[a]	Baseline Day 1[b]	48-Weeks Treatment Phase[c]						ESID[e]	30-Day FU[f]	Remarks
			Week 4	Week 12	Week 24	Week 28[d]	Week 36	Week 48			
Study Procedures											
HIV-1 genotype/phenotype			X	X	X	X	X	X	X		Performed using PhenoSense GT® Plus Integrase for participants with confirmed virologic rebound (2 consecutive HIV 1 RNA values ≥200 copies/mL at a scheduled or unscheduled visit after maintaining HIV 1 RNA <50 copies/mL) and a HIV 1 RNA >400 copies/mL at the time of confirmed rebound or later timepoints; confirmatory testing should be conducted 2 to 4 weeks after the initial HIV 1 RNA ≥200 copies/mL.
Whole blood sample storage		X									Will be stored and analyzed using Genosure Archive® if deemed necessary by the sponsor to characterize archived viral resistance.
Patient Reported Outcomes											
Dispense PRO device	X										Device for PROs will be dispensed to all participants during the Screening visit so the participant can complete the 7 days (prebaseline) DAILY EATS. The participants should bring PRO device to required study visits.
DAILY EATS		X			X			X			Completed at home for 7 consecutive days prior to the visit. Study staff should contact the participants prior to the visits to remind the participant to complete the 7 day DAILY EATS.
BSQ-8D		X			X			X	X		Should be completed during the study visit before all other study related procedures to prevent influencing participant perceptions; PGIC and PGIC S should be completed after the BSQ 8D and HIV SI.
HIV-SI		X			X			X	X		
PGIC					X			X	X		

Phase / Visit	Screening[a]	Baseline Day 1[b]	48-Weeks Treatment Phase[c]						ESID[e]	30-Day FU[f]	Remarks
			Week 4	Week 12	Week 24	Week 28[d]	Week 36	Week 48			
Study Procedures											
Other											
Plasma sample storage		X	X	X	X	X	X	X	X		Banked for possible additional protocol related testing (virology, safety). Plasma concentrations of DRV and COBI may be determined in participants experiencing virologic rebound or participants who discontinue the study early and have HIV 1 RNA ≥50 copies/mL using stored blood samples collected throughout the study, if deemed necessary. Plasma concentrations of INIs for the Delayed Switch arm may be determined in participants experiencing virologic rebound using stored blood samples collected throughout the study, if deemed necessary.

AE: adverse events; BP: blood pressure; BSQ 8D: Body Shape Questionnaire; C: cobicistat (Cobi); cm: centimeters; D: darunavir (DRV); DEXA: dual energy X ray absorptiometry; ESID: Early Study Intervention Discontinuation visit; eGFRcr: Creatinine based estimated glomerular filtration rate; F: Emtricitabine; FDC: fixed dose combination; FSH: follicle stimulating hormone; FU: Follow up; HBV: hepatitis B; HCV: hepatitis C; HIV 1 RNA: human immunodeficiency virus type 1 ribonucleic acid; HIV SI: HIV Symptom Index; PGIC: Patient Global Impression of Change; PGIC S: Patient Global Impression of Change–satiety; PRO: patient reported outcome; TAF: tenofovir alafenamide.

Unscheduled visit(s) may be required for safety reasons, for technical issues with the samples, or for confirmation of virologic rebound. When human immunodeficiency virus (HIV) 1 ribonucleic acid (RNA) repeat testing is required at an unscheduled visit, an HIV 1 genotype/phenotype plasma sample and a plasma storage sample should also be drawn at the same unscheduled visit.

a Evaluations to be completed within 30 days prior to baseline (Day 1). The Screening Phase may be extended on a case by case basis after discussion with the sponsor; however, no extensions beyond 6 weeks will be allowed.

b The baseline visit (Day 1) cannot proceed until the investigator has received all results of the screening visit and participant eligibility has been confirmed. Participants randomized to the D/C/F/TAF fixed dose combination (FDC) treatment arm (Immediate Switch) will be dispensed D/C/F/TAF FDC at the baseline visit; initiation of treatment with D/C/F/TAF FDC must take place within 24 hours after the baseline visit.

c All study visits are to be scheduled relative to the baseline visit date (Day 1) and are to occur at the end of Weeks 4, 12, 24, 36 and 48. The visit window is ±7 days of the protocol specified date through Week 48.

d For participants randomized to the Delayed Switch arm; 4 weeks after switch to D/C/F/TAF FDC.

e Participants who prematurely discontinue or change study intervention during the treatment phase (from Day 1 to Week 48) will be required to complete the early study intervention discontinuation (ESID) visit assessments within 1 week of stopping/changing study intervention.

f Required for any participant who has an ongoing adverse event (AE) or serious adverse event (SAE) at the time of his/her last study visit (unless consent is withdrawn); ±7 days window may be used.

2. INTRODUCTION

The primary study intervention is the darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) fixed-dose combination (FDC). The first approval for D/C/F/TAF FDC was granted by the European Commission on 25 September 2017. D/C/F/TAF is launched in Canada, United States of America (USA), Hong Kong, Argentina, Macau, European Union (EU), Norway, Iceland, and Liechtenstein. D/C/F/TAF FDC is a 4-agent tablet for oral once-daily use for the treatment of human immunodeficiency virus (HIV)-1 infection in adults. This tablet contains the protease inhibitor (PI) darunavir (D or DRV) (800 mg), the pharmacokinetic (PK) enhancer cobicistat (COBI or C) (150 mg), the nucleoside reverse transcriptase inhibitor (NRTI) emtricitabine (FTC or F) (200 mg), and the tenofovir (TFV) prodrug tenofovir alafenamide (TAF) (10 mg). The D/C/F/TAF FDC (SYMTUZA®) tablet was approved by the US Food and Drug Administration (FDA) as a complete regimen for the treatment of HIV-1 infection in adults who have no prior antiretroviral (ARV) treatment history or who are virologically-suppressed (human immunodeficiency virus type 1 ribonucleic acid [HIV-1 RNA] less than 50 copies per mL) on a stable ARV regimen for at least 6 months and have no known substitutions associated with resistance to DRV or TFV. [35,36]

The integrase inhibitor (INI) class represents one of the newer mainstream classes of ARVs. Currently, 4 INIs are FDA approved (bictegravir, dolutegravir, elvitegravir/cobicistat, and raltegravir) to treat both treatment naïve and certain treatment experienced patients.[4,17,20,34,36] Co-formulated single tablet regimens containing dolutegravir, elvitegravir/cobicistat and bictegravir have demonstrated favorable efficacy and tolerability profiles in registrational clinical studies.

Tenofovir alafenamide is an approved NRTI for use in combination with other antiretroviral agents for the treatment of HIV-1 infection and is contained in a number of fixed dose combinations or single tablet regimens.[10,14,17,28]

Participants not initially randomized to receive treatment with the D/C/F/TAF FDC will be assigned to maintain treatment on their baseline ARV regimen. The baseline/control ARV regimen in this study will be comprised of an INI + TAF/FTC for 24 weeks. After 24 weeks participants will switch to D/C/F/TAF FDC for an additional 24 weeks.

For the most comprehensive non-clinical and clinical information regarding D/C/F/TAF FDC, refer to the Investigators Brochure.[19] For further information on the INI + TAF/FTC ARV regimens, please refer to ARV-specific Prescribing Information.

The term “study intervention” throughout the protocol, refers to D/C/F/TAF FDC and INI + TAF/FTC ARV regimen; otherwise, the individual study intervention names are used.

The term “sponsor” used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

The term "participant" throughout the protocol refers to the common term "subject".

2.1. Study Rationale

The primary goal of this study is to assess the safety and tolerability of D/C/F/TAF FDC in HIV-1 infected participants who are virologically-suppressed (HIV-1 RNA <50 copies/mL) and have experienced rapid and significant body weight gain on an INI + TAF/FTC ARV regimen.

D/C/F/TAF FDC has been studied in treatment naïve HIV-1 infected patients as well as in virologically-suppressed switch patients. [6,15,29]

The efficacy and safety profile of D/C/F/TAF FDC was examined in 2 Phase 3 clinical studies (AMBER; ClinicalTrials.gov: NCT02431247, a study assessing the efficacy and safety of D/C/F/TAF FDC versus D/C+TDF/FTC in treatment naïve participants[15] and EMERALD; ClinicalTrials.gov: NCT02269917, a study assessing the efficacy and safety of switching to D/C/F/TAF FDC versus staying on a multi-tablet boosted protease inhibitor (PI)-based regimen with TDF/FTC in virologically-suppressed participants.[30] In both studies, D/C/F/TAF FDC demonstrated non-inferior efficacy and a safety profile consistent with that of the individual components of D/C/F/TAF. D/C/F/TAF FDC at Week 48 in these studies demonstrated high virologic response rates, low virologic failure/rebound rates, and there were no observed resistance-associated mutations (RAMs) to DRV or TFV that developed in any participant. Importantly, the safety and tolerability of D/C/F/TAF FDC was demonstrated from these studies, showing overall similar safety versus the control groups through 48 weeks, and low rates (<2%) of discontinuations due to adverse events (AE). In both studies, the change in body weight for participants starting or switching to D/C/F/TAF FDC was minimal. The median change in body weight in AMBER and EMERALD was 1.5 kg and 1.3 kg, respectively, at 48 weeks.

The INI class represents one of the newer mainstream classes of ARVs. Currently, 4 INIs are FDA approved (bictegravir, dolutegravir, elvitegravir/cobicistat, and raltegravir) to treat both treatment naïve and certain treatment experienced patients. Co-formulated single tablet regimens containing dolutegravir, elvitegravir/cobicistat, or bictegravir, in combination with other antiretroviral agents have demonstrated favorable efficacy and tolerability profiles in registrational clinical studies.

While this evidence has supported the placement of these regimens as part of Department of Health and Human Services (DHHS) recommended treatment options for most patients, recent data has suggested the INI class may be associated with significant body weight gain (≥3 kg over 6-12 months) or increases in body mass index (BMI).[2 5,18,22 27] Initially, these data were limited to either case reports,[3] or retrospective observational analyses[4,22,23] in both treatment naïve patients starting an INI-based regimen and suppressed patients switching treatment to an INI-based regimen. Recently, a larger randomized controlled study (NAMSAL ANRS 12313) compared a dolutegravir-based regimen with a low-dose efavirenz based regimen for the treatment of HIV-1 infection in a resource-limited setting. The results of this randomized, Phase 3 study showed the noninferiority of a dolutegravir-based regimen to a low-dose efavirenz based regimen with regard to viral suppression at week 48, however participants receiving treatment with DTG gained 5.0 kg compared to participants receiving treatment with Efavirenz (EFV) who gained 3.0 kg.[25]

Some studies have suggested that these body weight changes may occur rapidly and be sizable. Increases in body weight and/or BMI are of clinical concern, as obesity can lead to other metabolic complications such as hypertension, changes in lipid parameters, and/or insulin resistance, all of which ultimately may increase cardiovascular risk. Furthermore, it is not well understood how to manage patients who experience rapid body weight gain on an INI-based regimen. There is therefore, a need to conduct a well-controlled study of patients who experience rapid body weight gain on an INI-based regimen to examine if switching off the INI-based regimen results in improvement in body weight change and/or metabolic parameters. In a recent analysis of large electronic medical record system, virologically-suppressed patients switching to boosted darunavir demonstrated smaller increases in BMI relative to those patients who switched treatment to dolutegravir.[26]

As the association between INIs and changes in body weight is still being investigated, some have also questioned the role of TAF and changes in body weight. In the ADVANCE study, treatment naive participants were randomized to one of three regimens; dolutegravir with emtricitabine/tenofovir alafenamide, dolutegravir with emtricitabine/tenofovir disoproxil fumarate, or efavirenz/emtricitabine/tenofovir disoproxil fumarate. Over 96 weeks, participants randomized to either of the dolutegravir based regimens gained significantly more body weight compared to those randomized to the efavirenz based regimen. DTG + FTC/TAF 8 kg, DTG + FTC/TDF 5 kg, EFV/FTC/TDF 2 kg, ($p<0.001$ versus EFV/FTC/TDF).[39] In the AMBER study, participants initially randomized to receive D/C+TDF/FTC, and subsequently switched to D/C/F/TAF FDC gained an average of 1.24 kg after 48 weeks of treatment. Similar changes were observed in the EMERALD study when participants switched from a TDF/FTC based regimen to D/C/F/TAF FDC (Data on file). Given this possible relationship, the current study is designed to assess if body weight gain is slowed or reversed in participants already taking an INI-based regimen with TAF, when switching off of the INI to another TAF-based regimen. Therefore, there is plausibility to changes in weight following a switch from an INI to a boosted darunavir regimen in a randomized controlled trial.

TMC114FD2HTX4004 is a Phase 4, 48 week, randomized, active-controlled, open-label, prospective, multicenter, study to evaluate the safety and tolerability of switching to D/C/F/TAF FDC in HIV-1 infected individuals who are virologically-suppressed and have experienced rapid and significant body weight gain on their current stable INI + TAF/FTC ARV regimen.

2.2. Background

Nonclinical Studies

Based on the nonclinical program and clinical experience to date with all 4 compounds, no additive or synergistic toxicology/safety effects are expected for the D/C/F/TAF FDC beyond the expected PK boosting of DRV by COBI. In view of the established nonclinical profile for each of these compounds, new nonclinical studies to support the D/C/F/TAF FDC have not been conducted. The absence of nonclinical safety studies with the combination is in accordance with the FDA Guidance for Industry on the Nonclinical Safety Evaluation of Drug or Combinations.[38,37]

Toxicology

In DRV repeat dose toxicity studies, the key target organs/systems identified in rodents were the hematopoietic system, the blood coagulation system, liver, and thyroid. The effects observed in the liver and thyroid were consistent with the liver enzyme inducing property of DRV. In a 6-month study in rats, the combination of DRV with ritonavir showed a small increase in effect on red blood cell (RBC) count parameters, liver and thyroid in rats. These hematological, liver, and thyroid changes appeared to be not clinically relevant, as in clinical practice, DRV in combination with ritonavir or COBI is generally safe and well tolerated in HIV-infected patients. In COBI repeat-dose toxicity rat studies, the slight hepatocellular hypertrophy and follicular cell hyperplasia/hypertrophy in the thyroid, and the 1 follicular cell carcinoma in the thyroid (1 high-dose male animal in the 26-week study) are considered rodent-specific changes that are commonly seen with microsomal enzyme inducers. Given the species specificity of the effects, these findings are not of concern for humans. Minimal-to-mild increases in liver enzyme activities (alanine aminotransferase [ALT], bilirubin, and alkaline phosphatase [ALP]) were observed in dogs after 4 weeks of dosing, and hepatocyte vacuolation and/or hypertrophy were observed in the liver of dogs treated with COBI in 4-week and 39-week studies. These findings do not indicate a safety concern for D/C/F/TAF FDC.

Given the favorable toxicity profile of FTC and no evidence of overlapping toxicity, combinations with other agents are unlikely to induce new toxicities caused by FTC or to exacerbate the known toxicity of other agents (ie, DRV, COBI, and TAF).

For TAF, kidney (renal tubular karyomegaly and tubular degeneration) and bone (atrophy of metaphyseal cancellous bone) were the primary target organs in rats and dogs. The potential of the 2 renally excreted compounds (FTC and TAF) to interact has not been tested but the combination of FTC and TDF did not exacerbate the renal toxicity of TDF when tested in a 4-week dog study. While the combination of D/C/F/TAF is not anticipated to have an effect on kidney function, monitoring of creatinine along with other standard clinical pathology tests is performed in clinical studies of the D/C/F/TAF FDC.

DRV, COBI, and FTC have not shown any potential for bone toxicity in chronic rat and dog toxicity studies; thus, exacerbation of any TAF effects on bone is not expected with the D/C/F/TAF FDC. There were no drug-related effects on ophthalmic exams or microscopic exams of ocular tissue observed in repeat dose toxicity studies in mice (up to 13 weeks), rats (up to 26 weeks), and nonhuman primates (4 weeks) or in the 4-week dog toxicology study. None of the 4 components had positive

findings in genotoxicity studies. The combination of the 4 components is not expected to have an altered genotoxicity profile as compared with that of the individual agents. Carcinogenicity studies with DRV showed an increase in the incidence of hepatocellular adenomas and carcinomas in mice and rats and thyroid follicular cell adenomas in male rats, at exposure levels below those observed in humans at the recommended therapeutic doses. These findings are considered to be of limited to no relevance to humans based on mechanistic and epidemiological data. Although data is not available for all 4 compounds, it is considered unlikely that combination dosing would change these profiles based on the TAF chronic data and TDF carcinogenicity data.

No significant adverse effects have been observed in developmental toxicity studies with DRV, COBI, FTC, or TAF. No significant adverse effects have been observed in fertility toxicity studies with DRV, COBI, or FTC. The combination of the 4 components is not expected to have an altered reproductive toxicity profile based on the TAF chronic data and TDF reproductive toxicity data.

Overall, DRV safety pharmacology studies did not detect any significant nonclinical safety signals. The thorough QT studies (TMC114-C153, GS-US-216-0107 and GS-US-120-0107) were interpreted as negative according to the E14 International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guidelines since the results demonstrated that administration of respectively DRV/ ritonavir 1600/100 mg or 800/100 mg for 7 days, COBI doses of 250 mg or 400 mg, and TAF doses of 25 or 125 mg are not associated with a clinically relevant increase in QT interval.

Pharmacokinetic and Metabolism Profile

After oral administration, DRV was rapidly absorbed and eliminated. DRV is primarily eliminated by metabolism via the cytochrome 3A (CYP3A) iso-enzyme. DRV was an inhibitor of CYP3A4 at clinically relevant concentrations and showed a concentration-dependent effect on CYP3A4 induction in vitro. The exposure to DRV in humans was equivalent when co-administered with COBI as a booster compared to ritonavir as a booster.

After moderate doses of COBI, oral bioavailability in nonclinical species was low due to metabolic instability and resulting high first-pass elimination. COBI is a mechanism-based inactivators (MBIs) of human CYP3A enzymes. Overall, the difference in boosting effect of COBI across species including human is similar to that for ritonavir.

Emtricitabine shows high passive permeability. Emtricitabine does not undergo extensive first-pass or systemic metabolism and is eliminated primarily by renal excretion of unchanged drug. The total body clearance of FTC exceeds the glomerular filtration rate (GFR), suggesting the drug is actively secreted by renal tubules into the urine. TAF is a prodrug of TFV which is intracellularly converted to its pharmacologically active Tenofovir-diphosphate (TFV-DP) by cellular enzymes including Hepatic extraction of TAF was estimated to be approximately 65% in dogs. Renal excretion is the primary systemic route of elimination of TFV in all preclinical species tested.

Clinical Studies

The development program of the D/C/F/TAF FDC product is based on 7 clinical studies conducted with the D/C/F/TAF FDC, including 2 completed pivotal Phase 3 studies in anti-retroviral therapy (ART)-naïve and ART-experienced, virologically-suppressed HIV-1 infected participants (Studies TMC114FD2HTX3001 and TMC114IFD3013), 1 completed Phase 2 study in HIV-1 infected, ART-naïve participants (Study GS-US-299-0102), and 4 completed Phase 1 studies in healthy participants (Studies GS-US-299-0101, TMC114FD2HTX1001, TMC114FD2HTX1002, and TMC114FD2HTX1004).

Human Pharmacokinetics

The PK properties of the D/C/F/TAF FDC have been evaluated in healthy adult volunteers and in HIV-1 infected participants. DRV is primarily metabolized by CYP3A. COBI is an MBI of CYP3A, thereby enhancing the plasma concentrations of DRV considerably, to a similar extent as another PK booster, ritonavir. FTC is a nucleoside analogue of 2'-deoxycytidine, which is phosphorylated by cellular enzymes to form FTC triphosphate. TAF is a phosphonoamidate prodrug of TFV (2'-deoxyadenosine monophosphate analogue) and intracellular TFV is subsequently phosphorylated to the pharmacologically active metabolite TFV-DP. Once daily dosing of the D/C/F/TAF 800/150/200/10 mg FDC tablet in healthy volunteers resulted in similar drug exposures as the individual components. For information on absorption, distribution, metabolism, and elimination of the components of the D/C/F/TAF FDC tablets.[19]

Efficacy/Safety Studies

Below, an overview is provided of the clinical data that are relevant to the stage of clinical development of the D/C/F/TAF FDC: ie, Week-48 results from the pivotal Phase 3 studies in antiretroviral treatment (ART)-naïve (Study TMC114FD2HTX3001) and ART-experienced, virologically-suppressed participants (Study TMC114IFD3013), data on use of DRV/COBI in pregnant HIV-1 infected women, updated drug-drug interactions, information on marketing experience and updated reference safety information.

Efficacy

The Week-48 results from the 2 pivotal Phase 3 TMC114FD2HTX3001 and TMC114IFD3013 studies with the D/C/F/TAF FDC tablet demonstrate the following:

High response rate (defined as HIV-1 RNA <50 copies/mL; Food and Drug Administration [FDA]-defined snapshot approach) comparable to a control treatment in the randomized, active-controlled, double-blind, Phase 3 Study TMC114FD2HTX3001 in HIV-1 infected, ART-naïve participants: in the intent-to-treat (ITT) population, the proportion of virologic responders at Week 48 was 91.4% with the D/C/F/TAF FDC versus 88.4% with the control treatment (DRV/COBI+F/TDF). Very low virologic rebound rate (2.5% with the D/C/F/TAF FDC versus 2.1% with the control treatment consisting of a boosted PI combined with F/TDF) and high response rate (94.9% with the D/C/F/TAF FDC versus 93.7% with the control treatment) at Week 48 in the randomized, active-controlled, open-label, Phase 3 Study TMC114IFD3013 in HIV-1 infected, ART-experienced, virologically-suppressed (HIV-1 RNA <50 copies/mL) participants.

Immunologic benefits of treatment with the D/C/F/TAF FDC were demonstrated by increases in $CD4^+$ cell counts and were similar to control treatment. In the Phase 3 studies with the D/C/F/TAF FDC, no genotypic or phenotypic resistance was observed against DRV and TAF. Development of resistance to FTC was rare (1 participant treated with D/C/F/TAF developed an M184I/V mutation, conferring resistance to FTC).

Safety and Tolerability

Treatment with the D/C/F/TAF FDC was generally safe and well tolerated. No new adverse drug reactions (ADRs) were identified in the Week-48 analysis of the Phase 3 studies compared to the previously identified ADRs.[19]

2.3. Benefit-Risk Assessment

2.3.1. Benefits for Study Participation

The evidence for a positive benefit-risk balance for the D/C/F/TAF FDC is based on the favorable benefit-risk balance of the single agents (ie, DRV, COBI, FTC, and TAF), the FDCs DRV/COBI and FTC/TAF, and the completed and ongoing clinical studies with the D/C/F/TAF FDC.

Based on a review of nonclinical and clinical data, epidemiologic information, and scientific literature, no new data have been identified that modify the benefit-risk profile of the D/C/F/TAF FDC during the drug safety update report (DSUR) reporting period.[11] The D/C/F/TAF FDC continues to demonstrate a favorable benefit-risk profile. The sponsor will continue to monitor suspect adverse reactions in association with the use of the D/C/F/TAF FDC. Continuous safety monitoring will ensure that updated safety information is available. More detailed information about the known and expected benefits and risks of D/C/F/TAF FDC tablet may be found in the Investigator's Brochure.[19]

2.3.2. Benefit-Risk Assessment Considerations for Study Participation

Increases in body weight and/or BMI are of clinical concern, as obesity can lead to other metabolic complications such as hypertension, changes in lipid parameters, and/or insulin resistance, all of which ultimately may increase cardiovascular risk. This study aims to switch virologically-suppressed participants who have gained significant weight on an INI + TAF/FTC regimen to D/C/F/TAF FDC to understand if this weight gain can be attenuated or reversed.

The DHHS guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV acknowledge that switching virologically-suppressed patients to a new regimen may be prompted by AEs, such as weight gain for example. The Panel recommends carefully reviewing patient's antiviral treatment history and or available resistance test results to ensure the new regimen will maintain virologic suppression.

As part of this study, participants must not have had prior virologic failure on a darunavir based regimen and have no known darunavir resistance associated mutations. As D/C/F/TAF FDC has demonstrated high virologic response rates and low virologic rebound rates in virologically-

suppressed patients, and the proposed use of D/C/F/TAF FDC in this study is similar to that of study TMC114IFD3013, the risk of deleterious virologic outcomes is very likely minimal.

When switching treatments there is always the possibility of new onset adverse drug reactions. Based on data from 2 pivotal clinical studies TMC114FD2HTX3001 and TMC114IFD3013, the overall safety profile of D/C/F/TAF FDC has been well described. The most common adverse drug reactions (occurring at rates ≥1/10) are diarrhea, headache, and rash. Participants will be monitored clinically for AEs, and undergo relevant laboratory testing as outlined in the Schedule of Activities (SoA).

It is unknown if switching to D/C/F/TAF FDC will yield clinically relevant changes in body weight in patients who have gained weight on an INI + TAF/FTC ARV regimen. In study TMC114IDF3013, participants switching from a boosted-protease based regimen in combination with tenofovir disoproxil fumarate/emtricitabine to D/C/F/TAF FDC experienced a median increase in body weight of 1.3 kg through 48 weeks, while those remaining on boosted-protease based regimen in combination with tenofovir disoproxil fumarate/emtricitabine experienced a median increase in body weight of 0.5 kg. It is possible that TAF may contribute to changes in body weight. In study TMC114FD2HTX3001, treatment naive participants receiving D/C/F/TAF FDC experienced a median increase in body weight of 1.5 kg versus 0.0 kg for those participants assigned to darunavir/cobicistat in combination with tenofovir disoproxil fumarate/emtricitabine. As this study population will already be on a regimen containing TAF, the risk of additional weight gain associated with TAF is considered minimal.

Considering the measures taken to minimize risk to participants of this study, the potential risks identified in association with D/C/F/TAF FDC are justified by the potential benefits that may be afforded to virologically-suppressed HIV-1 infected participant experiencing rapid body weight gain with an INI + TAF/FTC ARV regimen.

3. OBJECTIVES AND ENDPOINTS

3.1. Week 24 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the percent change in body weight when switching to D/C/F/TAF FDC (Immediate Switch Arm) compared to continuing the current INI + TAF/FTC ARV regimen (Delayed Switch Arm) in virologically-suppressed (HIV-1 RNA <50 copies/mL) HIV-1 infected participants who have experienced rapid and significant body weight gain	• Percent change from Baseline in body weight at Week 24
Secondary	
Metabolic	
• To assess changes in body weight when switching to D/C/F/TAF FDC (Immediate Switch Arm) compared to continuing the current INI + TAF/FTC ARV regimen (Delayed Switch Arm)	• Change from Baseline in absolute body weight at Week 24 • Proportion of participants with % change in body weight >3% at Week 24 • Proportion of participants with % change in body weight >5% at Week 24 • Change from Baseline in BMI at Week 24
• To assess changes in body composition when switching to D/C/F/TAF FDC (Immediate Switch Arm) compared to continuing the current INI + TAF/FTC ARV regimen (Delayed Switch Arm)	• Change from Baseline in body composition as measured by DEXA scan at Week 24 • Change from Baseline in waist circumference at Week 24
• To assess change in blood pressure when switching to D/C/F/TAF FDC (Immediate Switch Arm) compared to continuing the current INI + TAF/FTC ARV regimen (Delayed Switch Arm)	• Change in SBP and DBP from Baseline at Week 24
• To assess changes in clinical laboratory tests when switching to D/C/F/TAF FDC (Immediate Switch Arm) compared to continuing the current INI + TAF/FTC ARV regimen (Delayed Switch Arm)	• Change from Baseline in fasting lipids at Week 24 • Change from Baseline in fasting glucose at Week 24 • Change from Baseline in HOMA-IR at Week 24 • Change from Baseline in HbA1c at Week 24 • Change from Baseline in leptin and adiponectin at Week 24
• To assess changes in liver biomarkers when switching to D/C/F/TAF FDC (Immediate Switch Arm) compared to continuing the current INI + TAF/FTC ARV regimen (Delayed Switch Arm)	• Change from Baseline in the proportion of participants with advanced fibrosis according to the NAFLD fibrosis score at Week 24 • Change from Baseline in the proportion of participants at high risk of NASH according to the HAIR score at Week 24
• To assess changes in concomitant medications of interest (including anti-hypertensive, anti-hyperglycemic, and lipid lowering agents) when switching to D/C/F/TAF FDC (Immediate Switch Arm) compared to continuing the current INI + TAF/FTC ARV regimen (Delayed Switch Arm)	• Proportion of participants having a dose-reduction or complete withdrawal of anti-hypertensive, anti-hyperglycemic, or lipid lowering agents in the Immediate Switch Arm or Delayed Switch Arm from Baseline to Week 24 • Proportion of participants initiating an anti-hypertensive, anti-hyperglycemic, or lipid lowering agent in the Immediate Switch Arm or Delayed Switch Arm from Baseline to Week 24

Objectives	Endpoints
Safety	
• To evaluate the safety of switching to D/C/F/TAF FDC (Immediate Switch Arm) compared to continuing the current INI + TAF/FTC ARV regimen (Delayed Switch Arm)	• Incidence of any Grade AEs (related and not related) through Week 24 • Incidence of Grade 3 and 4 AEs (related and not related) through Week 24 • Incidence of discontinuations due to AEs through Week 24 • Incidence of SAEs (related and not related) through Week 24 • Change from Baseline in clinical laboratory tests through Week 24 • Incidence of Grade 3 and 4 laboratory abnormalities through Week 24
Efficacy	
• To evaluate the virologic outcomes when switching to D/C/F/TAF FDC (Immediate Switch Arm) compared to continuing the current INI + TAF/FTC ARV regimen (Delayed Switch Arm)	• Proportion of participants with confirmed virologic rebound through Week 24 • Proportion of participants with virologic response (HIV-1 RNA<50 copies/mL) at Week 24 according to the FDA snapshot algorithm • Proportion of participants with virologic failure (HIV-1 RNA ≥50 copies/mL) at Week 24 according to the FDA snapshot algorithm • Proportion of participants having virologic response (HIV-1 RNA<200 copies/mL) at Week 24 according to the FDA snapshot algorithm • Proportion of participants having virologic failure (HIV-1 RNA ≥200 copies/mL) at Week 24 according to the FDA snapshot algorithm
• To evaluate immunological changes when switching to D/C/F/TAF FDC (Immediate Switch Arm) compared to continuing the current INI + TAF/FTC ARV regimen (Delayed Switch Arm)	• Change from Baseline in CD4+ cell count at Week 24
Resistance	
• To assess viral resistance in participants with confirmed HIV-1 RNA rebound for participants switching to D/C/F/TAF FDC (Immediate Switch Arm) compared to continuing the current INI + TAF/FTC ARV regimen (Delayed Switch Arm)	• Proportion of participants with pre-baseline PR, RT, and INI RAMs based on historical genotypes • Incidence of observed genotypic and phenotypic ARV resistance for participants meeting HIV-1 RNA rebound criteria through Week 24 • Proportion of participants with newly identified post-baseline RAMs and phenotypic resistance compared to pre-baseline resistance tests when available, upon meeting confirmed virologic rebound through Week 24
PROs	
• To assess changes in the burden of common symptoms associated with HIV treatment or disease for participants switching to D/C/F/TAF FDC (Immediate Switch Arm) compared to continuing the current INI + TAF/FTC ARV regimen (Delayed Switch Arm)	• Change from Baseline in the proportion of participants who have bothersome symptoms (scores of 2, 3 or 4) across all items of the HIV-SI at Week 24 • Change from Baseline in the proportion of participants who have any symptoms (scores of 1, 2, 3 or 4) across all items of the HIV-SI at Week 24 • Association between treatment arm and each bothersome symptom of the HIV-SI adjusting for Baseline variables at Week 24

Objectives	Endpoints
• To describe responses on the PGIC in participants switching to D/C/F/TAF FDC (Immediate Switch Arm) and in participants continuing the current INI + TAF/FTC ARV regimen (Delayed Switch Arm)	• PGIC at Week 24
Adherence	
• To evaluate adherence in participants switching to D/C/F/TAF FDC (Immediate Switch Arm) compared to continuing the current INI + TAF/FTC ARV regimen (Delayed Switch Arm)	• Adherence rates by participant self-report using 4-day recall at Weeks 4, 12 and 24
Exploratory	
Exploratory clinical biomarker	
• To assess changes in alpha-melanocyte stimulating hormone when switching to D/C/F/TAF FDC (Immediate Switch Arm) compared to continuing the current INI + TAF/FTC ARV regimen (Delayed Switch Arm)	• Change from Baseline in alpha melanocyte-stimulating hormone at Week 24
Exploratory PROs	
• To assess changes in eating-related concepts (hunger, appetite, cravings, and satiety) for participants switching to D/C/F/TAF FDC (Immediate Switch Arm) compared to continuing the current INI + TAF/FTC ARV regimen (Delayed Switch Arm)	• Change from Baseline in the scores on the DAILY EATS at Week 24
• To assess changes in concerns about body shape for participants switching to D/C/F/TAF FDC (Immediate Switch Arm) compared to continuing the current INI + TAF/FTC ARV regimen (Delayed Switch Arm)	• Change from Baseline in the scores on the BSQ-8D at Week 24 • Change from Baseline in the proportion of participants who have no concern (<19), mild concern (19-25), moderate concern (26-33) or marked concern (>33) with their body shape at Week 24

Abbreviations: AE: adverse event, ARV: antiretroviral, BMI: body mass index, BSQ 8D: body shape questionnaire, D/C/F/TAF FDC: Darunavir/Cobicistat/Emtricitabine/Tenofovir Alafenamide Fixed dose Combination, DBP: diastolic blood pressure, DEXA: dual energy X ray absorptiometry, FDA: Food Drug Administration, FTC: emtricitabine, HAIR: hypertension, age, insulin, resistance, HIV 1 RNA: human immunodeficiency virus type 1 ribonucleic acid, HIV SI: HIV Symptom Index, HOMA IR: homeostatic model assessment of insulin resistance, INI: integrase, NAFLD: non alcoholic fatty liver disease, NASH: Nonalcoholic fatty liver disease, PGIC: patient global impression of change, PR: protease, PROs: patient reported outcomes, RT: reverse transcriptase, SAE: serious adverse event, SBP: systolic blood pressure.

3.2. Week 48 Objectives and Endpoints

Objectives	Endpoints
Secondary	
Metabolic	
• To assess the percent change in body weight when switching to D/C/F/TAF FDC (Immediate Switch Arm)	• Percent change from Baseline in body weight at Week 48
• To assess change in body weight when switching to D/C/F/TAF FDC (Immediate Switch Arm)	• Change from Baseline in absolute body weight at Week 48 • Proportion of participants with % change in body weight >3% at Week 48 • Proportion of participants with % change in body weight >5% at Week 48 • Change from Baseline in BMI at Week 48
• To assess changes in body composition when switching to D/C/F/TAF FDC (Immediate Switch Arm)	• Change from Baseline in body composition as measured by DEXA scan at Week 48 • Change from Baseline in waist circumference at Week 48
• To assess change in blood pressure when switching to D/C/F/TAF FDC (Immediate Switch Arm)	• Change in SBP and DBP from Baseline at Week 48
• To assess changes in clinical laboratory tests when switching to D/C/F/TAF FDC (Immediate Switch Arm)	• Change from Baseline in fasting lipids at Week 48 • Change from Baseline in fasting glucose at Week 48 • Change from Baseline in HOMA-IR at Week 48 • Change from Baseline in HbA1c at Week 48 • Change from Baseline in leptin and adiponectin at Week 48
• To assess changes in liver biomarkers when switching to D/C/F/TAF FDC (Immediate Switch Arm)	• Change from Baseline in the proportion of participants with advanced fibrosis according to the NAFLD fibrosis score at Week 48 • Change from Baseline in the proportion of participants at high risk of NASH according to the HAIR score at Week 48
• To assess changes in concomitant medications of interest (including anti-hypertensive, anti-hyperglycemic, and lipid lowering agents) when switching to D/C/F/TAF FDC (Immediate Switch Arm)	• Proportion of participants having a dose-reduction or complete withdrawal of anti-hypertensive, anti-hyperglycemic, or lipid lowering agents in the Immediate Switch Arm from Baseline to Week 48 • Proportion of participants starting an anti-hypertensive, anti-hyperglycemic, or lipid lowering agent in the Immediate Switch Arm from Baseline to Week 48
Safety	
• To evaluate the safety of switching to D/C/F/TAF FDC (Immediate Switch Arm)	• Incidence of any Grade AEs (related and not related) through Week 48 • Incidence of Grade 3 and 4 AEs (related and not related) through Week 48 • Incidence of discontinuations due to AEs through Week 48 • Incidence of SAEs (related and not related) through Week 48 • Change from Baseline in clinical laboratory tests through Week 48 • Incidence of Grade 3 and 4 laboratory abnormalities through Week 48
Efficacy	
• To evaluate the virologic outcomes when switching to D/C/F/TAF FDC (Immediate Switch Arm)	• Proportion of participants with confirmed virologic rebound through Week 48

Objectives	Endpoints
	• Proportion of participants with virologic response (HIV-1 RNA<50 copies/mL) at Week 48 according to the FDA snapshot algorithm • Proportion of participants with virologic failure (HIV-1 RNA ≥50 copies/mL) at Week 48 according to the FDA snapshot algorithm • Proportion of participants having virologic response (HIV-1 RNA<200 copies/mL) at Week 48 according to the FDA snapshot algorithm • Proportion of participants having virologic failure (HIV-1 RNA ≥200 copies/mL) at Week 48 according to the FDA snapshot algorithm
• To evaluate immunological changes when switching to D/C/F/TAF FDC (Immediate Switch Arm)	• Change from Baseline in CD4+ cell count at Week 48
Resistance	
• To assess viral resistance in participants with confirmed HIV-1 RNA rebound when switching to D/C/F/TAF FDC	• Incidence of observed genotypic and phenotypic ARV resistance for participants meeting HIV-1 RNA rebound criteria through Week 48 • Proportion of participant with newly identified post-baseline RAMs and phenotypic resistance compared to pre-baseline resistance tests when available, upon meeting confirmed virologic rebound through Week 48
PROs	
• To assess changes in the burden of common symptoms associated with HIV treatment or disease for participants switching to D/C/F/TAF FDC (Immediate Switch Arm)	• Change from Baseline in the proportion of participants who have bothersome symptoms (scores of 2, 3 or 4) across all items of the HIV-SI at Week 48 • Change from Baseline in the proportion of participants who have any symptoms (scores of 1, 2, 3 or 4) across all items of the HIV-SI at Week 48
• To describe responses on the PGIC in participants switching to D/C/F/TAF FDC (Immediate Switch Arm)	• PGIC at Week 48
Adherence	
• To evaluate adherence in participants switching to D/C/F/TAF FDC (Immediate Switch Arm)	• Adherence rates by participant self-report using 4-day recall at Weeks 36 and 48
Exploratory	
Exploratory clinical biomarker	
• To assess changes in alpha melanocyte-stimulating hormone when switching to D/C/F/TAF FDC (Immediate Switch Arm)	• Change from Baseline in alpha melanocyte-stimulating hormone at Week 48
Exploratory PROs	
• To assess changes in eating-related concepts (hunger, appetite, cravings, and satiety) for participants switching to D/C/F/TAF FDC (Immediate Switch Arm)	• Change from Baseline in the scores on the DAILY EATS at Week 48
• To assess changes in concerns about body shape for participants switching to	• Change from Baseline in the scores on the BSQ-8D at Week 48

Objectives	Endpoints
D/C/F/TAF FDC (Immediate Switch Arm)	• Change from Baseline in the proportion of participants who have no concern (<19), mild concern (19-25), moderate concern (26-33) or marked concern (>33) with their body shape on the BSQ-8D at Week 48

Abbreviations: AE: adverse event, ARV: antiretroviral, BMI: body mass index, BSQ 8D: body shape questionnaire, D/C/F/TAF FDC: Darunavir/Cobicistat/Emtricitabine/Tenofovir Alafenamide Fixed dose Combination, DBP: diastolic blood pressure, DEXA: dual energy X ray absorptiometry, FDA: Food Drug Administration, FTC: emtricitabine, HAIR: hypertension, age, insulin, resistance, HIV 1 RNA: human immunodeficiency virus type 1 ribonucleic acid, HIV SI: HIV Symptom Index, HOMA IR: homeostatic model assessment of insulin resistance, INI: integrase, NAFLD: non alcoholic fatty liver disease, NASH: Nonalcoholic fatty liver disease, PGIC: patient global impression of change, PR: protease, PROs: patient reported outcomes, RT: reverse transcriptase, SAE: serious adverse event, SBP: systolic blood pressure.

3.3. Consistency of Effect of Baseline to Week 24 (Immediate Switch) versus Week 24 to Week 48 (Delayed Switch)

Additional secondary objectives/endpoints will evaluate the consistency of effect on outcomes from Baseline to Week 24 in the Immediate Switch Arm versus the Week 24 to Week 48 in the Delayed Switch Arm. The endpoints for the Delayed Switch Arm from Week 24 to Week 48 are the same as for the Immediate Switch to Week 24. Comparison will be made descriptively to evaluate the consistence of outcomes between these two arms for each endpoint.

Refer to Section 8, Study Assessments and Procedures for evaluations related to endpoints.

HYPOTHESIS

Based on the primary endpoint, the percent change in body weight at Week 24 from baseline in the Immediate Switch Arm is less than that of the Delayed Switch Arm (INI + TAF/FTC ARV).

4. STUDY DESIGN

4.1. Overall Design

This is a randomized, 48 week, active-controlled, open-label, prospective, multicenter, Phase 4 study to evaluate the safety and tolerability of switching to D/C/F/TAF FDC compared to continuing the current INI + TAF/FTC ARV regimen in virologically-suppressed HIV-1 infected adult participants who have experienced rapid and significant body weight gain while receiving an INI + TAF/FTC ARV regimen.

Approximately 110 participants will be included in this study. A maximum enrollment of approximately 70% male participants will be utilized to ensure adequate recruitment of female participants. A maximum enrollment of approximately 70% non-black participants will be utilized to ensure adequate recruitment of diverse races. Eligible participants are to:

- have documented HIV-1 infection currently treated with a stable ARV regimen consisting of an INI combined with TAF/FTC for ≥6 consecutive months preceding the screening visit,
- body mass index (BMI) of ≥18 kg/m^2 at the time of starting an INI + TAF/FTC ARV regimen,
- have a rapid and significant weight gain, defined as a ≥10% increase in body weight within a 36-month time period prior to screening and while on the current INI + TAF/FTC ARV regimen,

- be virologically-suppressed, with at least 1 plasma HIV-1 RNA measurement <50 copies/mL occurring between 12 and 2 months prior to screening while being on the stable INI + TAF/FTC ARV regimen and having HIV-1 RNA<50 copies/mL at the screening visit,

Not have had previous failure on DRV treatment or known documented history of ≥1 DRV resistance associated mutations (RAMs).

The study will consist of 3 phases:

- Screening (approximately 30 days [up to a maximum of 6 weeks])
- Open-Label Treatment (48 weeks)
- Follow-up (for any participant who has an ongoing AE or serious adverse event (SAE) at the time of his/her last study visit).

Screening Phase

The informed consent form (ICF) must be signed before any study-specific procedures at the start of the Screening Phase. After obtaining the ICF from the participant, selection criteria will be reviewed to confirm the participant's eligibility. At baseline (Day 1), participants who meet all eligibility criteria will be randomized in a 1:1 ratio to 1 of the following 2 treatment arms. Randomization will be stratified by sex (Male or Female) and race (Black/African American or Non-Black/African American) at Baseline. All enrolled participants will be assigned randomized treatments in an open-label manner.

- **D/C/F/TAF FDC Arm (Immediate Switch):** Switch to a regimen of DRV 800 mg + COBI 150 mg + FTC 200 mg + TAF 10 mg FDC once daily, (n 55) for 48 weeks;
- **Active-Control Arm (Delayed Switch):** Continue current INI + TAF/FTC ARV regimen, (n 55) for 24 weeks. After 24 weeks participants will switch to a regimen of DRV 800 mg + COBI 150 mg + FTC 200 mg + TAF 10 mg FDC once daily for an additional 24 weeks.

Treatment Phase

Participants randomized to the Immediate Switch Arm must start D/C/F/TAF FDC within 24 hours of the Baseline visit and will continue to receive D/C/F/TAF treatment for a total of 48 weeks.

Participants randomized to the Delayed Switch Arm, will continue their current INI + TAF/FTC ARV regimen for 24 weeks. After Week 24, all participants in the Delayed Switch Arm will receive the D/C/F/TAF FDC tablet and will be followed for an additional 24 weeks.

Participants will return for study visits at Weeks 4, 12, 24, 36, and 48. Additionally, participants randomized to the Delayed Switch Arm will have a study visit at Week 28 (ie, 4 weeks after switching from the INI + TAF/FTC ARV regimen to D/C/F/TAF FDC).

Key metabolic assessments include body weight measurements, body composition assessed via dual-energy x-ray absorptiometry (DEXA) scan, waist circumference measurements, vital sign measurements, select clinical laboratory tests (including fasting lipids, fasting glucose, homeostatic model assessment of insulin resistance [HOMA-IR], HbA1c, leptin, adiponectin), and liver biomarkers. Key efficacy assessments include HIV-1 viral load, $CD4^+/CD8^+$ cell count, and HIV-1

genotype/phenotype resistance testing (using PhenoSense GT® Plus Integrase), if necessary (refer to Section 8.1). Key safety assessments will include AEs, physical examinations, standard clinical laboratory tests, and pregnancy testing. Concomitant medications will be recorded. D/C/F/TAF FDC study intervention accountability and reasons for non-adherence will be monitored (refer to Section 8.2). Patient Reported outcomes (body shape questionnaire [BSQ-8D], DAILY EATS, HIV-Symptom Index [HIV-SI], and patient global impression of change [PGIC including PGIC-S]) will be completed.

Unscheduled visits can be conducted as needed based on individual tolerability issues, or virologic reasons (ie, suspected virologic rebound) that occur between scheduled visits.

HIV-1 genotypic and phenotypic resistance testing (PhenoSense GT® Plus Integrase) will be performed for participants with confirmed virologic rebound (2 consecutive HIV-1 RNA values ≥200 copies/mL at a scheduled or unscheduled visit) and a HIV-1 RNA >400 copies/mL at the time of confirmed rebound or at later timepoints. The confirmatory testing should be conducted 2 to 4 weeks after the initial HIV-1 RNA value ≥200 copies/mL. If genotypic/phenotypic resistance to study intervention is determined, study intervention may be discontinued, and the participant will be referred for continued medical care outside of the study if the decision is made to discontinue study intervention.

Plasma concentrations of DRV and COBI may be determined in participants experiencing virologic rebound using stored blood samples collected throughout the study, if deemed necessary. Plasma concentrations of INIs for the Delayed Switch Arm may be determined in participants experiencing virologic rebound using stored blood samples collected throughout the study, if deemed necessary.

The end of the study is defined as completion of the last data collection visit for the last participant participating in the study. For the purpose of the primary analysis, a participant will be considered to have completed the study if data collection as required per protocol through the complete course of 24 weeks of ART has been completed. The primary analysis of this study will be performed once all participants have completed the Week 24 visit or discontinued earlier. An interim analysis (IA) will be performed when approximately 60% of the planned 110 participants have completed the Week 12 visit and approximately 30% of participants have completed the Week 24 visit to assess sample size re-estimation (SSR) unblinded to ensure adequate power for the hypothesis testing for the primary endpoint.

Early Study Intervention Discontinuation (ESID): Participants who prematurely discontinue study intervention but have not withdrawn consent will be required to complete ESID assessments as soon as possible but within no later than 1 week of discontinuing study intervention.

At the end of the study (or at ESID), participants will resume routine clinical care with the care provider who will determine their future care. In anticipation of transitioning the participant to routine clinical care at the end of the study (or early discontinuation), the investigator should take steps to ensure that the participants' ART is not interrupted.

Follow-up Phase

A follow-up visit is required for any participant who has an ongoing AE or SAE after completion of the last study-related visit (unless consent is withdrawn). These participants are required to return to the site 30 days (±7 days) after completion of the last study-related visit (unless consent is withdrawn) and complete all procedures indicated in the Schedule of Activities (SoA).

A diagram of the study design is provided in Section 1.2, Schema.

4.2. Scientific Rationale for Study Design

The primary goal of this study is to assess the tolerability of D/C/F/TAF FDC in HIV-1 infected participant who are virologically-suppressed suppressed (HIV-1 RNA <50 copies/mL) and have experienced rapid and significant body weight gain on an INI + TAF/FTC ARV regimen.

Blinding, Control, Study Phase/Periods, Intervention Arms

An active control will be used to determine treatment effects in this study. Continuation of the current ARV regimen consisting of an INI + TAF/FTC was chosen as the active control as this study evaluates the impact of switching from an INI + TAF/FTC ARV regimen to D/C/F/TAF FDC on body weight relative to continuation of the baseline INI + TAF/FTC ARV regimen. Given possible changes in weight when switching ARV regimens, it is important to understand the implications of not switching regimens and any difference in weight change among a control group.

This study will not be blinded as eligible participants may be receiving multiple INI + TAF/FTC based ARV regimens. Some regimens may be multiple tablet regimens or single tablet regimens of different sizes. Creating identical placebos for all possible regimens included in the active control arm is not considered appropriate because this would result in an increased pill burden, loss of convenience, and ease of adherence for participants who are accustomed to a simplified regimen.

Randomization will be used to minimize bias in the assignment of participants to treatment arms, to increase the likelihood that known and unknown participant attributes (eg, demographic or baseline characteristics) are evenly balanced across treatment arms, and to enhance the validity of statistical comparisons across treatment arms.

Two stratification factors (sex [Male or Female] and race [Black/African American or Non-Black/African American] at Baseline) will be applied in the randomization process. These stratification factors were chosen as previous studies have identified these populations being at an increased risk of weight gain while taking an INI-based ARV regimen, therefore a need to ensure equal distribution across the treatment arms.

Primary Analysis Time Point and Study Period

As the primary aim of this study is to assess the safety and tolerability of switching from an INI + TAF/FTC regimen to D/C/F/TAF, the primary analysis will occur at Week 24. This time point was chosen to describe comparative tolerability across treatment arms based on findings from TMC114IDF3013. In this Phase 3 randomized controlled trial, of patients switching to D/C/F/TAF

from a Boosted-PI based regimen with TDF/FTC, 10 participants discontinued D/C/F/TAF prematurely due to adverse events through Week 24. The discontinuation rate due to adverse events did not increase significantly over the course of 48 weeks, as only one additional participant discontinued due to adverse events between Week 24 and Week 48. Furthermore, of 625 total adverse events reported through Week 48, 543 adverse events were reported during the first 24 weeks of treatment, indicating that most adverse events following a switch in ARV treatment occur within 24 weeks of switching. Significant changes in parameters such as changes in lipids, renal and bone makers were also detected as early as Week 24, providing further rationale that a 24-week time period will be sufficient to observe any changes in overall tolerability across the treatment arms.

As body weight can fluctuate, or additional changes occur over longer periods of time, a treatment duration up to 48 weeks was chosen to evaluate the sustained efficacy, tolerability and safety of the D/C/F/TAF FDC single-tablet regimen in the selected population. The study design also permits participants initially randomized to remain on their INI + TAF/FTC ARV regimen to switch to D/C/F/TAF after 24 weeks. This 48-week design allows for an analysis to determine if changes in metabolic endpoints exhibit a consistent effect after these patients switch to D/C/F/TAF over 24 weeks relative to the Immediate Switch Arm over the first 24 weeks of the study period.

To assure continued follow-up of the study participants and gain further safety information, participants who prematurely discontinue or change study treatment during the treatment phase will be asked to remain in the study and attend the ESID visit and 30-day follow-up (FU) visit, if applicable.

Toxicity Management

The combination of D/C/F/TAF is not anticipated to exacerbate known toxicities or lead to new toxicities (see Section 2.3, Benefit Risk Assessment). Measures and guidelines for the monitoring and management of specific toxicities with DRV, COBI, FTC, TAF or TDF, and concomitant ARVs are included in this protocol (see Section 8.2.6, Toxicity Management). The presented toxicity management guidelines are applicable throughout the entire study, including the screening phase and the 48-week treatment phase.

Safety and Efficacy Monitoring

All eligible participants for this study are virologically-suppressed and all study treatments utilized in this study are FDA approved for use in this population of patients. Given this there is no need to re-assess the risk/benefit profile of the product outside of the safety monitoring procedures outlined in this protocol.

4.2.1. Study-Specific Ethical Design Considerations

Potential participants will be fully informed of the risks and requirements of the study and, during the study, participants will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only participants who are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily will be enrolled.

The total blood volume to be collected in this study is approximately 261 mL.

This study involves radiation exposure from 3 whole body DEXA scans. As part of everyday living, everyone is exposed to a small amount of background radiation that comes from soil, rocks, outer space, and within the body itself. The radiation dose for all DEXA scans that the participant will receive in this study is expected to be about 0.03 mSv or equivalent to approximately 4 days of background radiation in the United States (US). The risks from these doses are small. This radiation exposure may not be necessary for the participants' medical care, but it is necessary to obtain the research information desired.

4.3. Justification for Dose

D/C/F/TAF FDC is an FDA approved at a dose of D/C/F/TAF 800/150/200/10 mg FDC. This dose has been studied in treatment naïve HIV-1 infected participants as well as in virologically-suppressed participants and is the dose recommended in the US Prescribing Information.[15,30]

4.4. End of Study Definition

A participant will be considered to have complete the study if he or she has completed the assessments at Week 48. The end of study is considered as the last data collection visit (week 48) for the last participant in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final participant visit at that study site, in the time frame specified in the Clinical Trial Agreement.

5. STUDY POPULATION

Screening for eligible participants will be performed in a Screening Phase of approximately 30 days (up to maximum 6 weeks) starting from the signature of the ICF. During the Screening Visit (Day -30), participants will undergo screening procedures outlined in the Schedule of Activities (SoA). Participants should not be randomized until all screening procedures have been completed and the investigator has determined that the participant meets the inclusion/exclusion criteria.

Refer to Section 5.4, Screen Failures for conditions under which the repeat of any screening procedures may be allowed.

The inclusion and exclusion criteria for enrolling participants in this study are described below. If there is a question about these criteria, the investigator must consult with the appropriate sponsor

representative and resolve any issues before enrolling a participant in the study. Waivers are not allowed.

For a discussion of the statistical considerations of participant selection, refer to Section 9.2, Sample Size Determination.

5.1. Inclusion Criteria

Each potential participant must satisfy all of the following criteria to be enrolled in the study:

1. at least 18 years of age, inclusive.

2. BMI of ≥18 kg/m^2 at time of starting an INI + TAF/FTC ARV regimen.

3. documented HIV-1 infection.

4. Criterion modified per Amendment 2

4.1 currently being treated with a stable ARV regimen consisting of an INI combined with TAF/FTC for ≥6 consecutive months preceding the screening visit and experienced a ≥10% increase in body weight within a -36-month time period prior to screening and while on the current INI + TAF/FTC ARV regimen.

5. documented evidence of being virologically-suppressed while on the current stable INI +TAF/FTC ARV regimen (described above) prior to screening: at least 1 plasma HIV-1 RNA measurement <50 copies/mL occurring between 12 and 2 months prior to the screening visit while on the stable INI + TAF/FTC ARV regimen and have HIV-1 RNA <50 copies/mL at the screening visit.

   A single viral load elevation of ≥50 copies/mL and <200 HIV-1 RNA copies/mL after previously reaching viral suppression within 12 months prior to screening is allowed, provided a subsequent viral load measurement is <50 HIV-1 RNA copies/mL prior to screening.

6. medically stable on the basis of physical examination, medical history, and vital signs, performed at screening. Any abnormalities, must be consistent with the underlying illness in the study population and this determination must be recorded in the participant's source documents and initialed by the investigator.

7. medically stable on the basis of clinical laboratory tests performed at screening. If the results of the serum chemistry panel including liver enzymes, other specific tests, blood coagulation, hematology, or urinalysis are outside the normal reference ranges, the participant may be included only if the investigator judges the abnormalities or deviations from normal to be not clinically significant or to be appropriate and reasonable for the population under study. This determination must be recorded in the participant's source documents and initialed by the investigator.

8. must be able to swallow whole or split tablets.

9. Must have adequate insurance in place that will cover the current INI + TAF/FTC ARV regimen for at least 6 months.

10. Criterion modified per Amendment 1

10.1 must sign an ICF indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study.

11. a female participant of childbearing potential must have a negative highly sensitive serum (β-hCG) at Screening and a negative urine pregnancy test at Baseline.

12. A female participant using oral contraceptives must use an additional contraceptive method (above that required in Inclusion Criterion [13]).

13. a female participant must be (as defined in Appendix 5: Contraceptive and Barrier Guidance and Collection of Pregnancy Information)

    a. Not of childbearing potential

    b. Of childbearing potential and

        - Practicing a highly effective method of contraception (failure rate of <1% per year when used consistently and correctly) and agrees to remain on a highly effective method while receiving study intervention and until 90 days after last dose the end of relevant systemic exposure. Examples of highly effective methods of contraception are located in Appendix 5: Contraceptive and Barrier Guidance and Collection of Pregnancy Information.
        - Pregnancy testing (urine) at the end of study intervention.

    Contraceptive (birth control) use by male or female participants should be consistent with local regulations regarding the acceptable methods of contraception for those participating in clinical studies.

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

14. a female participant must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for a period of 90 days after receiving the last dose of study intervention.

15. male participants should also be advised of the benefit for a female partner to use a highly effective method of contraception as condom may break or leak.

    male participants who have had a vasectomy without reversal operation minimally 2 months prior to screening are not required to use birth control methods.

16. a male participant must agree not to donate sperm for the purpose of reproduction during the study and for a minimum 90 days after receiving the last dose of study intervention (or longer, if dictated by local regulations).

17 Criterion added per the Amendment 3

A female participant must agree not to be pregnant, breastfeeding, or planning to become pregnant while enrolled in this study or within 90 days after the last dose of study intervention.

5.2. Exclusion Criteria

Any potential participant who meets any of the following criteria will be excluded from participating in the study:

1. known history of malignancy within the past 5 years or ongoing malignancy other than cutaneous Kaposi's sarcoma, basal cell carcinoma, or resected, noninvasive cutaneous squamous carcinoma.

2. known allergies, hypersensitivity, or intolerance to D/C/F/TAF FDC tablet or its excipients.[19]

3. known active cryptococcal infection, active toxoplasmic encephalitis, *Mycobacterium tuberculosis* infection, or another AIDS-defining condition within 90 days prior to Screening that in the judgement of the investigator would increase the risk of morbidity or mortality.

4. active hepatitis B (HBV) or hepatitis C virus (HCV) infection.

5. uncontrolled diabetes that will require treatment with insulin during the study period.

6. history of failure on DRV treatment or known documented history of ≥1 DRV RAMs. DRV RAMs include V11I, V32I, L33F, I47V, I50V, I54M/L, T74P, L76V, I84V, L89V (Note: If documented historical genotypes are available, the data must be made available to the sponsor for documentation of the criteria). If no historical genotype is available, the participant can be included, provided no previous failure on DRV treatment has been documented.

7. inadequate hematologic parameters at screening: platelets <50,000/uL, hemoglobin <8.5 g/dL, and absolute neutrophil count <1000/u/L.

8. evidence of Child Pugh Class C based on clinical laboratory testing and clinical evaluation.

9. screening hepatic transaminases (ALT and aspartate aminotransferase [AST]) >5x upper limit of the normal range (ULN).

10. screening creatinine based estimated glomerular filtration rate (eGFRcr) <30mL/min according to the Cockcroft-Gault formula for creatinine clearance.[8]

11. participants initiating or discontinuing concomitant medications associated with significant changes in weight within the last 90 days:

- Diabetes Therapies:
  - Insulin
  - Thiazolidinediones; eg: pioglitazone.
  - Sulfonylureas; eg: glipizide, glyburide, glimepiride, chlorpropamide, tolbutamide.
  - Biguanides/Meglitinides; eg: Metformin, Nateglinide.
  - Dipeptidyl peptidase-4 inhibitors; eg: linagliptin, saxagliptin, sitagliptin.
  - Glucagon-like peptide-1 agonists; eg: exenatide, liraglutide, pramlintide.
  - Alpha-Glucosidase inhibitors; eg: acarbose, miglitol.
- Psychiatric/Neurologic Therapies:
  - Tricyclic antidepressants; eg: amitriptyline, doxepin, imipramine, nortriptyline, trimipramine.
  - Selective Serotonin Reuptake Inhibitors; eg: sertraline, paroxetine, fluvoxamine.
  - Antipsychotics; eg: haloperidol, loxapine, clozapine, chlorpromazine, fluphenazine, risperidone, olanzapine, quetiapine.
  - Antiseizure/Anticonvulsants; ie, Valproic acid, carbamazepine, gabapentin, topiramate, zonisamide, lamotrigine.
  - Others: bupropion, nefazodone, lithium, mirtazapine.
- Steroid Hormones: chronic oral corticosteroids at an equivalent ≥5 mg of prednisone orally a day
  - Use of a methylprednisolone dose pack or use of acute steroids for treatment of allergic reactions for ≤7 days are not exclusionary.
- Hormone therapy/contraception; eg: estrogen, testosterone, progestogens, tesamorelin.
- Appetite Stimulants/Suppressants; eg: phentermine, topiramate, methylphenidate, amphetamine/dextroamphetamine, megestrol, oxandrolone, dronabinol.

12. receiving ongoing therapy with contraindicated drugs within 30 days of screening, not recommended drugs that cannot be adequately dose-adjusted, or participants with any known allergies to the excipients of the D/C/F/TAF FDC tablet.

13. current alcohol or substance use judged by the investigator to potentially interfere with participant study adherence or changes in body weight.

14. known, active, severe infections (other than HIV-1 infection) requiring parenteral antibiotic or antifungal therapy within 30 days prior to baseline.

15. received an investigational intervention (including investigational vaccines) or used an invasive investigational medical device within 90 days of baseline or is currently enrolled in an investigational study without prior approval from the sponsor.

16. pregnant, or breast-feeding, or planning to become pregnant while enrolled in this study or within 90 days after the last dose of study intervention.

17. plans to father a child while enrolled in this study or within 90 days after the last dose of study intervention.

18. any other condition or prior therapy for which, in the opinion of the investigator, participation would not be in the best interest of the participant (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

19. employee of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site, as well as family members of the employees or the investigator, or employees of Johnson & Johnson or Gilead.

20. unlikely to comply with the protocol requirements, based on clinical judgment.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of D/C/F/TAF FDC is given such that he or she no longer meets all eligibility criteria, then the participant should be excluded from participation in the study. The required source documentation to support meeting the enrollment criteria are noted in Appendix 3: Regulatory, Ethical, and Study Oversight Considerations.

5.3. Lifestyle Considerations

Potential participants must be willing and able to adhere to the following lifestyle restrictions during the course of the study to be eligible for participation:

1. Refer to Section 6.8, Concomitant Therapy for details regarding prohibited and restricted therapy during the study.

2. Agree to follow all requirements that must be met during the study as noted in the Inclusion and Exclusion Criteria (eg, contraceptive requirements).

3. All HIV-infected participants should be advised to take the necessary precautions to reduce the risk of transmitting HIV.

5.4. Screen Failures

Participant Identification, Enrollment, and Screening Logs

The investigator agrees to complete a participant identification and enrollment log to permit easy identification of each participant during and after the study. This document will be reviewed by the sponsor study-site contact for completeness.

The participant identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure participant confidentiality, no copy will be made. All reports and communications relating to the study will identify participants by participant identification and age at initial informed consent. In cases where the participant is not enrolled into the study, the date seen and age at initial informed consent will be used.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened after consultation with sponsor. Rescreened participants must be assigned new participant numbers.

5.5. Criteria for Temporarily Delaying Enrollment, Randomization, Administration of Study Intervention

Not Applicable

6. STUDY INTERVENTION

6.1. Study Interventions Administered

At the baseline visit (Day 1), eligible participants will be randomized in a 1:1 ratio to the Immediate Switch Arm (switch to D/C/F/TAF FDC) or the Delayed Switch Arm (maintain current INI + TAF/FTC ARV regimen). Randomization will be stratified by sex (Male or Female) and race (Black/African American or Non-Black/African American) at Baseline.

- **Immediate Switch Arm:** D/C/F/TAF FDC (DRV 800 mg + COBI 150 mg + FTC 200 mg + TAF 10 mg) once daily for 48 weeks.
- **Delayed Switch Arm:** continue current INI + TAF/FTC ARV regimen for 24 weeks. After 24 weeks participants will switch to a regimen of D/C/F/TAF FDC (DRV 800 mg + COBI 150 mg + FTC 200 mg + TAF 10 mg) once daily for an additional 24 weeks.

Participants randomized to the Immediate Switch Arm must start D/C/F/TAF FDC within 24 hours of the Baseline visit. D/C/F/TAF FDC tablet must be taken orally with food. Participants will be counseled to swallow D/C/F/TAF FDC tablet whole once daily at approximately the same time each day, according to their preference. D/C/F/TAF is to be taken with approximately 240 mL (8 ounces) of water. The D/C/F/TAF FDC tablet should be swallowed whole; alternatively, for participants who are unable to swallow the tablet whole, D/C/F/TAF FDC may be split into 2 pieces using a tablet-cutter, and the entire dose should be consumed immediately after splitting. Participants should not attempt to dissolve the tablet in water.

D/C/F/TAF FDC administration must be captured in the source documents and the CRF. Study-site personnel will instruct participants on how to store D/C/F/TAF FDC for at-home use as indicated for this protocol.

If participants notice that they have missed a D/C/F/TAF FDC intake and it is still within 12 hours of their regular dosing time, they should take the D/C/F/TAF FDC immediately with food. Participants can then continue their usual dosing schedule. If participants notice that they have missed a dose more than 12 hours after the time it is usually taken, they should be instructed not to take it and simply resume the usual dosing schedule. Participants should not take a double dose to make up for a missed dose.

Instructions regarding how to take D/C/F/TAF FDC tablet, what to do if a dose is missed and how to store the D/C/F/TAF FDC tablet will be provided on the wallet (study) card.

D/C/F/TAF FDC tablet will be manufactured and provided under the responsibility of the sponsor. Each D/C/F/TAF FDC tablet contains darunavir ethanolate equivalent to 800 mg of darunavir, 150 mg of cobicistat, 200 mg of emtricitabine (FTC), and tenofovir alafenamide fumarate equivalent to 10 mg of tenofovir alafenamide (TAF). The yellow to yellowish-brown, capsule-shaped, filmcoated tablet is debossed with “8121” on one side and “JG” on the other side. D/C/F/TAF FDC is packaged in high-density polypropylene (HDPE) bottles with a silica gel desiccant and child-resistant closure. Refer to the IB for a list of excipients.[19] D/C/F/TAF FDC labels will contain information to meet the applicable regulatory requirements. No D/C/F/TAF FDC can be repacked or relabeled without prior approval from sponsor.

For the Delayed Switch Arm, all components of the INI + TAF/FTC ARV regimen should be dosed and administered using the dosing schedule specified in the ARV agent’s US Prescribing Information. Applicable procedures and treatment guidance based on the Prescribing Information should be respected. If a participant accidentally misses a scheduled dose of any of the ARVs in the Delayed Switch Arm, the investigator should advise according to the PI in the individual package insert. Participants on Delayed Switch Arm will be provided with the wallet (study) card.

The times of the previous two doses of study intervention administration will be recorded at each visit. Prolonged temporary study intervention interruptions are only deemed acceptable if motivated by safety reasons and if they do not last longer than 4 consecutive weeks. The sponsor should be notified when such temporary interruption occurs.

For details on rescue medications, refer to Section 6.8. For a definition of study intervention overdose, refer to Section 6.7, Treatment of Overdose.

6.2. Preparation/Handling/Storage/Accountability

Preparation/Handling/Storage

All D/C/F/TAF FDC tablets must be stored 20°C to 25°C (between 68°F to 77°F) with excursions permitted to 15°C to 30°C (59°F to 86°F). Refer to the pharmacy manual/study site investigational product and procedures manual for additional guidance on D/C/F/TAF FDC preparation, handling,

and storage. Study site personnel will be instructed to dispense D/C/F/TAF FDC tablets only in the original container. Study site personnel will instruct participants to store D/C/F/TAF FDC tablets in the original container and to keep container tightly closed with desiccant inside to protect from moisture.

Accountability

The investigator is responsible for ensuring that all D/C/F/TAF FDC tablets received at the site is inventoried and accounted for throughout the study. The dispensing of D/C/F/TAF FDC tablets to the participant, and the return of D/C/F/TAF FDC tablets from the participant (if applicable), must be documented on the intervention accountability form. Participants must be instructed to return all original containers, whether empty or containing D/C/F/TAF FDC tablets. All D/C/F/TAF FDC tablets will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the D/C/F/TAF FDC tablets containers.

INI + TAF/FTC ARV regimen will not be supplied by the sponsor.

D/C/F/TAF FDC tablets must be handled in strict accordance with the protocol and the container label and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused D/C/F/TAF FDC tablets, and D/C/F/TAF FDC tablets returned by the participant, must be available for verification by the sponsor's study site monitor during on-site monitoring visits. The return to the sponsor of unused D/C/F/TAF FDC tablets, or used returned D/C/F/TAF FDC tablets for destruction, will be documented on the intervention return form. When the study site is an authorized destruction unit and D/C/F/TAF FDC tablets supplies are destroyed on-site, this must also be documented on the intervention return form.

D/C/F/TAF FDC tablets should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. D/C/F/TAF FDC tablets will be supplied only to participants participating in the study. Returned D/C/F/TAF FDC tablets must not be dispensed again, even to the same participant, unless the bottles are unopened. Whenever a participant brings his or her D/C/F/TAF FDC tablets to the study site for pill count, this is not seen as a return of supplies. D/C/F/TAF FDC tablets may not be relabeled for use by other participants. The investigator agrees neither to dispense the D/C/F/TAF FDC tablets from, nor store it at, any site other than the study sites agreed upon with the sponsor. Further guidance and information for the final disposition of unused D/C/F/TAF FDC are provided in the Site Investigational Product Procedures Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

Procedures for Randomization

Participants will be randomly assigned to 1 of 2 intervention arms based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. Randomization will be based on a computer-generated schedule, constructed via random permuted blocks to ensure balance across treatment arms in each strata of the stratification factors, and prepared before the start of the study by the sponsor.

Central randomization will be implemented in this study. Participants will be randomized in a 1:1 ratio to the Immediate Switch Arm (D/C/F/TAF FDC starting on Day 1 for 48 weeks), or the Delayed Switch Arm (continue current INI + TAF/FTC ARV regimen for 24 weeks then switch to D/C/F/TAF FDC for an additional 24 weeks).

Randomization will be stratified by sex (Male or Female) and race (Black/African American or Non-Black/African American) at Baseline. A maximum enrollment of approximately 70% male participants will be utilized to ensure adequate recruitment of female participants. A maximum enrollment of approximately 70% non-black participants will be utilized to ensure adequate recruitment of diverse races.

The randomization and baseline visit (Day 1) cannot proceed until the investigator has received all results of the screening visit and participant eligibility has been confirmed in interactive web response system (IWRS), which should occur within approximately 30 days (up to maximum 6 weeks) after the screening visit (for further details, see Section 8). It is the responsibility of the investigator to ensure that the participant is eligible for the study prior to enrollment. Randomization should be performed on the same day as the baseline visit (Day 1), provided that all screening procedures have been completed and participant eligibility has been confirmed.

The IWRS will assign open-label kit numbers at each study visit. D/C/F/TAF FDC will be dispensed to the participant in an open-label fashion. The requestor must use his or her own user identification and personal identification number when contacting the IWRS, and will then give the relevant participant details to uniquely identify the participant.

Blinding

As this is an open study, blinding procedures are not applicable.

6.4. Study Intervention Compliance

Study-site personnel will maintain a log of all D/C/F/TAF FDC tablets administered. D/C/F/TAF FDC tablets supplies for each participant will be inventoried and accounted. Participants will receive instructions on compliance with D/C/F/TAF FDC tablets administration at the Baseline visit. Treatment adherence will be assessed by participant self-report using 4-day recall at the time points specified in the Schedule of Activities (SoA). During the course of the study, the investigator or designated study-site personnel will be responsible for providing additional instruction to reeducate any participant who is not compliant with taking the D/C/F/TAF FDC tablets. Instructions regarding how to take D/C/F/TAF FDC, what to do if a dose is missed and how to store the D/C/F/TAF FDC will be provided on the wallet (study) card. All participants in the study will be provided with wallet (study) card.

6.5. Dose Modification

No dose modifications are allowed.

6.6. Continued Access to Study Intervention After the End of the Study

Participants will be instructed that D/C/F/TAF FDC will not be made available to them after they have completed/discontinued D/C/F/TAF FDC and that they should return to their primary physician to determine standard of care.

6.7. Treatment of Overdose

For D/C/F/TAF FDC any dose greater than 1 tablet within a 24-hour period ±12 hours is considered an overdose as per Prescribing information of D/C/F/TAF FDC tablet. The sponsor does not recommend specific intervention for an overdose.

Human experience of acute overdose with D/C/F/TAF is limited. If overdose occurs, the patient must be monitored for evidence of toxicity. There is no specific antidote for overdose with D/C/F/TAF. Treatment of overdose with D/C/F/TAF consists of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient.

For those randomized to the delayed switch arm, receiving an INI + FTC/TAF based regimen the individual prescribing information should be referenced to determine if an overdose has occurred, and how such overdose should be managed.

6.8. Concomitant Therapy

Prestudy therapies including all previous ARV treatments and non-ARV treatments received up to twelve months before Screening must be recorded.

Concomitant therapies must be recorded throughout the study beginning with Screening up to the last dose of study intervention. Concomitant therapies should also be recorded beyond the last study visit only in conjunction with new or worsening AEs, SAEs that meet the criteria outlined in Serious Adverse Events in Section 8.3.1, Time Period and Frequency for Collecting AEs and SAE Information.

All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; non-pharmacologic therapies such as electrical stimulation, acupuncture, special diets, exercise regimens) different from the study intervention must be recorded in the case report form (CRF). Recorded information will include a description of the type of therapy, duration of use, dosing regimen, route of administration, and its indication. Modification of an effective preexisting therapy should not be made for the explicit purpose of entering a participant into the study if such modification of treatment is not clinically acceptable. Any change in dosage of the medication must be reported in the electronic CRF (eCRF).

For those participants with treatment emergent hyperglycemia, hypertension or dyslipidemia, initiation of medications to address these AEs should be prescribed in accordance to national treatment guidelines (See Figure 4 in Appendix 9: Characteristics, Prevention, and Management of Cardiovascular Diseases in People Living with HIV by American Heart Association; page 14: Figure 4 in Appendix 10: 2017 American College of Cardiology (ACC) Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults; and page 6: Figure 2 in

Appendix 11: Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)]).

Investigators are reminded that certain medications may influence body weight changes or may be contraindicated and should be avoided (see disallowed concomitant therapy below and Exclusion Criteria No. 11). Should a participant have a need to initiate treatment with any excluded concomitant medication, it is recommended that investigators consult with the sponsor medical monitor beforehand to determine if an alternative therapy could be utilized that has no known impact on weight or if the participant should be discontinued from the study. If an excluded medication is initiated before discussion with the medical monitor, the investigator must notify the sponsor as soon as becoming aware.

Participants who experience clinically significant changes in body weight during the course of the study may require dose reductions or withdrawal of medications to treat hypertension, type II diabetes, or hyperlipidemia in order to avoid events such as hypoglycemia, hypotension, etc. As part of routine care at scheduled follow-up visits, participants should be assessed to determine if a dose reduction or withdrawal of medications for the treatment of such conditions is warranted. These changes will be recorded in the CRF.

Contraindicated and Disallowed Concomitant Agents

DRV co-administered with COBI is an inhibitor of CYP3A, CYP2D6, and P-glycoprotein (P-gp). Cobicistat also inhibits the transporters breast cancer resistance protein (BCRP), multi-antimicrobial extrusion protein (MATE)-1, organic anion-transporting polypeptide (OATP)1B1 and OATP1B3. Cobicistat is not expected to inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9 or CYP2C19. Cobicistat is not expected to induce CYP1A2, CYP3A4, CYP2C9, CYP2C19, uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1), or multidrug resistance protein 1 (MDR1).

D/C/F/TAF FDC tablet should not be co-administered with medicinal products that are highly dependent on CYP3A for clearance and for which increased plasma concentrations are associated with serious and/or life-threatening events (narrow therapeutic index). These medicinal products include alfuzosin, astemizole, carbamazepine, cisapride, colchicine (in participants with renal and/or hepatic impairment), dronedarone, elbasvir/grazoprevir, ergot alkaloids (eg, dihydroergotamine, ergotamine, ergonovine and methylergonovine), lomitapide, lovastatin, lurasidone, oral midazolam, phenobarbital, phenytoin, pimozide, ranolazine, rifampin, sildenafil (when used for treatment of pulmonary arterial hypertension), simvastatin, St John's Wort, terfenadine, and triazolam.

Emtricitabine is not an inhibitor of human CYP450 enzymes. In vitro and clinical drug interaction studies have shown that the potential for CYP-mediated interactions involving FTC with other medicinal products is low. Emtricitabine is primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion. No drug interactions due to competition for renal excretion have been observed; however, coadministration of FTC with drugs that are eliminated by active tubular secretion may increase concentrations of FTC and/or the co-administered drug. Drugs that decrease renal function may increase concentrations of FTC.

Tenofovir alafenamide is a substrate of the efflux transporter P-gp. Drugs that induce P-gp activity are expected to decrease the absorption of TAF, resulting in decreased plasma concentrations of TAF, which may lead to loss of therapeutic effect of D/C/F/TAF FDC tablet and development of resistance. These medicinal products include antimycobacterials (rifabutin, rifampin, rifapentine) and anticonvulsants (carbamazepine, oxcarbazepine, phenobarbital, phenytoin). Coadministration of D/C/F/TAF FDC tablet with drugs that inhibit P-gp may increase the absorption and plasma concentration of TAF.

Given the possibility for PK interactions, investigators should refer to the IB for the D/C/F/TAF FDC tablet and individual Prescribing Information for the components of the D/C/F/TAF FDC tablet for potential contraindications and management of drug interactions to preserve participant safety during the study.

Refer to the current individual agents' PI of the continued INI + TAF/FTC ARV regimen for guidance with regard to dose adjustments for concomitant use with other medications, and for contraindicated medications or medications that are not recommended for concomitant use.

All contraindicated or disallowed medications must be discontinued at least 30 days before the Screening Visit (Day 1) and for the duration of the study. If such discontinuation of treatment is not clinically acceptable, the participant should not be allowed to participate in the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

- A participant's study intervention must be discontinued if:
- The participant withdraws consent to receive assigned study intervention.
- The investigator believes that for safety reasons or tolerability reasons (eg, AE) it is in the best interest of the participant to discontinue study intervention.
- The participant becomes pregnant while taking study intervention (Refer to Appendix 5: Contraceptive and Barrier Guidance and Collection of Pregnancy Information). Study intervention should discontinue only after the participant has obtained alternative ARV therapy through a health care provider.
- The study is discontinued at the request of the sponsor, concerned regulatory agency, or Independent Ethics Committee/Institutional Review Board (IEC/IRB).
- The participant experiences unacceptable toxicity (as defined in Section 8.2.6, Toxicity Management).

A participant's study intervention may be discontinued if:

- An SAE occurs.

- The participant fails to comply with the protocol or study staff requirements.
- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree.
- The participant starts disallowed treatment, or requires new onset treatment with one of the disallowed medications (please refer to Section 6.8, Concomitant Therapy).
- The participant experiences virologic rebound; if genotypic/phenotypic resistance to study intervention is determined, study intervention may be discontinued, and the participant will be referred for continued medical care outside of the study.
- The investigator considers, for any other reason, it is in the best interest of the participant that he/she is withdrawn. The sponsor should be contacted for further discussion and final decision.

If a participant discontinues study intervention for any reason except for withdrawal of consent before the end of the study, ESID assessments should be obtained as soon as possible but no later than 1 week of discontinuing study intervention. For participants who discontinue study intervention for any reason and have HIV-1 RNA ≥400 copies/mL at the last viral load measurement, the ESID assessments will also include genotypic and phenotypic resistance testing (using PhenoSense GT® Plus Integrase). In case of early discontinuation, an HIV-1 resistance report will be forwarded to the participant's primary care provider to assist in the selection of a new ARV regimen. If the reason for withdrawal from the study is withdrawal of consent, then no additional assessments are allowed.

D/C/F/TAF FDC assigned to the participant who discontinued D/C/F/TAF FDC may not be assigned to another participant. Additional participants will not be entered.

7.1.1. Temporary Discontinuation

Prolonged temporary study intervention interruptions are only deemed acceptable if, motivated by safety reasons and if they do not last longer than 4 consecutive weeks. The sponsor should be notified when such temporary interruption occurs.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant will be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent
- Death

When a participant withdraws before completing the study, the reason for withdrawal is to be documented in the CRF and in the source document. If the reason for withdrawal from the study is withdrawal on consent, then no additional assessments are allowed.

Withdrawal of Consent

A participant declining to return for scheduled visits does not necessarily constitute withdrawal of consent. Alternate follow-up mechanisms that the participant agreed to when signing the consent form apply (eg, consult with family members, contacting the participant's other physicians, medical records, data base searches) as local regulations permit.

Withdrawal of consent should be an infrequent occurrence in clinical studies[32], therefore, prior to the start of the study the sponsor and the investigator should discuss and reach a clear understanding of what constitutes withdrawal of consent in the context of the available reduced follow-up mechanisms listed.

7.2.1. Withdrawal From the Use of Research Samples

Withdrawal From the Use of Samples in Future Research

The participant may withdraw consent for use of samples for research (refer to Long-term Retention of Samples for Additional Future Research in Appendix 3: Regulatory, Ethical, and Study Oversight Considerations). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. A participant cannot be deemed lost to follow-up until all reasonable efforts made by the study-site personnel to contact the participant are deemed futile. The following actions must be taken if a participant fails to return to the study site for a required study visit:

- The study-site personnel must attempt to contact the participant to reschedule the missed visit as soon as possible, to counsel the participant on the importance of maintaining the assigned visit schedule, to ascertain whether the participant wishes to or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every reasonable effort to regain contact with the participant (where possible, 3 telephone calls, e-mails, fax, and, if necessary, a certified letter to the participant's last known mailing address, or local equivalent methods). These contact attempts should be documented in the participant's medical records.
- Should the participant continue to be unreachable, they will be considered to have withdrawn from the study.

If a participant is lost to follow-up, every reasonable effort must be made by the study site personnel to contact the participant and determine the reason for discontinuation/withdrawal. The measures taken to follow up must be documented. Refer to Section 7.2, Participant Discontinuation/Withdrawal From the Study.

8. STUDY ASSESSMENTS AND PROCEDURES

Overview

The Schedule of Activities (SoA) summarizes the frequency and timing of metabolic, efficacy, safety, PROs, and other measurements applicable to this study. Additional visits may be required if, in the investigator's opinion, further clinical or laboratory evaluation is needed.

When an HIV-1 RNA repeat testing is required at an unscheduled visit to confirm protocol virologic rebound, an HIV-1 genotype/phenotype plasma sample and a plasma storage sample should also be drawn at the same unscheduled visit. Findings during these unscheduled visits or assessments need to be reported in the eCRF.

Some flexibility in the planning of the visits is allowed, however, the total treatment duration at the end of the study period should be 48 weeks. All study visits through Week 48 are to be completed within ±7 days of the protocol-specified visit date.

All PRO assessments (BSQ-8D, HIV-SI and PGIC [including PGIC-S]) should be completed during the study visit before any tests, procedures, or other consultations to prevent influencing participant perceptions. The PGIC and PGIC-S should be completed after the participant completes the BSQ-8D and HIV-SI.

Other measurements may be done earlier than specified timepoints if needed. Actual dates and times of assessments (if applicable) will be recorded in the source documentation and CRF.

Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participation in the study. If a serum or urine pregnancy test is positive, the participant will be withdrawn from the study. For each participant, the maximum amount of blood drawn from each participant in this study will not exceed 261 mL.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples or for confirmation of virologic rebound.

Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the CRF or laboratory requisition form.

Refer to the Schedule of Activities (SoA) for the timing and frequency of all sample collections.

Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the laboratory manual

Study-Specific Materials

The investigator will be provided with the following supplies:

- Investigator's Brochure for D/C/F/TAF[19]
- pharmacy manual/study site investigational product and procedures manual
- laboratory manual and laboratory supplies
- Electronic Data Capture (eDC) Manual
- sample ICF
- Interactive Web Response System manual
- Dual-energy X-ray absorptiometry (DEXA) manual
- Patient Reported Outcomes (PROs) manual
- Contact Information Page

8.1. Assessments

8.1.1. Primary Endpoint (Percent Change in Body Weight)

Body weight will be evaluated at time points specified in the Schedule of Activities (SoA). Body weight will be measured using a calibrated scale. Attention should be given to weigh the participant on the same scale through the duration of the study. Participants should be weighed wearing underwear and a gown. Participants will be instructed to take off their shoes and to empty their bladders before being weighed. If disrobing for weighing is logistically impossible, the participant must be dressed as lightly as possible, with consistency from visit to visit. The scale should be calibrated according to the manufacturers specifications and at the frequency recommended by the manufacturer before the first participant is weighted. Calibration must be documented in the calibration log.

8.1.2. Metabolic Assessments

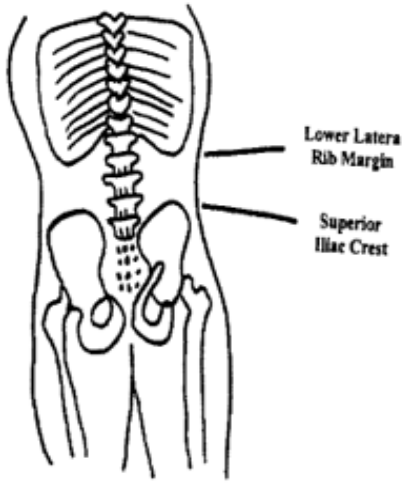
Systolic and diastolic blood pressure (SBP, DBP), pulse rate (supine after at least 5 minutes rest) will be recorded in a quiet setting without distractions, at the time points specified in the Schedule of Activities (SoA). Blood pressure and pulse/heart rate measurements will be assessed with a completely automated technique. Manual techniques will be used only if an automated device is not available. Body Mass Index will be calculated using body weight collected as described in Section 8.1.1 and height measured at screening. Height will be measured using a wall-mounted stadiometer or one mounted on a balance beam scale, whichever is most appropriate for the individual participant. Participants should be wearing socks or barefoot and should not be wearing shoes.

Body composition will be assessed at time points specified in the Schedule of Activities (SoA) via whole body DEXA scans. DEXA scans may be performed between screening and baseline (+2 weeks), at Weeks 24, 48, and the ESID visit (±10 days) (only to be performed at ESID if the last scan is more than 12 weeks from the date of the ESID visit and the ESID visit takes place before Week 48). A rescan for technical reasons at all scheduled time points is allowed within 2 weeks. A complete

description of the procedures for the DEXA scans will be provided in the DEXA manual. Reading of the DEXA scans will be performed centrally.

Waist circumference will be measured at time points specified in the Schedule of Activities (SoA). Waist circumference will be measured with the participant standing, wearing underwear, with or without a gown. The measurement will be performed at a level midway between the superior aspect of the iliac crests and the lower lateral margin of the ribs (see Figure 2). The measurement need not be at the level of the umbilicus. The measuring tape will be kept horizontal. Non-alcoholic fatty liver disease (NAFLD) Fibrosis and hypertension, age, insulin, resistance (HAIR) scores will be calculated based on receipt of central laboratory assessments and clinical status of the participant (Appendix 2: Clinical Laboratory Tests and Calculations)

Figure 2: Waist Circumference Measurement



Fasting clinical laboratory tests will be assessed at time points specified in the Schedule of Activities (SoA) to assess changes in the following metabolic parameters:

- lipids, calculated homeostatic model assessment of insulin resistance (HOMA-IR), HbA1C, leptin, adiponectin, and alpha melanocyte-stimulating hormone. If a participant has not fasted prior to the visit, the visit may proceed, but participant must return within 72 hours in a fasted state to have a blood draw for the metabolic assessments.

8.1.3. Efficacy Assessments

8.1.3.1. Antiviral Efficacy and Immunologic Change

Blood samples for determination of plasma HIV-1 RNA viral load and immunologic parameters will be taken at the time points specified in the Schedule of Activities (SoA).

Plasma viral load will be measured using a validated assay at a central laboratory (ie, Roche COBAS AmpliPrep/COBAS TaqMan HIV-1 Test, Version 2.0.) The assay linear range is 20 to 10,000,000 copies/mL with a lower limit of quantification (LLOQ) of 20 copies/mL and a limit of detection (LOD) of 20 copies/mL). Immunologic change will be determined by changes in $CD4^+$ cell count (absolute and %).

Changes in viral load, changes in $CD4^+$ cell counts (either decreases or increases) or detected resistance will be part of the efficacy analysis and should not be reported as AEs or SAEs.

8.1.3.2. Resistance Determinations

Samples for HIV-1 genotype/phenotype resistance testing (PhenoSense GT® Plus Integrase) will be taken at the time points specified in the Schedule of Activities (SoA).

For participants with confirmed virologic rebound (2 consecutive HIV-1 RNA values ≥200 copies/mL at a scheduled or unscheduled visit) and with a HIV-1 RNA value ≥400 copies/mL, HIV-1 genotypic/phenotypic resistance testing will be performed on the confirmed rebound sample if HIV-1 RNA ≥400 copies/mL or on a following visit with HIV-1 RNA ≥400 copies/mL. Other time points may still be analyzed if deemed necessary by the sponsor. For further details on the management of virologic rebound, see Appendix 13: Management of Virologic Rebound. Whole blood samples will be taken for storage and will be analyzed if deemed necessary by the sponsor to characterize archived viral resistance (GenoSure Archive®).

8.1.3.3. Management of Virologic Rebound

Participants with HIV-1 RNA ≥200 copies/mL will be managed as follows:

- If a single viral load measurement is ≥200 copies/mL after having previously been <50 copies/mL, participants should be contacted preferably within 48 hours to assess potential causes (eg, active substance abuse, depression, other intercurrent illnesses, lack of adherence) and adequate intervention should be provided (eg, additional adherence counseling). HIV-1 RNA testing should be repeated at a scheduled or unscheduled visit 2 to 4 weeks after the date of the initial viral load result of HIV-1 RNA ≥200 copies/mL.

- Upon confirmation of HIV-1 RNA ≥200 copies/mL, potential causes of virologic rebound should be documented. Assessment should include adherence, concomitant medication, and comorbidities (eg, active substance abuse, depression, other intercurrent illnesses, lack of adherence).

- If virologic rebound is confirmed at the scheduled or unscheduled visit and the HIV-1 RNA value is ≥400 copies/mL, the blood sample from that visit or a following visit with HIV-1 RNA ≥400 copies/mL will be used for HIV-1 genotypic and phenotypic testing (using PhenoSense GT® Plus Integrase).

- If genotypic/phenotypic resistance to study intervention is determined, study intervention may be discontinued at the discretion of the investigator. In case of early discontinuation, and HIV-

1 RNA ≥400 copies/mL, an HIV-1 genotypic/phenotypic resistance report, if available, will be forwarded to the investigator and/or participant's primary care provider in order to assist in the selection of a new ARV regimen.

- If no resistance is detected from genotypic/phenotypic resistance testing, the participant may remain on study intervention and the viral load will be further monitored. Genotypic/phenotypic resistance testing at other time points may be requested if deemed necessary by the sponsor. Investigators should carefully evaluate the benefits and risks of remaining on study intervention for each individual participant and document this assessment in the on-site medical record. Investigators who opt to discontinue study intervention for an individual participant must discuss this with the sponsor's medical monitor prior to study intervention discontinuation.

Evaluations may be performed at other time points at the sponsor's discretion. Additional exploratory resistance assays may be performed. A schematic overview of the guidance for management of participants who meet the criteria for virologic rebound is provided in Appendix 13: Management of Virologic Rebound.

8.1.4. Adherence

Treatment adherence for the study will be assessed by participant self-report using a 4-day recall for D/C/F/TAF FDC and participants receiving an INI + TAF/FTC ARV regimen at the time points specified in the Schedule of Activities (SoA).

8.2. Safety Assessments

Adverse events will be reported and followed by the investigator as specified in Section 8.3, Adverse Events and Serious Adverse Events and Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

Special attention will be paid to those participants who discontinue the study for an AE, or who experience severe (Grade 3) or potentially life-threatening (Grade 4) AEs, or SAEs. For reported HIV events, further details will be recorded if these events are AIDS-defining illnesses (World Health Organization Clinical Staging of HIV/AIDS, located in Appendix 12: WHO Clinical Staging of HIV/AIDS. For participants with specific adverse events, toxicity management should be done as described in Section 8.2.6.

Any clinically relevant changes occurring during the study must be recorded on the AE section of the CRF. Clinical events and clinically significant laboratory abnormalities will be graded according to the Division of AIDS (DAIDS) as specified in Appendix 7: DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events. Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable condition is reached. All Grade 3 and Grade 4 laboratory abnormalities and all laboratory abnormalities resulting in an increase of 2 DAIDS grades from baseline will be followed until return to baseline or within 1 grade from baseline (ie, ≤Grade 2). The study will include evaluations of safety and tolerability according to the time points provided in the Schedule of Activities (SoA).

Evaluations at the ESID visit showing abnormal results indicating a possible causal relationship with the study intervention must be followed by the investigator (as often as deemed prudent) until satisfactory clinical resolution or stabilization. Certain long-term adverse events of anti-retroviral therapy (ART) cannot be followed to resolution within the setting of this protocol; in these cases, follow-up will be the responsibility of the treating physician, which will be agreed upon with the sponsor's medical monitor.

Safety will be evaluated throughout the study from the time a signed and dated informed consent form (ICF) is obtained until completion of the participant's last study-related activity.

8.2.1. Physical Examination

A complete physical examination will be conducted at the time points in the Schedule of Activities (SoA). Complete physical examinations include general appearance; skin (and mucus membranes); eyes; ears, nose, and throat; head, neck, and thyroid; heart; lung, chest (incl. breasts); abdomen; genitalia; anorectal; lymph nodes; musculoskeletal; and neurological. Urogenital/anorectal examination will be performed at the discretion of the investigator if clinically relevant. Participants should be undressed during the complete physical examinations, which should be performed by a licensed medical doctor, physician's assistant or nurse practitioner in accordance with local guidelines. Physical examination will also include evidence of ascites or encephalopathy at Screening in order to fully calculate Child Pugh Class.

Symptom directed physical examinations may be conducted at all other scheduled and unscheduled study visits based on reported safety or tolerability issues.

8.2.2. Vital Signs

Pulse/heart rate (supine after at least 5 minutes rest) and blood pressure will be assessed will be conducted at all study visits.

Blood pressure and pulse/heart rate measurements should be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones).

8.2.3. Electrocardiogram (ECG)

Not applicable

8.2.4. Clinical Safety Laboratory Assessments

Blood samples for serum chemistry and hematology and a urine sample for urinalysis will be collected as noted in Appendix 2: Clinical Laboratory Tests and Calculations. All clinical laboratory testing will be performed by the central laboratory and results will be sent to the investigator. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents.

The central laboratory will send the investigator and sponsor an alert form whenever a Grade 3 or Grade 4 laboratory abnormality (see Appendix 7: DAIDS Table for Grading the Severity of Adult

and Pediatric Adverse Events) is observed. In case a Grade 3 or Grade 4 laboratory abnormality occurs, a confirmatory test should be performed preferably within 72 hours after the results have become available, before study intervention interruption or discontinuation, unless such delay is not consistent with good medical practice.

If a Grade 3 or Grade 4 laboratory abnormality is well documented before the start of the study and not considered a safety concern by the investigator, a confirmatory retest is not mandatory. The following laboratory abnormalities do not warrant mandatory confirmation:

- Asymptomatic Grade 3 or Grade 4 glucose elevations in participants with pre-existing diabetes.
- Asymptomatic Grade 3 or Grade 4 triglyceride or cholesterol elevations.

For more details on the management of Grade 3 and 4 laboratory toxicities that occur during the open-label treatment phase, see Section 8.2.6, and Appendix 6: Management of Clinically Significant Laboratory Toxicities.

8.2.5. Patient-reported Outcomes

Following PROs will be assessed at the time points indicated in the Schedule of Activities (SoA), (Appendix 8: Patient Reported Outcomes Questionnaires). Participants will complete the PROs using the sponsor-provided electronic devices. Study site personnel will train the participants on how to use the electronic device. All PRO assessments will be done in English-speaking and Spanish-speaking participants.

The BSQ-8D, HIV-SI and PGIC (including PGIC-S) should be completed by the participants during the study visit before all other study-related procedures to prevent influencing participant perceptions. The PGIC and PGIC-S should be completed after the participant completes the BSQ-8D and HIV-SI.

8.2.5.1. HIV-Symptom Index (HIV-SI)

The HIV-SI is a validated PRO instrument that assesses the burden of 20 common symptoms associated with HIV treatment or disease.[21] Respondents are asked about their experience with each of 20 symptoms during the past 4 weeks using a 5-point, Likert-type scale. Response options and scores are as follows: (0) “I don’t have this symptom;” (1) “I have this symptom and it doesn’t bother me;” (2) “I have this symptom and it bothers me a little;” (3) “I have this symptom and it bothers me;” (4) “I have this symptom and it bothers me a lot.” The 20 symptoms comprising the HIV-SI are fatigue/loss of energy, difficulty sleeping, nervous/anxious, diarrhea/loose bowels, changes in body composition, feeling sad/down/depressed, bloating/pain/gas in stomach, muscle aches/joint pain, problems with sex, trouble remembering, headaches, pain/numbness/tingling in hands/feet, skin problems/rash/itching, cough/trouble breathing, fever/chills/sweats, dizzy/lightheadedness, body weight loss/wasting, nausea/vomiting, hair loss/changes, and loss of appetite/food taste. Symptoms scores can be dichotomized into not bothersome (scores of 0 or 1) or bothersome (scores of 2, 3 and 4) and overall bothersome symptom count at baseline can be generated by counting the number of individual symptoms scored as bothersome.[13]

8.2.5.2. Body Shape Questionnaire (BSQ-8D)

The BSQ-8D is an 8-item version of the 34-item self-report questionnaire that was developed and validated to measure concerns about body shape; in particular, it focused on the phenomenal experience of "feeling fat".[9,16] Respondents are asked about how they have been feeling about their appearances over the past four weeks. Each item from this questionnaire is answered using a 6-point Likert scale: 1 (never), 2 (rarely), 3 (sometimes), 4 (often), 5 (very often), and 6 (always) and the overall score is the total across the 8 items.

8.2.5.3. DAILY EATS

The DAILY EATS will be administered to measure eating-related concepts such as hunger, appetite, cravings, and satiety. The home-based DAILY EATS should be completed daily, preferably in the evening, and, whenever possible, in the same setting for 7 consecutive days. The site should contact participants approximately 7 days prior to the Baseline (Day 1), Week 24 and Week 48 visits, preferably by telephone, to remind the completion of the DAILY EATS for 7 consecutive days prior to the applicable visit. For participants who discontinue early from study intervention, no DAILY EATS completion is required at the ESID visit.

8.2.5.4. Patient Global Impression of Change

The PGIC is a global index that is used to rate the overall status of the participant related to the participant's overall condition. It is rated by the participant and is based on the single question, "Compared to before starting the study or compared to the Week 24 visit, my overall status is," where response choices include 1 very much improved, 2 much improved, 3 minimally improved, 4 no change, 5 minimally worse, 6 much worse, and 7 very much worse.

The single-item PGIC for satiety (PGIC-S), with question, "Compared to before starting the study or compared to the Week 24 visit, how would you rate your satisfaction (fullness) after meals in the past 7 days?" and where response choices include 1 much more satisfied (full), 2 moderately more satisfied (full), 3 a little more satisfied (full), 4 no change, 5 a little less satisfied (full), 6 moderately less satisfied (full), and 7 much less satisfied (full), will also be used. The content validity of the PGIC-S has been demonstrated in overweight and obese patients with and without T2DM, although the psychometric properties of the PGIC-S were not evaluated.

8.2.6. Toxicity Management

The toxicity management guidelines in this section are applicable throughout the entire study starting from when the participant starts study intervention through the study period.

General guidance for the management of toxicities is provided in Section 8.2.6. Guidance for specific toxicities is provided in Sections 8.2.6.1 through 8.2.6.8. In addition, see Section 8.2, Safety Assessments, Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting, and Appendix 6: Management of Clinically Significant Laboratory Toxicities. Questions regarding toxicity management should be directed to the sponsor's medical monitor.

8.2.6.1. General Guidance for the Management of Clinical Events and Laboratory Abnormalities

Grade 1 and 2

Continue study intervention at the discretion of the investigator.

Grade 3

- For a Grade 3 clinical event or clinically relevant laboratory abnormality, study intervention may be continued if the event is considered to be unrelated to study intervention.
- For a Grade 3 clinical event, or clinically relevant laboratory abnormality confirmed by repeat testing (see Section 8.2), that is considered related to study intervention, study intervention should be withheld until the toxicity returns to baseline or within 1 grade from baseline, ie, ≤Grade 2.
- Mandatory confirmation is not warranted for asymptomatic Grade 3 glucose elevations in participants with preexisting diabetes, and for asymptomatic Grade 3 triglyceride or cholesterol elevations.
- If a laboratory abnormality recurs to ≥Grade 3 following rechallenge with study intervention and is considered to be related to study intervention, study intervention should be permanently discontinued, and the participant managed according to local practice. Recurrence of laboratory abnormalities considered unrelated may not require permanent discontinuation.

Grade 4

- For a Grade 4 clinical event or clinically relevant laboratory abnormality confirmed by repeat testing (see Section 8.2), that is considered related to study intervention, study intervention should be permanently discontinued, and the participant managed according to local practice. The participant should be followed as clinically indicated until the laboratory abnormality returns to baseline or is otherwise explained, whichever occurs first. A clinically relevant Grade 4 laboratory abnormality that is not confirmed upon repeat testing should be managed according to the algorithm for the new toxicity grade.
- Mandatory confirmation is not warranted for asymptomatic Grade 4 glucose elevations in participants with preexisting diabetes, and for asymptomatic Grade 4 triglyceride or cholesterol elevations.
- Study intervention may be continued without dose interruption for a clinically nonrelevant Grade 4 laboratory abnormalities (eg, Grade 4 creatine phosphokinase after strenuous exercise, or triglyceride elevation that is nonfasting or that can be medically managed), or a clinical event considered unrelated to study intervention.

A schematic overview of these guidelines is provided in Appendix 6: Management of Clinically Significant Laboratory Toxicities.

8.2.6.2. Cutaneous Events/Rash

Darunavir is a sulfonamide. Participants who previously experienced sulfonamide allergy will be allowed to enter the study. To date, no potential for cross-sensitivity between drugs in the sulfonamide class and DRV has been identified.

Cutaneous events/rash should be captured in the AE section of the eCRF.

Management of cutaneous events/rash will be at the discretion of the investigator, taking into account the following protocol procedures (see also Table 1), and should follow generally accepted medical standards. Cetirizine, levocetirizine, topical corticosteroids, and antipruritic agents will be allowed at the investigator's discretion for treatment of all grades of rashes.

Grade 1 and 2 Cutaneous Reaction/Rash

A Grade 1 cutaneous reaction/rash is defined as localized rash. A Grade 2 cutaneous reaction/rash is defined as diffuse rash or target lesions.

Participants experiencing a Grade 1 or 2 rash or cutaneous event may continue treatment or have their study intervention interrupted at the investigator's discretion. Safety sampling (processed by the central laboratory) at the time of the rash and clinical follow-up for these AEs will be at the discretion of the investigator; however, close clinical follow-up is recommended to monitor for any progression of the adverse event.

Grade 3 and 4 Cutaneous Reaction/Rash

A Grade 3 cutaneous reaction/rash is defined as:

- Diffuse rash with vesicles or limited number of bullae or superficial ulceration of mucous membrane limited to 1 site.
- For the purpose of this study, the sponsor considers qualifying as a Grade 3 rash:
- Cutaneous reaction/rash with at least 1 of the following:

elevations of ALT/AST >2× baseline but ≥5×ULN

fever ≥38°C or 100°F

serum sickness-like reaction

eosinophil count >1,000/mm^3

- The syndromes of drug rash with eosinophilia and systemic symptoms (DRESS) and acute generalized exanthematous pustulosis (AGEP)

A Grade 4 cutaneous reaction/rash is defined as:

- Extensive or generalized bullous lesions
- Stevens-Johnson syndrome (SJS)
- Ulceration of mucous membrane involving at least 2 distinct mucosal sites
- Toxic epidermal necrolysis (TEN)

Participants experiencing a Grade 3 or 4 rash or cutaneous event must have their study intervention discontinued. Referral to a dermatologist and biopsy are required for these events preferably within 24 hours after the site becomes aware of the cutaneous event/rash.

Safety testing (to be processed by the central laboratory) of the following parameters is required to determine possible liver or systemic abnormalities: ALT, AST, bilirubin (total, direct and indirect), creatinine and a hematology profile. Close clinical follow-up and appropriate medical intervention should be instituted for these events; daily follow-up is recommended for 5 days from the onset of the event to monitor for progression of the event and weekly afterwards as long as Grade 3 or 4 rash is present. Once Grade 3 or 4 rash has resolved to ≤Grade 2 rash, follow-up should be done according to the instructions for Grade 1 or 2 rash.

Table 1: Summary of Cutaneous Reaction/Rash Follow-up

DAIDS Toxicity Grade	Definitions	Investigator Action
Grade 1	Localized rash	Participant may continue study intervention
Grade 2	Diffuse rash Target lesions	Participant may continue study intervention
Grade 3	Diffuse rash with vesicles or limited number of bullae Superficial ulcerations of mucous membrane limited to 1 site For the purpose of this protocol, the sponsor considers qualifying as a Grade 3 rash the following: Cutaneous reaction/rash with at least 1 of the following: – Elevations in alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) (>2× baseline but ≥5× upper limit of normal range (ULN) – Fever ≥38°C or 100°F – Serum sickness-like reaction – Eosinophils >1,000/mm^3	Permanently discontinue study intervention Referral to a dermatologist and biopsy, preferably within 24 hours after the site becomes aware of the cutaneous event/rash Laboratory assessments need to be performed
Grade 4	Extensive or generalized bullous lesions Stevens-Johnson syndrome (SJS) Ulceration of mucous membrane involving at least 2 distinct mucosal sites Toxic epidermal necrolysis (TEN)	Permanently discontinue study intervention Referral to a dermatologist and biopsy, preferably within 24 hours after the site becomes aware of the cutaneous event/rash Laboratory assessments need to be performed

8.2.6.3. Acute Systemic Allergic Reaction

Management of acute systemic allergic reactions will be at the discretion of the investigator, taking into account the following protocol procedures (see also Table 2), and should follow generally accepted medical standards.

Grade 1

A Grade 1 acute systemic allergic reaction is defined as localized urticaria (wheals) with no medical intervention indicated.

Participants may continue study intervention or have their study intervention interrupted at the investigator's discretion. The participant should be advised to contact the investigator immediately if there is any worsening of the pruritus, or if any systemic signs or symptoms develop. Antihistamines or topical corticosteroids or antipruritic agents may be prescribed as long as these are in line with the (dis)allowed medications as indicated in Section 6.7, Concomitant Therapy, or in the local Prescribing Information of the ARV agents.

Grade 2

A Grade 2 acute systemic allergic reaction is defined as localized urticaria with medical intervention indicated, or mild angioedema with no intervention indicated.

Participants may continue study intervention or have their study intervention interrupted at the investigator's discretion. If there is any worsening of the allergic reaction, the participant should be advised to contact the investigator immediately and to discontinue study intervention. Antihistamines or topical corticosteroids or antipruritic agents may be prescribed as supportive care as long as these are in line with the (dis)allowed medications as indicated in Section 6.7, Concomitant Therapy, or in the local Prescribing Information of the ARV agents.

Grade 3

A Grade 3 acute systemic allergic reaction is defined as generalized urticaria, or angioedema with intervention indicated or symptoms of mild bronchospasm. Participants will permanently discontinue study intervention. Participants will be treated as clinically appropriate. Standard management should be undertaken.

Grade 4

A Grade 4 acute systemic allergic reaction is defined as acute anaphylaxis, or life-threatening bronchospasm, or laryngeal edema. Participants will permanently discontinue study intervention. Participants will be treated as clinically appropriate. Standard management should be undertaken.

Table 2: Summary of Allergic Reaction Follow-up

DAIDS Toxicity	Definitions	Investigator Action
Grade 1	Localized urticaria (wheals) with no medical intervention indicated	Participant may continue study intervention
Grade 2	Localized urticaria with intervention indicated, or mild angioedema with no intervention indicated	Participant may continue study intervention
Grade 3	Generalized urticaria, or angioedema with intervention indicated, or symptoms of mild bronchospasm	Permanently discontinue study intervention
Grade 4	Acute anaphylaxis, or life-threatening bronchospasm, or laryngeal edema	Permanently discontinue study intervention

8.2.6.4. Potential Renal Toxicity

Estimated creatinine clearance (eCrCl) will be calculated according to the Cockcroft-Gault formula will be followed post baseline during the treatment phase. The eGFRs calculations will be performed and provided to the investigator by the central laboratory. Any participants who have an eCrCl of <50 and a decrease of 20% in eCrCl from baseline, or who have other clinical and/or laboratory evidence of acute renal failure will be discussed with the sponsor's medical monitor and may permanently discontinue study intervention.

The eCrCl calculations will be performed and provided to the investigator by the central laboratory. Participants with negative or trace proteinuria at baseline who develop >1+ proteinuria on urinalysis must have urinalysis repeated, with a concurrent urine and serum chemistry, within 2 weeks of receipt of results. Upon confirmation of proteinuria, participants will be asked to return to the site for a scheduled or unscheduled follow-up visit. It is recommended that the investigator contacts the sponsor's medical monitor to discuss if further consultation with a nephrologist is clinically warranted.

Once an individual participant has developed any of these renal changes and the above management guidelines have been applied, it is not necessary to further unscheduled repeat evaluations if it is determined that it is safe for the participant to continue on treatment with standard visits as described in the protocol.

8.2.6.5. Potential Posterior Uveitis Cases

In a 9-month toxicology study conducted in dogs, some animals administered the highest dose of TAF (12 to 18 mg/kg) had minimal mononuclear cell infiltration in the posterior uvea, considered secondary to general debilitation; this finding did not occur in animals given lower doses and it has not occurred in other animal studies. This preclinical finding has also not been observed in humans where the dose is much lower, nor have there been reports of posterior uveitis in human clinical studies. Nonetheless, if participants develop signs or symptoms of posterior uveitis, which include notable eye pain or redness, reduced visual acuity, or "floaters", investigators in this study should inform the sponsor's medical monitor and determine, based on their medical judgment, the need for

ophthalmologic evaluation including dilated fundoscopy, and if required, optical coherence tomography.

8.2.6.6. Hyperglycemia

Grade 3: 13.89 to 27.75 mmol/L (250-500 mg/dL)

Grade 4: >27.75 mmol/L (>500 mg/dL)

Toxicity management decisions should be based on fasted results. If elevated glucose levels are from a nonfasted blood draw, the draw must be repeated after an 8-hour fast.

Participants who experienced asymptomatic glucose elevations of Grade 3 and participants with preexisting diabetes who experienced asymptomatic glucose elevations of Grade 4 may continue study intervention unless clinical assessment foresees an immediate health risk to the participant. Appropriate clinical management of hyperglycemia must be started in a timely fashion if applicable. Participants with persistent Grade 3 or 4 glucose elevations despite appropriate anti-hyperglycemic treatment should permanently discontinue study intervention.

For those participants with treatment emergent hyperglycemia, initiation of medications to address these AE should be prescribed in accordance to national treatment guidelines (See page 6: Figure 2 in Appendix 11: Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD).

Should a participant have a need to initiate treatment with any excluded concomitant medication, it is recommended that investigators consult with the sponsor medical monitor beforehand to determine if an alternative therapy could be utilized that has no known impact on weight or if the participant should be discontinued from the study. If an excluded medication is initiated before discussion with the medical monitor, the investigator must notify the sponsor as soon as becoming aware.

Investigators are reminded that certain medications may influence body weight changes and should be avoided. (see disallowed concomitant therapy below). Participants should not initiate therapy with concomitant medications associated with significant weight changes during the course of the study as listed in Exclusion Criteria No. 11.

Participants who experience clinically significant changes in body weight during the course of the study may require dose reductions or withdrawal of medications to treat type II diabetes in order to avoid events such as hypoglycemia. As part of routine care at scheduled follow-up visits, participants should be assessed to determine if a dose reduction or withdrawal of medications for the treatment of such conditions is warranted. These changes should be recorded in the CRF.

8.2.6.7. Hypertriglyceridemia and Hypercholesterolemia

Hypertriglyceridemia: Grade 3: 5.7 to 11.4 mmol/L (>500-1,000 mg/dL)

Grade 4: >11.4 mmol/L (>1,000 mg/dL)

Hypercholesterolemia: Grade 3: ≥7.77 mmol/L (>300 mg/L)

Grade 4: Not applicable

Toxicity management decisions should be based on fasted results. If elevated lipid levels are from a nonfasted blood draw, the draw must be repeated after an 8-hour fast.

Participants who experienced asymptomatic triglyceride or cholesterol elevations of Grade 3 or 4 may continue study intervention unless clinical assessment foresees an immediate health risk to the participant.

Hypertriglyceridemia and hypercholesterolemia should be treated according to the specific guidelines for treating HIV-positive participants (see Figure 4 in Appendix 9: Characteristics, Prevention, and Management of Cardiovascular Diseases in People Living with HIV by American Heart Association. The presence or absence of other significant cardiovascular risk factors, which include smoking, age, family history of premature cardiovascular disease, diabetes, hypertension, low high-density lipoprotein (HDL), and prior history of cardiovascular disease should be taken into account. Appropriate clinical management of hyperlipidemia in the setting of HIV should be started in a timely fashion if applicable and taking into account the disallowed medications (refer to Section 6.8, Concomitant Therapy).

8.2.6.8. Lipodystrophy/Fat Redistribution/Body Changes

Investigators are requested to avoid using the term ‘lipodystrophy acquired’ or ‘fat redistribution’ to describe and report body fat abnormalities, as these terms are not descriptive nor fully accurate. The different symptoms and gradings are listed in the DAIDS grading table (Appendix 7: DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events) under Endocrine/Metabolic. The following terms are included: lipohypertrophy, lipoatrophy, and gynecomastia. Although metabolic abnormalities such as hyperlipidemia or hyperglycemia are often associated with body changes, these events should be recorded separately at AE reporting.

8.3. Adverse Events, Serious Adverse Events, and Other Safety Reporting

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

Adverse events (AEs) will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally acceptable representative) for the duration of the study.

For further details on AEs and SAEs (Definitions and Classifications; Attribution Definitions; Severity Criteria; Special Reporting Situations; Procedures) as well as product quality complaints, refer to Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.3.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All Adverse Events

All AEs and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until completion of the participant's last study-related procedure, which may include contact for follow-up of safety. Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of study intervention, must be reported using the SAE Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

Serious Adverse Events

All SAEs occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

Information regarding serious adverse events will be transmitted to the sponsor using the Serious Adverse Event Form and Safety Report Form of the CRF, which must be completed and reviewed by a physician from the study site, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of a serious adverse event should be transmitted electronically or by facsimile (fax).

8.3.2. Follow-up of Adverse Events and Serious Adverse Events

Adverse events, including pregnancy, will be followed by the investigator as specified in Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.3.3. Regulatory Reporting Requirements for Serious Adverse Events

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate IEC/IRB that approved the protocol unless otherwise required and documented by the IEC/IRB.

8.3.4. Pregnancy

All initial reports of pregnancy in female participants or partners of male participants must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported using the SAE Form. Any participant who becomes pregnant during the study must be promptly withdrawn from the study.

Because the effect of the D/C/F/TAF FDC on sperm is unknown, pregnancies in partners of male participants included in the study will be reported as noted above.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

8.3.5. Adverse Events of Special Interest

Not applicable.

8.4. Pharmacokinetics

Plasma samples may be used to evaluate the concentration of DRV and COBI in participants experiencing confirmed virologic rebound using stored blood samples collected throughout the study at the discretion of the sponsor. Plasma concentrations of INIs for the Delayed Switch arm may be determined in participants experiencing confirmed virologic rebound using stored blood samples collected throughout the study, if deemed necessary by the sponsor. Genetic analyses will not be performed on these plasma samples. Participant confidentiality will be maintained.

8.4.1. Evaluations

Venous blood samples of approximately 3mL will be collected for measurement of plasma concentrations of DRV and COBI in participants experiencing confirmed virologic rebound using stored blood samples collected throughout the study at the discretion of the sponsor. Plasma concentrations of INIs for the Delayed Switch arm may be determined in participants experiencing confirmed virologic rebound using stored blood samples collected throughout the study, if deemed necessary by the sponsor.

Urine samples will be collected for measurement of various parameters as mentioned in Schedule of Activities (SoA).

8.4.2. Pharmacokinetic Parameters and Evaluations

Not applicable.

8.5. Genetics

Not applicable.

8.6. Biomarkers

Alpha Melanocyte-Stimulating Hormone

Alpha melanocyte-stimulating hormone has multiple functions. Melanocyte-stimulating hormone is produced from the same precursor molecule as adrenocorticotropic hormone called pro-opiomelanocortin (POMC). The presence of alpha melanocyte-stimulating hormone induces a satiety response. This effect is enhanced by leptin, a hormone released from fat cells. A decrease in the presence of alpha melanocyte-stimulating hormone may lead to increased food intake and obesity. As an exploratory endpoint, levels of alpha melanocyte-stimulating hormone will be collected to

determine if there is a change in the amount of circulating hormone in patients who have rapidly gained weight on an INI + TAF/FTC versus being switched over to D/C/F/TAF.[33]

Leptin

Leptin is a hormone secreted by adipose tissue that regulates a variety of immune, metabolic, and neuroendocrine functions. It also helps to maintain energy balance. Leptin works to regulate glucose and lipid metabolism by affecting pancreatic release of insulin and plays a role in increasing insulin sensitivity. Leptin increases thermogenic energy expenditure which prevents fat accumulation. Leptin also plays a role in the maintenance of weight by inducing satiety via a hypothalamic signal during and after a meal. In collecting the leptin levels in those patients who have rapidly gained weight on an INI + TAF/FTC regimen, we are interested to see if these levels are changed while on the baseline regimen compared to when participants are switched over to D/C/F/TAF.[37]

Adiponectin

Adiponectin is an adipokine that enhances energy metabolism and fatty acid oxidation. It also promotes insulin sensitivity. Adiponectin is released by adipose tissue. The levels of adiponectin in the blood are inversely related to adipose tissue mass. Lower levels of adiponectin in the blood are associated with metabolic disease. Adiponectin levels will be collected to see if there is a change in levels in those participants who have rapidly gained weight on an INI + TAF/FTC compared to when participants are switched to D/C/F/TAF.[7]

8.6.1. Pharmacodynamics

Not applicable.

8.7. Immunogenicity Assessments

Not Applicable

8.8. Health Economics OR Medical Resource Utilization and Health Economics

Not applicable.

9. STATISTICAL CONSIDERATIONS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the data collected in this study is outlined below. Specific details will be provided in the Statistical Analysis Plan.

9.1. Statistical Hypotheses

The statistical hypothesis is the following:

H_0: Dt-Dc 0 versus H_1: Dt -Dc≠0.

Where H_0 is the null hypothesis, H_1 is the alternative hypothesis; Dt %body weight change from baseline at Week 24 for treatment D/C/F/TAF, Dc for the Delayed Switch arm.

The statistical hypothesis will be tested using repeated measures longitudinal method (linear mixed-effects model) at 0.05 significance level, 2-sided.

9.2. Sample Size Determination

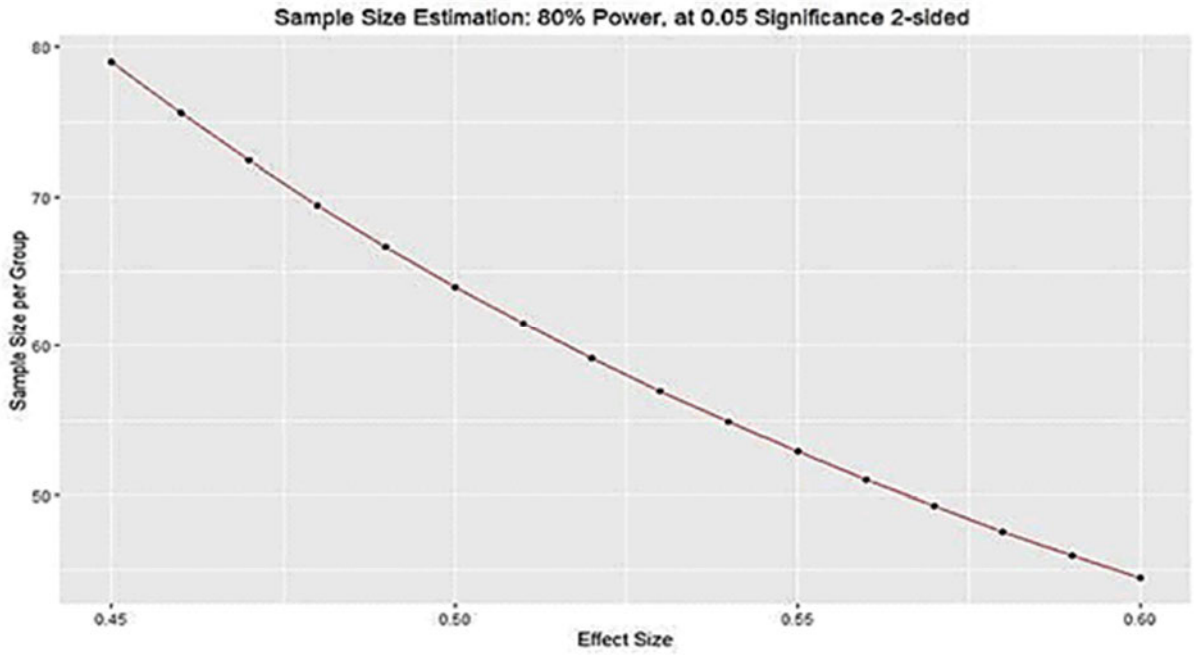
Using a T-test with 80% power to detect a difference of 3% at the significance level of 0.05, 2-sided, the sample size per treatment arm is a simple function of effect size (ES): n_{arm} 16/(ES)^2. The effect size is the standardized difference: ES Δ/σ, where Δ is the difference between the two arms, and σ^2 is the common variance. Since there was no direct data on the study population to assume the observed difference, Δ 3% is considered a clinical meaningful difference. Internal data from 2 Phase 3 studies[15,29] on D/C/F/TAF FDC arm from different HIV patient populations (naive, switch) have shown the % body weight change in the range of 1.5% to 1.8% and standard deviation from 4.0 to 4.6 (Table 3 and Figure 3), resulting a range of ES and corresponding sample size.

Table 3: Phase 3 Studies on D/C/F/TAF FDC Arm

Study	AMBER D/C/F/TAF arm	EMERALD D/C/F/TAF arm
N % body weight change from baseline at week 24 (SD)	347 1.5 (4.6)	738 1.8 (4.0)
N % body weight change from baseline at week 48 (SD)	340 2.3 (5.0)	728 1.9 (5.1)

(Data on file)
Abbreviations: D/C/F/TAF FDC: darunavir/cobicistat/emtricitabine/tenofovir alafenamide fixed dose combination, N: number, SD: standard deviation

Figure 3: Sample Size Estimation by Treatment Effect Size



Given the uncertainty of either the Δ or the variability, an adaptive unblinded SSR is planned to re-estimate the sample size in an IA to ensure adequate power in the hypothesis testing for the primary endpoint using the conditional power approach. An initial sample size of 55 participants per treatment arm (110 participants total) will be used for a treatment effect size of 0.54 (ADDPLAN version 6). The IA is planned when approximately 60% of the initial planned 110 participants have completed the Week 12 Visit and approximately 30% of participants have completed the Week 24 visit to re-estimate the sample size to ensure adequate power for the hypothesis testing. All cumulative data will be used for the IA. The planned maximum total sample size after SSR is 150 participants. Details for the SSR, threshold for the conditional power, and protection of overall significance level will be provided in the statistical plan for the IA and monitoring (Section 9.6).

9.3. Populations for Analysis Sets

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign the informed consent form (ICF)
Intent-to-treat (ITT)	includes all randomized participants who received at least 1 dose of study intervention. Participants will be assessed according to their randomized treatment arm, regardless of the treatment they received.
Per-protocol (PP)	includes a subset of participants in the ITT who are in-compliance with the protocol.
Safety	includes all randomized participants who received at least 1 dose of study intervention. Participants will be assessed according to the actual intervention they received.

For all participants who receive at least 1 dose of study intervention descriptive statistics will be provided. Participant information will be analyzed based on the ITT population, unless otherwise specified.

9.4. Statistical Analyses

The statistical analysis plan will be finalized prior to DBL and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1. General Considerations

The following analyses will be performed:

- An interim analysis at week 12 for monitoring purpose including an unblinded sample size re-estimation and futility analysis (see also Section 9.6).
- The primary analysis: once all participants have completed the Week 24 assessments or discontinued earlier. The primary hypothesis will be tested at an overall significance level of 0.05, 2-sided in a longitudinal data with repeated measures model (Section 9.4.2).
- The Week 48 analysis: once all participants have completed the Week 48 assessments or discontinued earlier. Descriptive statistics will be conducted.

9.4.2. Primary Analysis

The primary endpoint analyses will be based on the ITT population. The analysis will be conducted using linear mixed-effects model with participant as random effect adjusted by baseline BMI and stratification factors in a longitudinal data with repeated measures (percent body weight change measured at multiple visits).[40]

9.4.3. Secondary Analyses

9.4.3.1. Metabolic Analyses

For the metabolic endpoints of change from baseline, the same statistical model as described for the primary endpoint will be used for analysis. All other endpoints will be analyzed using descriptive statistics.

9.4.3.2. Resistance/Efficacy Analyses

HIV-1 genotypes, and phenotypes (PhenoSense GT® Plus Integrase) if applicable, will be analyzed from samples of participants with virologic rebound and with HIV-1 RNA ≥400 copies/mL.

The proportion of virologic suppression (HIV-1 RNA<50 copies/mL) and failure (HIV-1 RNA ≥50 copies/mL) using the FDA snapshot algorithm in the ITT will also be analyzed as a secondary endpoint at Weeks 24 and 48 using descriptive statistics along with 95% confidence interval (CI, Wilson score method).

The proportion of participants experiencing virologic rebound through Week 24 and 48 will be tabulated using descriptive statistics along with the 95% confidence intervals (CI, Wilson score method).

The changes from screening/baseline in $CD4^+$ cell count at Weeks 24 and 48 will be summarized using descriptive statistics.

The number of identified protease (PR) mutations (including International AIDS Society [IAS]-USA primary and secondary PI resistance-associated mutations [RAMs], reverse transcriptase (RT) mutations (including IAS-USA nucleoside/nucleotide RT inhibitor [N[t]RTI] RAMs, IAS-USA non-nucleoside RT inhibitor [N[t]RTI] RAMs), and integrase (INI) mutations (including International AIDS Society [IAS]-USA INI-RAMs and IAS-USA primary INI mutations), as well as specific mutations associated with resistance to DRV, FTC, and TAF, will be tabulated based on the observed virologic rebound through the study period. Retrospectively, fold change (FC) in 50% effective concentration (EC_{50}) of ARVs may be analyzed and tabulated dependent on the number of virologic rebounds and phenotypes available through the study period.

9.4.3.3. Adherence Analyses

Treatment adherence based on participant self-report, using a 4-day recall will be summarized by means of descriptive statistics and frequency tabulations for both D/C/F/TAF and the INI + TAF/FTC ARV regimen.

Adherence rates will be reported according to the proportion of participants missing 0, 1, 2, 3 or 4 doses using participant self-report 4-day recall at Weeks 4, 12, 24, 36, and 48.

9.4.4. Safety Analyses

All safety analyses will be made on the Safety Population. For all safety endpoints descriptive statistics will be used to summarize the endpoints.

Adverse Events

The verbatim terms used in the CRF by investigators to identify AEs will be categorized according to system organ class and graded according to DAIDS as specified in Appendix 7: DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events. Any AE occurring at or after the initial administration of study intervention through the day of last dose plus 7 days is considered to be treatment-emergent. All reported treatment-emergent adverse events (TEAEs) will be included in the analysis. For each AE, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by intervention arm.

Summaries, listings, datasets, or participant narratives may be provided, as appropriate, for those participants who die, who discontinue intervention due to an AE, or who experience a severe or a serious adverse event.

Clinical Laboratory Tests

Laboratory data will be summarized by treatment arm and type of laboratory test. Reference ranges and markedly abnormal results (specified in the Statistical Analysis Plan) will be used in the summary of laboratory data. Descriptive statistics will be calculated for all laboratory analyte for observed values and for changes from Screening/Baseline at each scheduled time point. Laboratory

abnormalities will be categorized according to analyte and graded according to DAIDS as specified in Appendix 7: DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events.

Vital Signs

Descriptive statistics of vital signs including temperature, pulse/heart rate, body weight, and blood pressure (systolic and diastolic) (supine) values and changes from baseline will be summarized at each scheduled time point. The percentage of participants with values beyond clinically important limits will be summarized. Vital signs abnormalities will be categorized according to parameter and graded according to DAIDS as specified in Appendix 7: DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events.

Physical Examination

Descriptive statistics of changes from baseline will be summarized at each scheduled time point.

Physical examination findings will be summarized at each scheduled time point. Descriptive statistics will be calculated at baseline and for observed values and changes from baseline at each scheduled time point. Frequency tabulations of the abnormalities will be made.

9.4.5. Patient-reported Outcomes Analyses

Descriptive statistics for absolute values will be calculated for each PRO measure including BSQ-8D, HIV-SI, DAILY EATS, and PGIC and at each timepoint per Schedule of Activities (SoA). In addition, changes from baseline in the proportion of participants who have bothersome symptoms (scores of 2, 3 or 4) across all items of the HIV-SI at Weeks 24 and 48, changes from baseline in the proportion of participants who have any symptoms (scores of 1, 2, 3 or 4) across all items of the HIV-SI at Weeks 24 and 48, and changes from baseline in the scores on the BSQ-8D and proportion of participants who have no concern (<19), mild concern (19-25), moderate concern (26-33) or marked concern (>33) with their body shape at Weeks 24 and 48 and changes from baseline in the scores on the DAILY EATS at Weeks 24 and 48 will be summarized. Association between treatment arm and each bothersome symptom of the HIV-SI adjusting for baseline variables at Weeks 24 will be calculated. To understand meaningful change in scores on PRO measures, PGIC-S will be used as an anchor to assess meaningful change scores for the DAILY EATS in participants living with HIV.

9.5. Interim Analysis

An IA will be performed when approximately 60% of the initial planned 110 participants have completed the Week 12 Visit and approximately 30% of participants have completed the Week 24 Visit to assess SSR unblinded to ensure adequate power for the hypothesis testing for the primary endpoint.

9.6. Data Monitoring Committee or Other Review Board

A Data Review Committee (DRC) will be established to evaluate SSR at an IA from this study. An adaptive unblinded SSR is planned to re-estimate the sample size to ensure adequate power in the hypothesis testing for the primary endpoint using the conditional power approach, in which the thresholds of conditional power will be considered in relation to the required sample sizes. An IA is

planned when approximately 60% of the initial planned 110 participants have completed the Week 12 Visit and approximately 30% of participants have completed the Week 24 Visit to re-estimate the sample size to ensure adequate power for the hypothesis testing. In addition, a futility will be evaluated regarding the statistical hypothesis based on available interim data and conditional power. All cumulative data will be used in a Bayesian posterior predictive probability approach to assess SSR and futility. Further details regarding the derivation of the conditional power and the choice of threshold for the conditional power for SSR, futility and protection of overall significance level will be provided in the DRC charter and DRC SAP. The SSR and futility analysis will be guided by the DRC, and the study team will remain blinded to the analysis. It is not the intention to stop the study early in case of superiority of the D/C/F/TAF FDC regimen versus the Delayed Switch arm. The DRC will consist of 2 medical experts in the relevant therapeutic area and 1 statistician, independent to the study team. The DRC responsibilities, authorities, and procedures will be provided in the DRC charter.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations

AE	adverse event
AIDS	Acquired Immunodeficiency Syndrome
ALT	alanine aminotransferase
ARV	antiretroviral
ART	antiretroviral therapy
AST	aspartate aminotransferase
BMI	body metabolic index
BSQ-8D	body shape questionnaire
C	cobicistat (COBI)
CI	confidence interval
CRF	case report form(s) (paper or electronic as appropriate for this study)
D	darunavir (DRV)
DAIDS	Division of Acquired Immunodeficiency Syndrome
DBP	diastolic blood pressure
DEXA	dual-energy X-ray absorptiometry
DHHS	Department of Health and Human Services
eCrCl	estimated creatinine clearance
eDC	electronic data capture
eGFRcr	creatinine-based estimated glomerular filtration rate
ESID	early study intervention discontinuation
F	emtricitabine
FDA	food drug administration
FDC	fixed-dose combination
HAIR	hypertension, age, insulin, resistance
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HIV-1 RNA	human immunodeficiency virus type-1 ribonucleic acid
HIV-SI	HIV-Symptom Index
HOMA-IR	homeostatic model assessment of insulin resistance
IA	interim analysis
IAS-USA	International AIDS Society-United States of America
ICF	informed consent form
IEC	independent ethics committee
INI	integrase
IRB	Institutional Review Board
ITT	intent-to-treat
IWRS	interactive web response system
NAFLD	non-alcoholic fatty liver disease
NRTI	nucleoside reverse transcriptase inhibitor
PGIC	patient global impression of change
PGIC-S	patient global impression of change– Satiety
PI	protease inhibitor
PQC	product quality complaint
PK	pharmacokinetic
PR	protease
PRO	patient reported outcomes
RAM	resistance-associated mutations
RT	reverse transcriptase
SAEs	serious adverse events
SAP	statistical analysis plan
SBP	systolic blood pressure
SSR	sample size re-estimation
SUSARs	suspected unexpected serious adverse reactions
TAF	tenofovir alafenamide

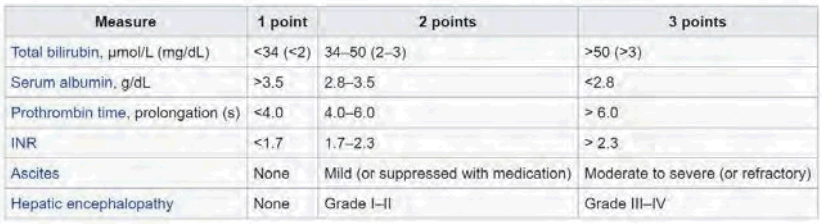
10.2. Appendix 2: Clinical Laboratory Tests and Calculations

The following tests will be performed according to the Schedule of Activities (SoA) by the central laboratory:

Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters	
Hematology*	Platelet count Red blood cell count Hemoglobin HbA1c Hematocrit Absolute neutrophil count CD4+ cell count CD8+ cell count CD4+/CD8+ ratio International normalized ratio (INR)**	White Blood Cell (CBC) count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
	* A whole blood sample will be taken for storage and will only be analyzed if deemed necessary by the sponsor to characterize archived viral resistance at predefined time points, see Schedule of Activities (SoA) and stored for future analysis if needed. ** Screening Only	
Clinical Chemistry (fasting samples will be taken for the measurement)	Sodium Potassium Chloride Bicarbonate Blood urea nitrogen (BUN) Serum Creatinine, including calculated eCrCl Glucose Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Insulin	Bilirubin (total, direct, indirect) Alkaline phosphatase (ALP) Calcium Calcium corrected for albumin Phosphate Albumin Total protein
	• In case of rash, safety blood samples need to be taken and are to be processed by the central laboratory. For details on rash management, see Section 8.2.6.2, Cutaneous Events/Rash.	
Routine Urinalysis	Dipstick Specific gravity pH Glucose Protein Blood Ketones Bilirubin Urobilinogen Nitrite Leukocyte esterase	Urine chemistry panel (only in the setting of a suspected renal adverse event): Urine Creatinine Urine Sodium Urine Phosphate Urine Glucose Urine Albumin Urine Protein Serum creatinine
	If dipstick results are abnormal, flow cytometry will be used to measure sediment. In case of discordance between the dipstick results and the flow cytometry results, the sediment will be examined microscopically. In the microscopic examination, observations other than the presence of WBC, RBC, and casts may also be reported by the laboratory.	
Other Screening Tests	• Hepatitis C virus (HCV) testing (HCV antibodies [Ab] and HCV RNA level [only if HCV Ab+]) and hepatitis B virus (HBV) testing (anti hepatitis B core [HBc], anti hepatitis B surface [HBs], hepatitis B surface antigen [HBsAg]) (at screening only). Whenever clinically relevant, the investigator can request additional tests at other visits. • Urine Pregnancy Testing for women of childbearing potential only. A serum human chorionic gonadotropin pregnancy test will be assessed at Screening at a central laboratory. A urine pregnancy test will be performed at subsequent study visits as	
Fasting Metabolic Profile	Total, high density lipoprotein [HDL] and low density lipoprotein [LDL], cholesterol, triglycerides, glucose. If a participant has not fasted prior to the visit, the visit may proceed, but participant must return within 72 hours in a fasted state to have a blood draw for the metabolic assessments.	

Calculations

Body Mass Index (BMI) (kg/m^2)	Weight (kg) / [Height (m)]^2
Child Pugh Class	
eGFRcr (Cockcroft-Gault Formula)	CrCl (male) = ([140-age] × weight in kg)/(serum creatinine × 72) CrCl (female) = ([140-age] × weight in kg)/(serum creatinine × 72) × 0.85 **Note:** If a participant's actual body weight is greater than 20% over their Ideal Body Weight, the participant's Adjusted BodyWeight will be used for eGFRcr (Cockcroft-Gault Formula): **Ideal Body Weight (IBW):** Male: 50kg + 0.9kg x (height(cm) – 152) Female: 45.5kg + 0.9kg x (height(cm) – 152) **Adjusted Body Weight:** IBW (kg) + 0.4 x (Weight(kg) – IBW (kg))
HOMA-IR (mg/dL)	Fasting insulin x Fasting glucose / 405
Non-Alcoholic Fatty Liver Disease (NAFLD) Fibrosis Score[1]	-1.675 + 0.037 × age (years) + 0.094 × BMI (kg/m^2) + 1.13 × IFG/diabetes (yes = 1, no = 0) + 0.99 × AST/ALT ratio – 0.013 × platelet (×109/l) – 0.66 × albumin (g/dl) NAFLD Score <-1.455 = F0-F2 NAFLD Score -1.455 – 0.675 = indeterminate score NAFLD Score >0.675 = F3-F4
NASH: HAIR Scores[12]	HAIR score (0–3) is calculated by adding Hypertension = 1, ALT >40 IU =1, and IR index >5.0 = 1 A score of ≥2 is high risk for NASH.

Measure	1 point	2 points	3 points
Total bilirubin, µmol/L (mg/dL)	<34 (<2)	34–50 (2–3)	>50 (>3)
Serum albumin, g/dL	>3.5	2.8–3.5	<2.8
Prothrombin time, prolongation (s)	<4.0	4.0–6.0	> 6.0
INR	<1.7	1.7–2.3	> 2.3
Ascites	None	Mild (or suppressed with medication)	Moderate to severe (or refractory)
Hepatic encephalopathy	None	Grade I–II	Grade III–IV

10.3. Appendix 3: Regulatory, Ethical, and Study Oversight Considerations

REGULATORY AND ETHICAL CONSIDERATIONS

Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human participants. Compliance with this standard provides public assurance that the rights, safety, and well-being of study participants are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the participants, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involve only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the CRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study intervention to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, participant compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrollment of the first participant:

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the participants)
- Investigator's Brochure (or equivalent information) and amendments/addenda
- Sponsor-approved participant recruiting materials
- Information on compensation for study-related injuries or payment to participants for participation in the study, if applicable

- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for participants
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for participants, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and participant compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

Other Ethical Considerations

For study-specific ethical design considerations, refer to Section 4.2.1.

FINANCIAL DISCLOSURE

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information in accordance with local regulations to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Refer to Required Prestudy Documentation (above) for details on financial disclosure.

INFORMED CONSENT PROCESS

Each participant must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study- related activity. The ICF(s) that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the participant can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential participants the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Participants will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the participant will receive for the treatment of his or her disease. Participants will be told that alternative treatments are available, or they can remain on their current ARV regimen if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a participant identification register for the purposes of long-term follow up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the participant, to the extent permitted by the applicable law(s) or

regulations. By signing the ICF the participant is authorizing such access, which includes permission to obtain information about his or her survival status. It also denotes that the participant agrees to allow his or her study physician to recontact the participant for the purpose of obtaining consent for additional safety evaluations, and subsequent disease-related treatments, if needed.

The participant will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the participant's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the participant.

DATA PROTECTION

Privacy of Personal Data

The collection and processing of personal data from participants enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of participants confidential.

The informed consent obtained from the participant includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The participant has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

LONG-TERM RETENTION OF SAMPLES FOR ADDITIONAL FUTURE RESEARCH

Blood samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand D/C/F/TAF FDC tablet, to understand HIV-1 infection and to understand differential intervention responders. The research may begin at any time during the study or the poststudy storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Participants may withdraw their consent for their samples to be stored for research (refer to Section 7.2.1, Withdrawal From the Use of Research Samples).

COMMITTEES STRUCTURE

The DRC will consist of two medical experts in the relevant therapeutic area and one statistician, independent to the study team. The DRC responsibilities, authorities, and procedures will be provided in the DRC charter.

PUBLICATION POLICY/DISSEMINATION OF CLINICAL STUDY DATA

All information, including but not limited to information regarding D/C/F/TAF FDC tablet or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation supplied by the sponsor to the investigator and not previously published, and any data, including research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of D/C/F/TAF FDC tablet, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator for the study. Results of analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report.

Study participant identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors (ICMJE) guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and

substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 18 months after the study end date, or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the existence of and the results of clinical studies as required by law. The disclosure of the final study results will be performed after the end of study in order to ensure the statistical analyses are relevant.

DATA QUALITY ASSURANCE

Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, periodic monitoring visits by the sponsor, direct transmission of clinical laboratory data from a central laboratory into the sponsor's data base, and electronic transmission of electronic PRO data to the electronic PRO vendor data base then to the Sponsor’s clinical data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for eCRF completion will be provided and reviewed with study-site personnel before the start of the study. The sponsor will review eCRFs for accuracy and completeness during on- site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study data base they will be verified for accuracy and consistency with the data sources.

CASE REPORT FORM COMPLETION

Case report forms are prepared and provided by the sponsor for each participant in electronic format. All data relating to the study must be recorded in eCRF. All eCRF entries, corrections, and alterations must be made by the investigator or authorized study-site personnel. The investigator must verify that all data entries in the eCRF are accurate and correct.

The study data will be transcribed by study-site personnel from the source documents onto an eCRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the participant's source documents. Data must be entered into eCRF in English. The eCRF must be completed as soon as possible after a participant visit and the forms should be available for review at the next scheduled monitoring visit.

All participative measurements (eg, pain scale information or other questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible.

If necessary, queries will be generated in the eDC tool. If corrections to an eCRF are needed after the initial entry into the eCRF, this can be done in either of the following ways:

- Investigator and study-site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Sponsor or sponsor delegate can generate a query for resolution by the investigator and study-site personnel.

SOURCE DOCUMENTS

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: participant identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all AEs and follow-up of AEs; concomitant medication; intervention receipt/dispensing/return records; study intervention administration information; and date of study completion and reason for early discontinuation of study intervention or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

The following data will be recorded directly into the electronic device to collect PROs and will be considered source data:

- HIV-SI
- BSQ-8D
- DAILY EATS
- PGIC, PGIC-S

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by participant interview or other protocol required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

An eSource system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the sponsor. If eSource is utilized, references made to the eCRF in the protocol include the eSource system, but information collected through eSource may not be limited to that found in the eCRF.

MONITORING

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first postinitiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the eCRF with the source documents (eg, hospital/clinic/physician's office medical records). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

ON-SITE AUDITS

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Participant privacy must, however, be respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

RECORD RETENTION

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all eCRF and all source documents that support the data collected from each participant, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

STUDY AND SITE START AND CLOSURE

First Act of Recruitment

The first site open is considered the first act of recruitment and it becomes the study start date.

Study Termination

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

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

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

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

10.4. Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

ADVERSE EVENT DEFINITIONS AND CLASSIFICATIONS

Adverse Event

An adverse event (AE) is any untoward medical occurrence in a clinical study participant administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH])

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects AE starting with the signing of the ICF (refer to All Adverse Events under Section 8.3.1, Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events Information, for time of last adverse event recording).

Serious Adverse Event

A serious adverse event (SAE) based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (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 were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

If a serious and unexpected AE occurs for which there is evidence suggesting a causal relationship between the study intervention and the event (eg, death from anaphylaxis), the event must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (eg, all-cause mortality).

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For D/C/F/TAF FDC tablet, the expectedness of an AE will be determined by whether or not it is listed in the applicable full Prescribing Information current at the time the event is reported.

ATTRIBUTION DEFINITIONS

Assessment of Causality

The causal relationship to study treatment is determined by the Investigator. The following selection should be used to assess all adverse events (AE).

Related

There is a reasonable causal relationship between study treatment administration and the AE.

Not Related

There is not a reasonable causal relationship between study treatment administration and the AE.

The term "reasonable causal relationship" means there is evidence to support a causal relationship.

SEVERITY CRITERIA

An assessment of severity grade will be made using the general categorical descriptors outlined in the DAIDS toxicity grading table in Appendix 7: DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events. The investigator should use clinical judgment DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events.in assessing the severity of events not directly experienced by the participant (eg, laboratory abnormalities).

A distinction should be made between seriousness and severity of adverse events. An AE assessed as Grade 4 (potentially life-threatening) should not be confused with a serious adverse event. Severity is a category utilized for rating the intensity of an event, and both AEs and SAEs can be assessed as Grade 4. An event is defined as ‘serious’ when it meets one of the predefined outcomes listed above.

Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities are usually not recorded as AEs or serious adverse events. However, laboratory abnormalities independent of the underlying medical condition that require medical or surgical intervention or lead to study intervention interruption or discontinuation must be recorded

as an AE as well as a SAE, if applicable. Laboratory or other abnormal assessments (eg, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definitions as described above. If the laboratory abnormality is part of a syndrome, the syndrome/diagnosis (ie, anemia) must be recorded and not the laboratory result (ie, decreased hemoglobin).

SPECIAL REPORTING SITUATIONS

Safety events of interest on a sponsor study intervention in an interventional study that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a sponsor study intervention
- Suspected abuse/misuse of a sponsor study intervention
- Accidental or occupational exposure to a sponsor study intervention
- Any failure of expected pharmacologic action (ie, lack of effect) of a sponsor study intervention
- Unexpected therapeutic or clinical benefit from use of a sponsor study intervention
- Medication error, intercepted medication error, or potential medication error involving a Johnson & Johnson medicinal product (with or without patient exposure to the Johnson & Johnson medicinal product, eg, product name confusion, product label confusion, intercepted prescribing or dispensing errors)
- Exposure to a sponsor study intervention from breastfeeding

Special reporting situations should be recorded in the CRF. Any special reporting situation that meets the criteria of a serious adverse event should be recorded on the serious adverse event page of the CRF.

PROCEDURES

All Adverse Events

All AEs, regardless of seriousness, severity, or presumed relationship to study intervention, must be recorded using medical terminology in the source document and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the eCRF their opinion concerning the relationship of the AE to study therapy. All measures required for AE management must be recorded in the source document and reported according to sponsor instructions.

For all studies with an outpatient phase, including open-label studies, the participant must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the participant is participating in a clinical study

- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical staff only)
- Site number
- Participant number
- Any other information that is required to do an emergency breaking of the blind

Serious Adverse Events

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the participant's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study intervention or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (participant or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Suspected transmission of an infectious agent by a medicinal product will be reported as a serious adverse event. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a participant's participation in a study must be reported as a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (eg, social reasons such as pending placement in long-term care facility).
- Surgery or procedure planned before entry into the study (must be documented in the CRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered serious adverse events. Any AE that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.

Disease progression should not be recorded as an AE or SAE term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the SAE definition (refer to Adverse Event Definitions and Classifications in Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting).

CONTACTING SPONSOR REGARDING SAFETY

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed in the Contact Information page(s), which will be provided as a separate document.

PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel within 24 hours after being made aware of the event.

If the defect is combined with a SAE, the study-site personnel must report the PQC to the sponsor according to the SAE reporting timelines (refer to Section 8.3.1, Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed in the Contact Information page(s), which will be provided as a separate document.

10.5. Appendix 5: Contraceptive and Barrier Guidance and Collection of Pregnancy Information

Participants must follow contraceptive measures as outlined in Section 5.1, Inclusion Criteria. Pregnancy information will be collected and reported as noted in Section 8.3.4, Pregnancy, and Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Woman Not of Childbearing Potential

- **premenarchal**
  A premenarchal state is one in which menarche has not yet occurred.
- **postmenopausal**
  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in female participants not using hormonal contraception or hormonal replacement therapy (HRT), however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- **permanently sterile**
  Permanent sterilization methods include hysterectomy, bilateral salpingectomy, bilateral tubal occlusion/ligation procedures, and bilateral oophorectomy.

Note: If the childbearing potential changes after start of the study (eg, a premenarchal female participant experiences menarche) or the risk of pregnancy changes (eg, a female participant who is not heterosexually active becomes active), a female participant must begin a highly effective method of contraception, as described throughout the inclusion criteria. If reproductive status is questionable, additional evaluation should be considered.

Contraceptive (birth control) use by male or female participants should be consistent with local regulations regarding the acceptable methods of contraception for those participating in clinical studies.

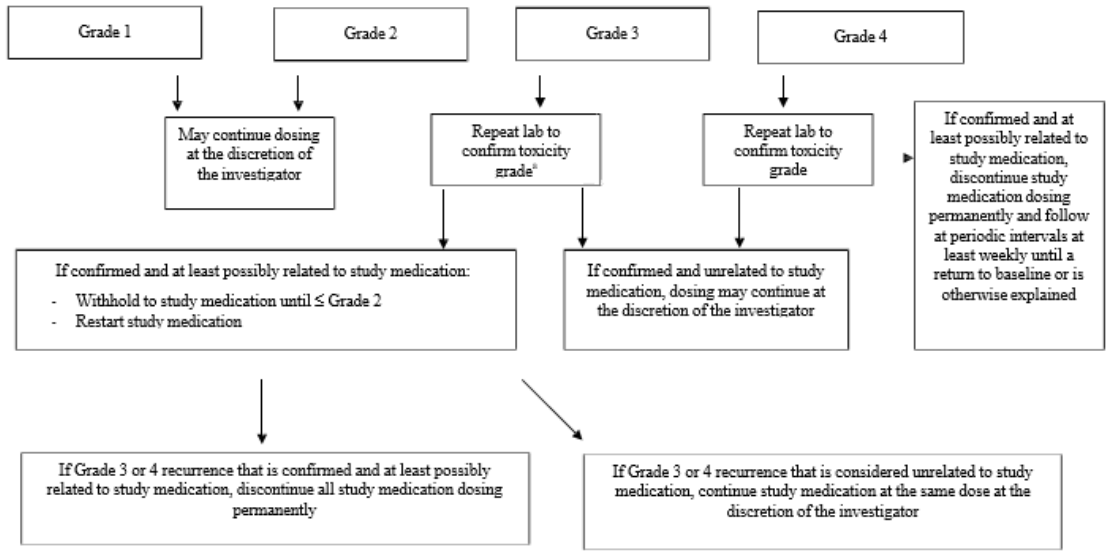
Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

Examples of Contraceptives

EXAMPLES OF CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
USER INDEPENDENT **Highly Effective Methods That Are User Independent** *Failure rate of ≤1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)
• Bilateral tubal occlusion
• Vasectomized partner *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 74 days.)*
USER DEPENDENT **Highly Effective Methods That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*
• Estrogen-based hormonal contraception may not be reliable when taking the study drug. Therefore, to be eligible for this study, women of childbearing potential should either use: – a double-barrier method (male condom + either diaphragm or cervical cap); *OR* – non-estrogen hormonal based contraceptives in combination with a barrier contraceptive (male condom, diaphragm or cervical cap, or female condom); *OR* – intrauterine device in combination with a barrier contraceptive (male condom, diaphragm or cervical cap, or female condom). **Note**: A male condom and female condom should not be used together due to risk of breakage or damage caused by latex friction.
• Progestogen-only hormone contraception associated with inhibition of ovulation[b] –oral –injectable
• Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*
NOT ALLOWED AS SOLE METHOD OF CONTRACEPTION DURING THE STUDY (not considered to be highly effective - failure rate of >1% per year)
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.
• Male or female condom with or without spermicide[c]
• Cap, diaphragm, or sponge with spermicide
• A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]
• Periodic abstinence (calendar, symptothermal, postovulation methods)
• Withdrawal (coitus-interruptus)
• Spermicides alone
• Lactational amenorrhea method (LAM)
a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

b) Hormonal contraception may be susceptible to interaction with the study intervention, which may reduce the efficacy of the contraceptive method. In addition, consider if the hormonal contraception may interact with the study intervention.
c) Male condom and female condom should not be used together (due to risk of failure with friction).

10.6. Appendix 6: Management of Clinically Significant Laboratory Toxicities



[a] Mandatory confirmation is not warranted for asymptomatic Grade 3 or Grade 4 glucose elevations in participants with pre-existing diabetes, and asymptomatic Grade 3 or Grade 4 triglyceride or cholesterol elevations.

10.7. Appendix 7: DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (v 2.1, July 2017), or 'DAIDS grading table', is a descriptive terminology to be utilized for adverse event reporting in this study. A grading (severity) scale is provided for each adverse event term.

General Considerations

The *Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1* consists of parameters, or AEs, with severity grading guidance that are to be used in DAIDS clinical trials for safety data reporting to maintain accuracy and consistency in the evaluation of AEs. The term "severe" is not the same as the term "serious" in classifying AEs. The severity of a specific event describes its intensity, and it is the intensity which is graded. Seriousness, which is not graded, relates to an outcome of an AE and is a regulatory definition.

Clinical sites are encouraged to report parameters in the DAIDS grading table as they are written to maintain data consistency across clinical trials. However, since some parameters can be reported with more specificity, clinical sites are encouraged to report parameters that convey additional clinical information. For example, diarrhea could be reported as neonatal diarrhea; seizures, as febrile seizures; and pain, as jaw pain.

The DAIDS grading table provides an AE severity grading scale ranging from grades 1 to 5 with descriptions for each AE based on the following general guidelines:

- Grade 1 indicates a mild event
- Grade 2 indicates a moderate event
- Grade 3 indicates a severe event
- Grade 4 indicates a potentially life-threatening event
- Grade 5 indicates death (*Note*: This grade is not specifically listed on each page of the grading table).

Other points to consider include:

- Use age and sex values as applicable.
- Unless noted, laboratory values are for term neonates. Preterm neonates should be assessed using local laboratory normal ranges.
- Where applicable, Standard International (SI) units are included in italics.

Selecting and Reporting a Primary AE Term

When selecting a primary AE term to report, sites should select the term that best describes what

occurred to the participant. For example, a participant may present with itching, urticaria, flushing, angioedema of the face, and dyspnea. If the underlying diagnosis is determined to be an acute allergic reaction, sites should report "Acute Allergic Reaction" as the primary AE term.

Determining Severity Grade for Parameters between Grades

If the severity of an AE could fall in either one of two grades (i.e., the severity of an AE could be either grade 2 or grade 3), sites should select the higher of the two grades.

Estimating Severity Grade for Parameters Not Identified in the Grading Table

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

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

Major Clinical Conditions
Cardiovascular

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

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

Cardiovascular

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

[2] As per Bazett's formula.

Dermatologic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Alopecia (scalp only)	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	NA	NA
Bruising	Localized to one area	Localized to more than one area	Generalized	NA
Cellulitis	NA	Non parenteral treatment indicated (e.g., oral antibiotics, antifungals, antivirals)	IV treatment indicated (e.g., IV antibiotics, antifungals, antivirals)	Life threatening consequences (e.g., sepsis, tissue necrosis)
Hyperpigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Hypopigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Petechiae	Localized to one area	Localized to more than one area	Generalized	NA
Pruritus[3] (without skin lesions)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA

3 For pruritus associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section (page 23).

Rash *Specify type, if applicable*	Localized rash	Diffuse rash OR Target lesions	Diffuse rash AND Vesicles or limited number of bullae or superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Stevens Johnson syndrome OR Toxic epidermal necrolysis

Endocrine and Metabolic

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

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

Endocrine and Metabolic

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

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

Gastrointestinal

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

Gastrointestinal

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

Musculoskeletal

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

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

Neurologic

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

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

D

Pregnancy, Puerperium, and Perinatal

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

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

Psychiatric

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

Respiratory

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

Sensory

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

Systemic

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

[8] Definition: A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and/or shortness of breath.
[9] For pain associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section (page 23).

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

[10] Definition: A disorder characterized by fever, arthralgia, myalgia, skin eruptions, lymphadenopathy, marked discomfort, and/or dyspnea.

[11] WHO reference tables may be accessed by clicking the desired age range or by accessing the following URLs: http://www.who.int/growthref/who2007_bmi_for_age/en/ for participants > 5 to 19 years of age and http://www.who.int/childgrowth/standards/chart_catalogue/en/ for those ≤ 5 years of age.

Urinary

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

Site Reactions to Injections and Infusions

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

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

*Laboratory Values**
Chemistries

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

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

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

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

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

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

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

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

Hematology

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

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

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

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

Urinalysis

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

Total Bilirubin Table for Term and Preterm Neonates

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Total Bilirubin[18], High (mg/dL; *µmol/L*)[19]				
Term Neonate[20] *< 24 hours of age*	4 to < 7 *68.4 to < 119.7*	7 to < 10 *119.7 to < 171*	10 to < 17 *171 to < 290.7*	≥ 17 *≥ 290.7*
24 to < 48 hours of age	5 to < 8 *85.5 to < 136.8*	8 to < 12 *136.8 to < 205.2*	12 to < 19 *205.2 to < 324.9*	≥ 19 *≥ 324.9*
48 to < 72 hours of age	8.5 to < 13 *145.35 to < 222.3*	13 to < 15 *222.3 to < 256.5*	15 to < 22 *256.5 to < 376.2*	≥ 22 *≥ 376.2*
72 hours to < 7 days of age	11 to < 16 *188.1 to < 273.6*	16 to < 18 *273.6 to < 307.8*	18 to < 24 *307.8 to < 410.4*	≥ 24 *≥ 410.4*
7 to 28 days of age (breast feeding)	5 to < 10 *85.5 to < 171*	10 to < 20 *171 to < 342*	20 to < 25 *342 to < 427.5*	≥ 25 *≥ 427.5*
7 to 28 days of age (not breast feeding)	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN
Preterm Neonate[20] *35 to < 37 weeks gestational age*	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).
32 to < 35 weeks gestational age and < 7 days of age	NA	NA	10 to < 14 *171 to < 239.4*	≥ 14 *≥ 239.4*
28 to < 32 weeks gestational age and < 7 days of age	NA	NA	6 to < 10 *102.6 to < 171*	≥ 10 *≥ 171*
< 28 weeks gestational age and < 7 days of age	NA	NA	5 to < 8 *85.5 to < 136.8*	≥ 8 *≥ 136.8*
7 to 28 days of age (breast feeding)	5 to < 10 *85.5 to < 171*	10 to < 20 *171 to < 342*	20 to < 25 *342 to < 427.5*	≥ 25 *≥ 427.5*
7 to 28 days of age (not breast feeding)	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN

[18] Severity grading for total bilirubin in neonates is complex because of rapidly changing total bilirubin normal ranges in the first week of life followed by the benign phenomenon of breast milk jaundice after the first week of life. Severity grading in this appendix corresponds approximately to cut offs for indications for phototherapy at grade 3 and for exchange transfusion at grade 4.

[19] A laboratory value of 1 mg/dL is equivalent to 17.1 µmol/L.

[20] Definitions: Term is defined as ≥37 weeks gestational age; near term, as ≥ 35 weeks gestational age; preterm, as <35 weeks gestational age; and neonate, as 0 to 28 days of age.

10.8. Appendix 8: Patient Reported Outcomes Questionnaires

10.8.1. HIV-Symptom Index (HIV-SI)

INSTRUCTIONS: Please answer the following questions by placing a (../) in the appropriate box.

A) The following questions ask about symptoms you might have had during the **past four weeks.** Please check the box that describes how much you have been bothered by **each** symptom

(Check one.)	I DO NOT HAVE THIS SYMPTOM	I HAVE THIS SYMPTOM AND…			
		It doesn't bother me	It bothers me a little	It bothers me	It bothers me alot
1. Fatigue or loss of energy?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
2. Fever, chills or sweats?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
3. Feeling dizzy or lightheaded?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
4. Pain, numbness or tingling in the hands or feet?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
5. Trouble remembering?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
6. Nausea or vomiting?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
7. Diarrhea or loose bowel movements?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
8. Felt sad, down or depressed?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
9. Felt nervous or anxious?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
10. Difficulty falling or staying asleep?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
11. Skin problems, such as rash, dryness or itching?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

US:ENG (United States/English)

(Check one.)	I DO NOT HAVE THIS SYMPTOM	I HAVE THIS SYMPTOM AND…			
		It doesn't bother me	It bothers me a little	It bothers me	It bothers me alot
12. Cough or trouble catching your breath?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
13. Headache?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
14. Loss of appetite or a change in the taste of food?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
15. Bloating, pain or gas in your stomach?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
16. Muscle aches or joint pain?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
17. Problems with having sex, such as loss of interest or lack of satisfaction?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
18. Changes in the way your body looks such as fat deposits or weight gain?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
19. Problems with weight loss or wasting?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
20. Hair loss or changes in the way your hair looks?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

Thank you very much for completing this questionnaire.

US:ENG (United States/English)

10.8.2. Body Shape Questionnaire (BSQ-8D)

BSQ-8D

We should like to know how you have been feeling about your appearance over the **PAST FOUR WEEKS**. Please read each question and circle the appropriate number to the right. Please answer all the questions.

OVER THE PAST FOUR WEEKS:

	Never	Rarely	Sometimes	Often	Very often	Always
1. Have you been so worried about your shape that you have been feeling you ought to	1	2	3	4	5	6
2. Have you noticed the shape of other women and felt that your own shape compared	1	2	3	4	5	6
3. Has being naked, such as when taking a bath, made you feel fat?.....	1	2	3	4	5	6
4. Have you not gone out to social occasions (e.g. parties) because you have felt bad about your	1	2	3	4	5	6
5. Have you worried about other people seeing rolls of fat around your waist or	1	2	3	4	5	6
6. When in company have your worried about taking up too much room (e.g. sitting on a sofa, or a bus	1	2	3	4	5	6
7. Have you pinched areas of your body to see how much fat there is?.....	1	2	3	4	5	6
8. Have you avoided situations where people could see your body (e.g. communal changing rooms or swimming	1	2	3	4	5	6

BSQ-8D (Men)

We should like to know how you have been feeling about your appearance over the **PAST FOUR WEEKS**. Please read each question and circle the appropriate number to the right. Please answer all the questions.

OVER THE PAST FOUR WEEKS:

	Never	Rarely	Sometimes	Often	Very often	Always
1. Have you been so worried about your shape that you have been feeling you ought to	1	2	3	4	5	6
2. Have you noticed the shape of other men and felt that your own shape compared unfavourably?.....	1	2	3	4	5	6
3. Has being naked, such as when taking a bath, made you feel fat?.....	1	2	3	4	5	6
4. Have you not gone out to social occasions (e.g. parties) because you have felt bad about your	1	2	3	4	5	6
5. Have you worried about other people seeing rolls of fat around your waist or	1	2	3	4	5	6
6. When in company have your worried about taking up too much room (e.g. sitting on a sofa, or a bus seat)?.....	1	2	3	4	5	6
7. Have you pinched areas of your body to see how much fat there is?.....	1	2	3	4	5	6
8. Have you avoided situations where people could see your body (e.g. communal changing rooms or swimming	1	2	3	4	5	6

10.8.3. DAILY EATS

DAILY EATS V2.0 7-Day Diary

General Instructions

- Please answer every question at approximately the same time each evening (e.g., just before bedtime) for the next 7 days.
- You are being asked to complete this questionnaire as part of the study to find out more information about how your weight affects your life, if at all?
- Please read each question carefully and do not skip any questions.
- Please answer each question without input from anyone else.
- There are no right or wrong answers so use your best judgment based on what you think the question is asking.
- Please bring the device to your next scheduled visit

THANK YOU

DAY 1

For the following questions, please select the one response that best describes your answer.

A. Overall, how hungry did you feel in the past 24 hours?

0	1	2	3	4	5	6	7	8	9	10
Not hungry at all										Extremely hungry

B. What was the hungriest you felt in the past 24 hours?

0	1	2	3	4	5	6	7	8	9	10
Not hungry at all										Extremely hungry

C. How was your appetite (desire to eat) in the past 24 hours?

0	1	2	3	4	5	6	7	8	9	10
No appetite at all										Extremely big appetite

D. How strong were your cravings for unhealthy foods in the past 24 hours?

0	1	2	3	4	5	6	7	8	9	10
No cravings at all										Extremely strong cravings

E. How satisfied (comfortably full) did you feel after eating your meals in the past 24 hours?

0	1	2	3	4	5	6	7	8	9	10
Not at all satisfied										Completely satisfied

DAY 2

For the following questions, please select the one response that best describes your answer.

A. Overall, how hungry did you feel in the past 24 hours?

0	1	2	3	4	5	6	7	8	9	10
Not hungry at all										Extremely hungry

B. What was the hungriest you felt in the past 24 hours?

0	1	2	3	4	5	6	7	8	9	10
Not hungry at all										Extremely hungry

C. How was your appetite (desire to eat) in the past 24 hours?

0	1	2	3	4	5	6	7	8	9	10
No appetite at all										Extremely big appetite

D. How strong were your cravings for unhealthy foods in the past 24 hours?

0	1	2	3	4	5	6	7	8	9	10
No cravings at all										Extremely strong cravings

E. How satisfied (comfortably full) did you feel after eating your meals in the past 24 hours?

0	1	2	3	4	5	6	7	8	9	10
Not at all satisfied										Completely satisfied

DAY 3

For the following questions, please select the one response that best describes your answer.

A. Overall, how hungry did you feel in the past 24 hours?

0	1	2	3	4	5	6	7	8	9	10
Not hungry at all										Extremely hungry

B. What was the hungriest you felt in the past 24 hours?

0	1	2	3	4	5	6	7	8	9	10
Not hungry at all										Extremely hungry

C. How was your appetite (desire to eat) in the past 24 hours?

0	1	2	3	4	5	6	7	8	9	10
No appetite at all										Extremely big appetite

D. How strong were your cravings for unhealthy foods in the past 24 hours?

0	1	2	3	4	5	6	7	8	9	10
No cravings at all										Extremely strong cravings

E. How satisfied (comfortably full) did you feel after eating your meals in the past 24 hours?

0	1	2	3	4	5	6	7	8	9	10
Not at all satisfied										Completely satisfied

DAY 4

For the following questions, please select the one response that best describes your answer.

A. Overall, how hungry did you feel in the past 24 hours?

0	1	2	3	4	5	6	7	8	9	10
Not hungry at all										Extremely hungry

B. What was the hungriest you felt in the past 24 hours?

0	1	2	3	4	5	6	7	8	9	10
Not hungry at all										Extremely hungry

C. How was your appetite (desire to eat) in the past 24 hours?

0	1	2	3	4	5	6	7	8	9	10
No appetite at all										Extremely big appetite

D. How strong were your cravings for unhealthy foods in the past 24 hours?

0	1	2	3	4	5	6	7	8	9	10
No cravings at all										Extremely strong cravings

E. How satisfied (comfortably full) did you feel after eating your meals in the past 24 hours?

0	1	2	3	4	5	6	7	8	9	10
Not at all satisfied										Completely satisfied

DAY 5

For the following questions, please select the one response that best describes your answer.

A. Overall, how hungry did you feel in the past 24 hours?

0	1	2	3	4	5	6	7	8	9	10
Not hungry at all										Extremely hungry

B. What was the hungriest you felt in the past 24 hours?

0	1	2	3	4	5	6	7	8	9	10
Not hungry at all										Extremely hungry

C. How was your appetite (desire to eat) in the past 24 hours?

0	1	2	3	4	5	6	7	8	9	10
No appetite at all										Extremely big appetite

D. How strong were your cravings for unhealthy foods in the past 24 hours?

0	1	2	3	4	5	6	7	8	9	10
No cravings at all										Extremely strong cravings

E. How satisfied (comfortably full) did you feel after eating your meals in the past 24 hours?

0	1	2	3	4	5	6	7	8	9	10
Not at all satisfied										Completely satisfied

DAY 6

For the following questions, please select the one response that best describes your answer.

A. Overall, how hungry did you feel in the past 24 hours?

0	1	2	3	4	5	6	7	8	9	10
Not hungry at all										Extremely hungry

B. What was the hungriest you felt in the past 24 hours?

0	1	2	3	4	5	6	7	8	9	10
Not hungry at all										Extremely hungry

C. How was your appetite (desire to eat) in the past 24 hours?

0	1	2	3	4	5	6	7	8	9	10
No appetite at all										Extremely big appetite

D. How strong were your cravings for unhealthy foods in the past 24 hours?

0	1	2	3	4	5	6	7	8	9	10
No cravings at all										Extremely strong cravings

E. How satisfied (comfortably full) did you feel after eating your meals in the past 24 hours?

0	1	2	3	4	5	6	7	8	9	10
Not at all satisfied										Completely satisfied

DAY 7

For the following questions, please select the one response that best describes your answer.

A. Overall, how hungry did you feel in the past 24 hours?

0	1	2	3	4	5	6	7	8	9	10
Not hungry at all										Extremely hungry

B. What was the hungriest you felt in the past 24 hours?

0	1	2	3	4	5	6	7	8	9	10
Not hungry at all										Extremely hungry

C. How was your appetite (desire to eat) in the past 24 hours?

0	1	2	3	4	5	6	7	8	9	10
No appetite at all										Extremely big appetite

D. How strong were your cravings for unhealthy foods in the past 24 hours?

0	1	2	3	4	5	6	7	8	9	10
No cravings at all										Extremely strong cravings

E. How satisfied (comfortably full) did you feel after eating your meals in the past 24 hours?

0	1	2	3	4	5	6	7	8	9	10
Not at all satisfied										Completely satisfied

10.8.4. Patient Global Impression of Change (PGIC)

PATIENT GLOBAL IMPRESSION OF CHANGE (PGIC)

Compared to before starting the study, my overall status is:

[1] ☐ Very Much Improved

[2] ☐ Much Improved

[3] ☐ Minimally Improved

[4] ☐ No Change

[5] ☐ Minimally Worse

[6] ☐ Much Worse

[7] ☐ Very Much Worse

PATIENT GLOBAL IMPRESSION OF CHANGE (PGIC)

Compared to the Week 24 visit, my overall status is:

[1] ☐Very Much Improved

[2] ☐ Much Improved

[3] ☐ Minimally Improved

[4] ☐ No Change

[5] ☐ Minimally Worse

[6] ☐ Much Worse

[7] ☐ Very Much Worse

10.8.5. Patient Global Impression of Change-Satiety (PGIC-S)

Patient Global Impression of Change - Satiety (PGIC-S)

Compared to before starting the study, how would you rate your satisfaction (fullness) after meals in the past 7 days?

[1] ☐ Much more satisfied (full)

[2] ☐ Moderately more satisfied (full)

[3] ☐ A little more satisfied (full)

[4] ☐ No change

[5] ☐ A little less satisfied (full)

[6] ☐ Moderately less satisfied (full)

[7] ☐ Much less satisfied (full)

Compared to the Week 24 visit, how would you rate your satisfaction (fullness) after meals in the past 7 days?

[1] ☐ Much more satisfied (full)

[2] ☐ Moderately more satisfied (full)

[3] ☐ A little more satisfied (full)

[4] ☐ No change

[5] ☐ A little less satisfied (full)

[6] ☐ Moderately less satisfied (full)

[7] ☐ Much less satisfied (full)

10.9. Appendix 9: Characteristics, Prevention, and Management of Cardiovascular Diseases in People Living with HIV by American Heart Association

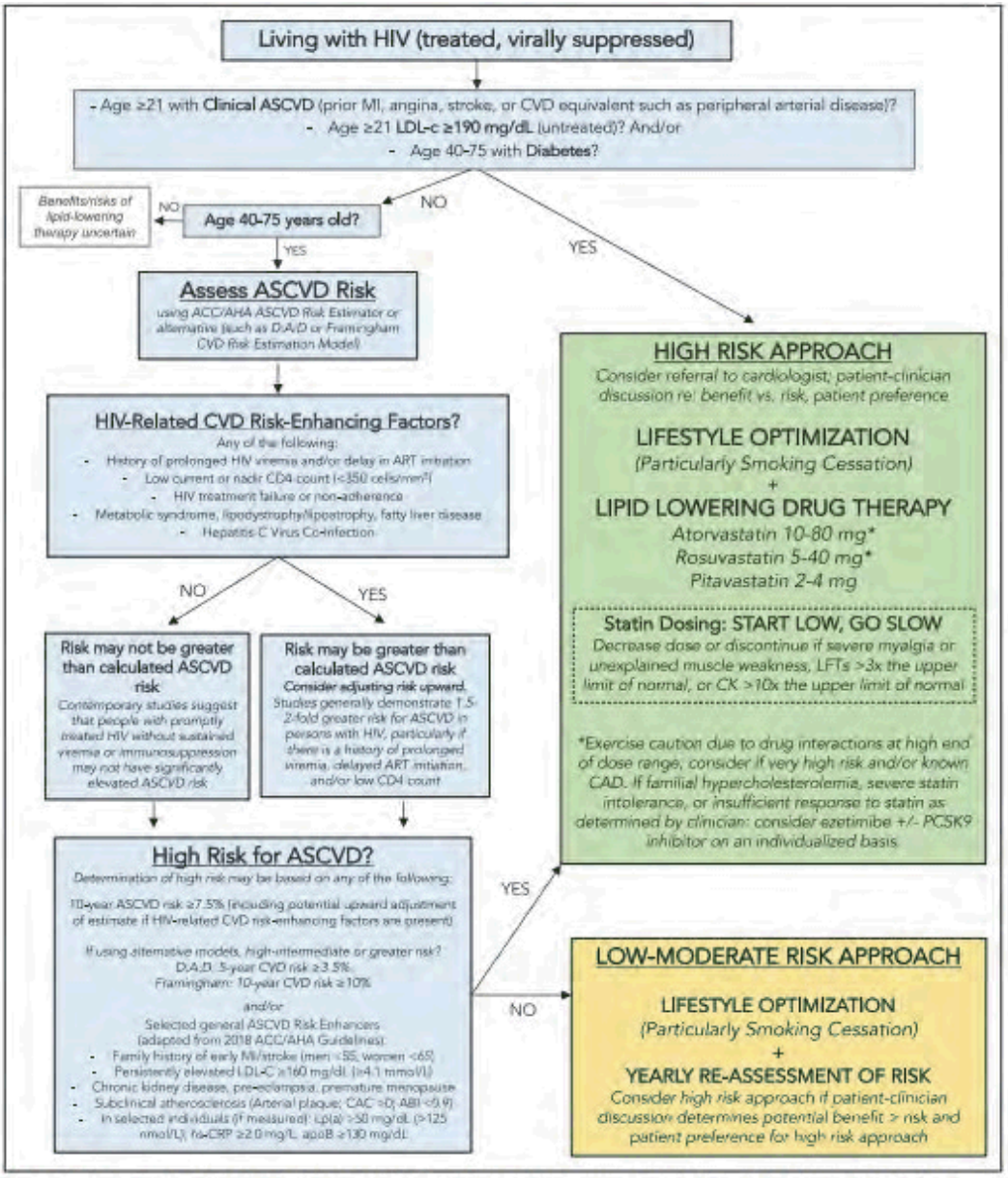
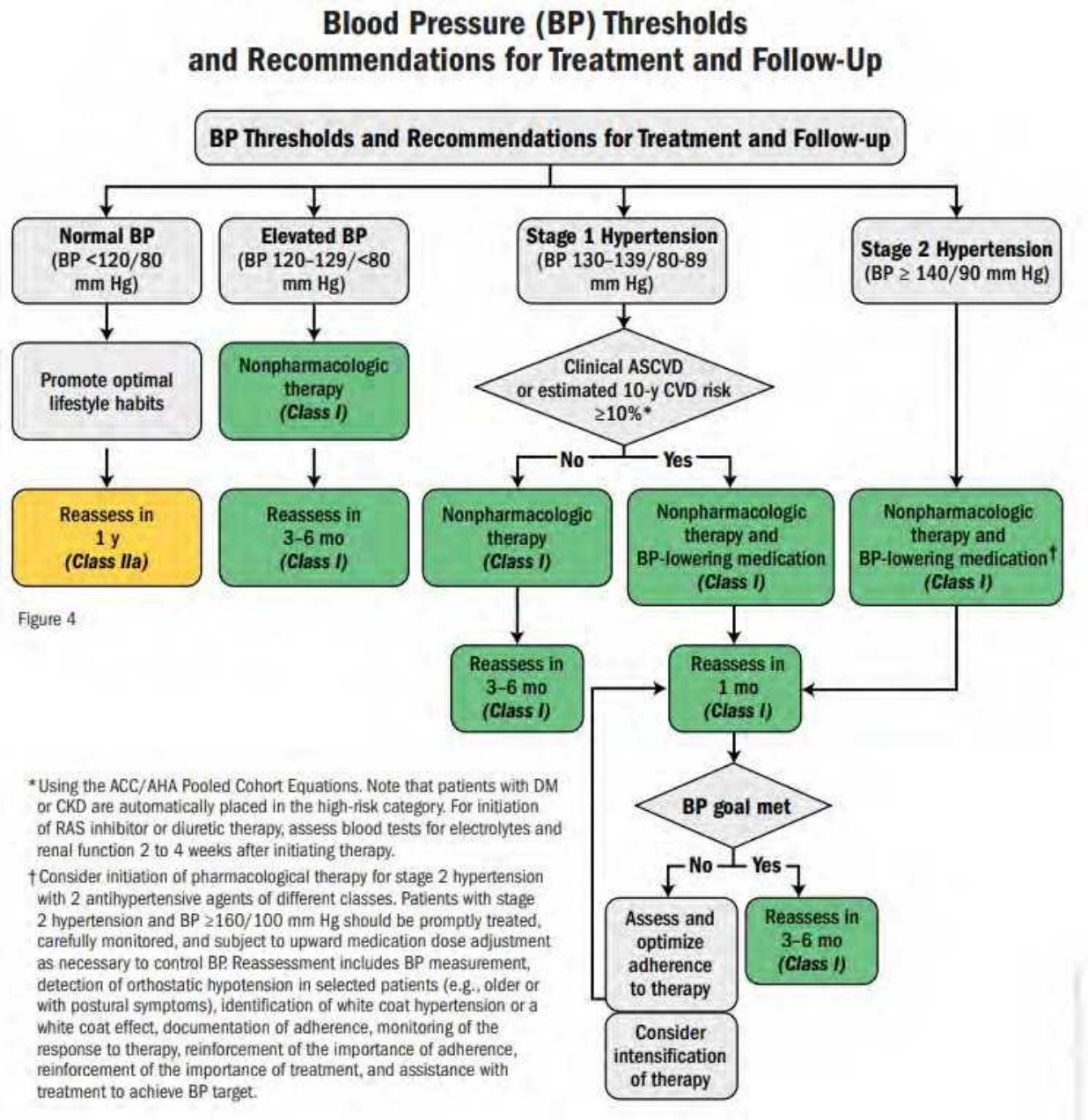


Figure 4. Pragmatic approach to atherosclerotic cardiovascular disease (ASCVD) risk assessment and prevention in treated HIV infection.
This figure applies to people with treated HIV. For people with uncontrolled HIV, the first priority is appropriate HIV therapy to achieve viral suppression per the HIV provider. Thresholds based on findings of elevated CVD risk at current or nadir CD4 count <200, <350, and <500 cells/mm³ in Silverberg et al,[25] Lichtenstein et al,[26] and Triant et al.[27] Hazard ratios and incidence rate ratios of 1.4 to 2.1 for myocardial infarction (MI) for people living with HIV (PLWH) vs uninfected people demonstrated in Freiberg et al,[5] Triant et al,[28] and Silverberg et al.[25] Hazard ratio of stroke for PLWH vs uninfected people was 1.40 in Chow et al.[4] ABI indicates ankle-brachial index; ACC/AHA, American College of Cardiology/American Heart Association; apoB, apolipoprotein B; ART, antiretroviral therapy; CAC, coronary artery calcium; CAD, coronary artery disease; CK, creatine kinase; CVD, cardiovascular disease; D:A:D, Data Collection on Adverse Events of Anti-HIV Drugs; hs-CRP, high sensitivity C-reactive protein; LFT, liver function test; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein A; and PCSK9, proprotein convertase subtilisin-kexin type 9.

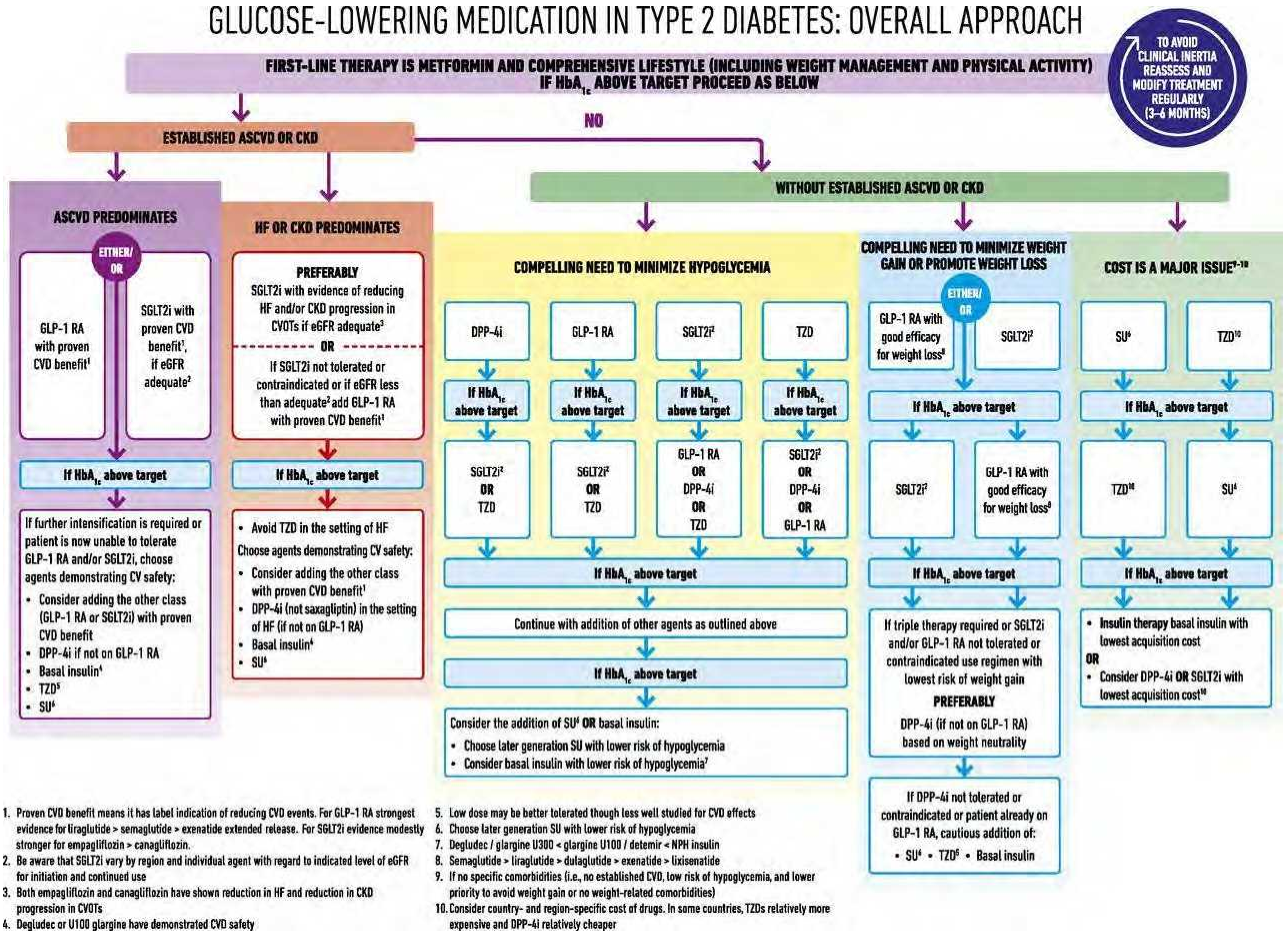
Feinstein MJ, Hsue PY, Benjamin LA, et al. Characteristics, Prevention, and Management of Cardiovascular Disease in People Living With HIV: A Scientific Statement From the American Heart Association. Circulation. 2019;140(2):e98 e124.

10.10. Appendix 10: 2017 American College of Cardiology (ACC) Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults



Whelton PK, Carey RM, et al. 2017 Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults. A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. Sep 2017, 23976; DOI: 10.1016/j.jacc.2017.07.745.

10.11. Appendix 11: Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)



Davies JD, D'Alession DR, Fradkin J, et al. Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. Dec 2018; 41(12): 2669 2701.

10.12. Appendix 12: WHO Clinical Staging of HIV/AIDS

The clinical stages of HIV infection for adults and adolescents are defined as follows. (Adapted from: 1993 Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR 1992;41(RR-17):1-19; and WHO 2007 Case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children [Table 3]).[31,41]

Clinical Stage 1

Clinical Stage 1 consists of one or more of the conditions listed below in adolescents or adults (≥13 years) with documented HIV infection. Conditions listed in Clinical Stages 2, 3 or 4 must not have occurred.

- Asymptomatic HIV infection
- Persistent generalized lymphadenopathy

Clinical Stage 2

Clinical Stage 2 consists of symptomatic conditions in an HIV-infected adolescents or adults that are not included among conditions listed in Clinical Stage 3, and that meet one or more of the following criteria:
a) the conditions are attributed to HIV infection or are indicative of a defect in cell-mediated immunity; or
b) the conditions are considered by physicians to have a clinical course or to require management that is complicated by HIV infection. Examples of conditions in Clinical Stage 2 include, but are not limited to the following.

- Moderate unexplained weight loss (<10% of presumed or measured body weight)
- Recurrent respiratory tract infections sinusitis, tonsillitis, otitis media and pharyngitis)
- Herpes zoster
- Angular cheilitis
- Recurrent oral ulceration
- Papular pruritic eruptions
- Seborrhoeic dermatitis
- Fungal nail infections

Clinical Stage 3

Clinical Stage 3 includes the clinical conditions listed in the AIDS surveillance case definition. For classification purposes, once a Clinical Stage 3 condition has occurred, the person will remain in Clinical Stage 3. Conditions in Clinical Stage 3 include the following.

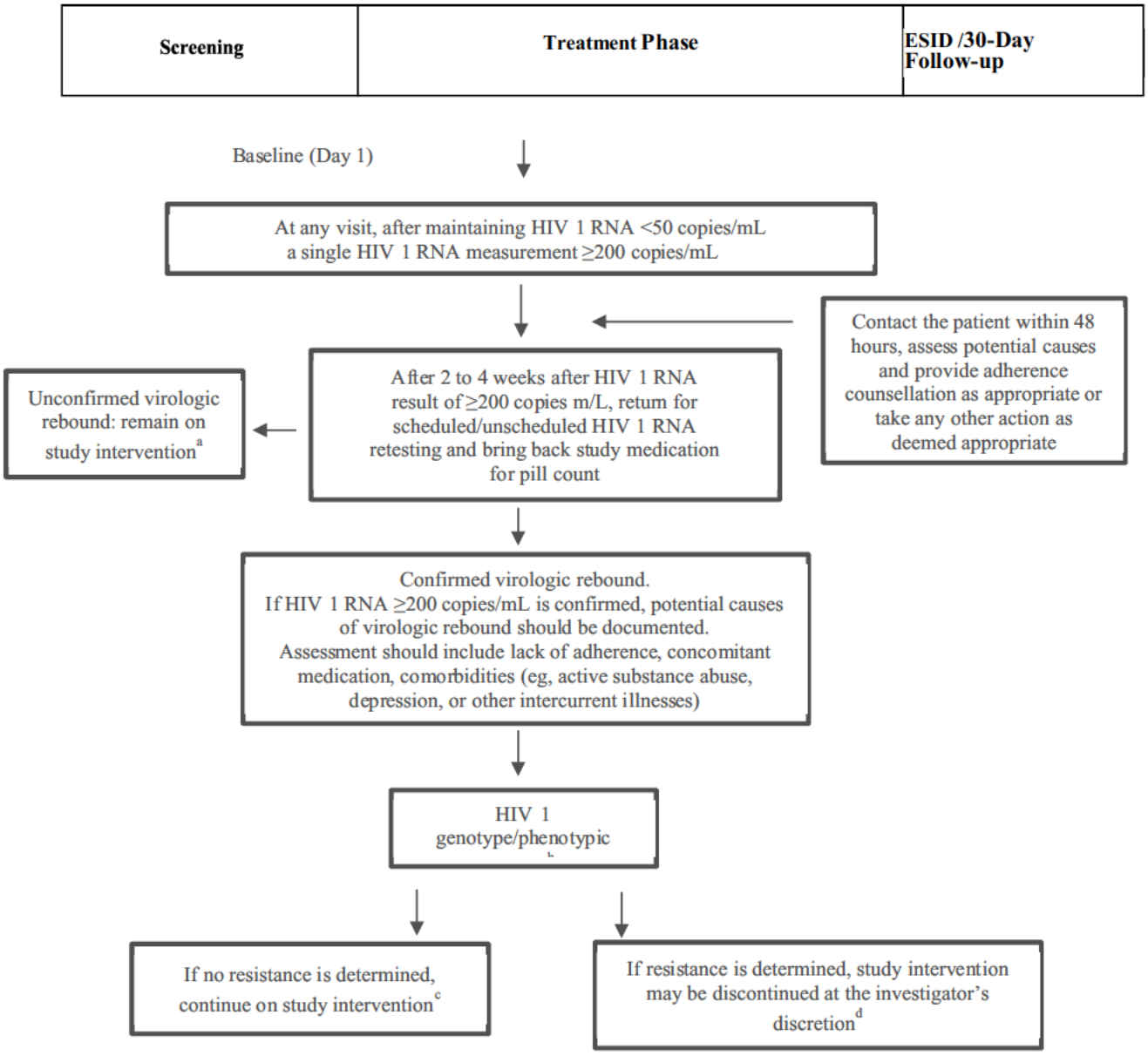
- Unexplained (not explained by other causes) severe weight loss (>10% of presumed or measured body weight)
- Unexplained chronic diarrhea for longer than 1 month
- Unexplained persistent fever (above 37.6°C intermittent or constant, for longer than 1 month)
- Persistent oral candidiasis

- Oral hairy leukoplakia
- Pulmonary tuberculosis (current)
- Severe bacterial infections (such as pneumonia, empyema, pyomyositis, bone or joint infection, meningitis or bacteremia)
- Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis
- Unexplained anemia (<8 g/dL), neutropenia (<0.5x10^9/L) or chronic thrombocytopenia (<50x10^9/L)

Clinical Stage 4

- HIV wasting syndrome:
- Pneumocystis pneumonia
- Recurrent severe bacterial pneumonia
- Chronic herpes simplex infection (orolabial, genital or anorectal of more than one month's duration or visceral at any site)
- Esophageal candidiasis (or candidiasis of trachea, bronchi or lungs)
- Extrapulmonary tuberculosis
- Kaposi's sarcoma
- Cytomegalovirus infection (retinitis or infection of other organs)
- Central nervous system toxoplasmosis
- HIV encephalopathy
- Extrapulmonary cryptococcosis including meningitis
- Disseminated non-tuberculous mycobacterial infection
- Progressive multifocal leukoencephalopathy
- Chronic cryptosporidiosis (with diarrhea)
- Chronic isosporiasis
- Disseminated mycosis (coccidiomycosis or histoplasmosis)
- Recurrent non-typhoidal Salmonella bacteremia
- Lymphoma (cerebral or B-cell non-Hodgkin) or other solid HIV-associated tumors
- Invasive cervical carcinoma
- Atypical disseminated leishmaniasis
- Symptomatic HIV-associated nephropathy or symptomatic HIV-associated cardiomyopathy

10.13. Appendix 13: Management of Virologic Rebound



a If HIV 1 RNA ≥200 copies/mL is not confirmed, participants will remain on their current study intervention and the viral load will be further monitored.

b If HIV 1 RNA ≥200 copies/mL is confirmed and HIV 1 RNA value is ≥400 copies/mL, the blood sample from the retesting visit or a following visit with HIV 1 RNA ≥400 copies/mL will be used for HIV 1 genotypic/phenotypic testing.

c The participant may remain on study intervention and the viral load will be further monitored. Genotype/phenotype testing at other time points may be requested if deemed necessary by the sponsor. Investigators should carefully evaluate the benefits and risks of remaining on study intervention for each individual participant and document this assessment in the on site medical record. Investigators who opt to discontinue study intervention for an individual participant must inform the sponsor's medical monitor prior to study intervention discontinuation.

d In case of early discontinuation, an HIV 1 genotypic/phenotypic resistance report, if available, will be forwarded to the investigator in order to assist in the selection of a new ARV regimen.

10.14. Appendix 14: Protocol Amendment History

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

Amendment 2 (21-May-2021)

Overall Rationale for the Amendment: The overall reason for this amendment is to account for new data and investigator feedback indicating 10% weight gain may not occur within 12 months but could occur more gradually over a longer period of time.

Section number and Name	Description of Change	Brief Rationale
1.1. Synopsis (Overall Design); 1.2 Schema; 4.1. Overall Design; 5.1. Inclusion Criteria #4	Eligible patients could have a rapid and significant body weight gain which is defined as a ≥10% increase within a 12-to-36-month time period.	To account for new data and investigator feedback.
5.5. Criteria for Temporarily Delaying Enrollment, Randomization, Administration of Study Intervention; 8.7. Immunogenicity Assessments	Sections were added to align with the template.	To adapt/follow the new protocol template.
6.5 Dose Modification; 6.6 Continued Access to Study Intervention After the End of the Study; 6.7. Treatment of Overdose 8.6.1. Pharmacodynamics	Moved the Section to align with the template	To adapt/follow the new protocol template.
6.7. Treatment of Overdose	The text was modified (new text in bold and deletion in strike through) to: For D/C/F/TAF FDC ~~anything~~ any dose greater than 1 tablet within a 24-hour period ±12 hours. ~~This~~ is **considered an overdose** as per Prescribing information of D/C/F/TAF FDC tablet.	The sentences defining an overdose were revised for better clarity.
8.3 Adverse Events, Serious Adverse Events, and Other Safety Reporting	The title of the Section 8.3 was changed from 'Adverse Events and Serious Adverse Events' to Adverse Events, Serious Adverse Events, and Other Safety Reporting'.	To adapt/follow the new protocol template.
8.7 Immunogenicity Assessments	Added the section to align with the new template	To adapt/follow the new protocol template.
9.3. Population for Analysis Sets	The title of the Section 9.3 was changed from 'Population for Analyses' to 'Population for Analysis Sets'.	To adapt/follow the new protocol template.

Section number and Name	Description of Change	Brief Rationale
Appendices	Updated the Appendices per the new protocol template.	To adapt/follow the new protocol template.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted

Amendment 1 (24-April-2020)

Overall Rationale for the Amendment: The overall reason for this amendment is to eliminate the need to monitor and analyze anticipated events and to remove the Anticipated Events Safety Monitoring Plan included in Appendix 2 of the protocol, and to evaluate the proportion of participants with >3% change in body weight at Week 24 and Week 48.

Section number and Name	Description of Change	Brief Rationale
8.3. Adverse Events and Serious Adverse Events; 8.3.3. Regulatory Reporting Requirements for Serious Adverse Events	Deleted text related to anticipated adverse events and removed cross-reference to Appendix 2 (Anticipated Events) from the protocol.	To delete the non-applicable formal Anticipated Events Safety Monitoring Plan. As the current study TMC114FD2HTX4004 has unblinded study design and the study population consist of virologically suppressed patients, the number of suspected unexpected serious adverse reactions (SUSARS) is expected to be low and there is no need to monitor and analyze the anticipated events.
Appendix 2: Anticipated Events	Appendix 2 has been removed from the protocol and subsequent appendices have been renumbered.	
1.1. Synopsis (Week 24 Objectives and Endpoints); 3.1. Week 24 Objectives and Endpoints; 3.2. Week 48 Objectives and Endpoints	Added new secondary endpoints, 'Proportion of participants with % change in body weight >3% at Week 24' and 'Proportion of participants with % change in body weight >3% at Week 48'.	To identify participants with 3% to 5% changes in body weight, as sustained body weight loss of as little as 3%-5% may lead to clinically meaningful reductions in some cardiovascular risk factors
1.1. Synopsis (Overall Design, Efficacy Assessments); 1.3. Schedule of Activities (SoA); 4.1. Overall Design; 7.1. Discontinuation of Study Intervention; 8.1.3.2. Resistance Determinations; 8.1.3.3. Management of Virologic Rebound; 9.4.3.2. Resistance/Efficacy Analyses	Specified PhenoSense GT® Plus Integrase as the test to be utilized for human immunodeficiency virus (HIV)-1 genotypic and phenotypic resistance testing in participants with confirmed virologic rebound.	To ensure that nucleoside reverse transcriptase inhibitor (NRTI), non-nucleoside reverse transcriptase inhibitor (NNRTI), protease inhibitor (PI) and integrase (INI) drug class resistance in participants with confirmed virologic rebound is reported
Appendix 14 (now Appendix 13)	Footnote b was updated by adding 'PhenoSense GT® Plus Integrase'.	

Section number and Name	Description of Change	Brief Rationale
1.3. Schedule of Activities; 8.1.3.2. Resistance Determinations	Specified Genosure Archive® as the test to be utilized to characterize archived viral resistance of the whole blood sample collected at Baseline Day 1.	To clarify the type of assay that will be used to assess baseline resistance if needed
Appendix 3 (now Appendix 2): Clinical Laboratory Tests and Calculations	Added footnote that International normalized ratio (INR) will only be assessed at Screening.	To specify that INR will be assessed at Screening only
Appendix 3 (now Appendix 2): Clinical Laboratory Tests and Calculations	Added formula for calculation of Ideal Body Weight and Adjusted Body Weight.	To specify that if a participant's actual body weight is greater than 20% of their Ideal Body Weight, the participant's Adjusted Body Weight will be used for eGFRcr (Cockcroft-Gault Formula)
5.1. Inclusion Criteria	The text 'Contraceptive (birth control) use by men or women should be consistent with local regulations regarding the acceptable methods of contraception for those participating in clinical studies. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies' originally included under inclusion criterion 10 was removed.	To remove the duplicate text related to contraception from inclusion criterion 10 because it is also included in inclusion criterion 13
Title page (Confidentiality Statement); Running footer	Replaced the original Confidentiality Statement with a new statement, and added a running footer to note exemptions.	Updated Confidentiality Statement in accordance with clinical trial protocol template change
Throughout the protocol	Minor grammatical and formatting changes were made References were updated..	Minor errors were noted.
1.1. Synopsis (Objectives and Endpoints); 2.1. Study Rationale; 3.1. Week 24 Objectives and Endpoints; 3.2. Week 48 Objectives and Endpoints; Appendix 1	Full form of 'BMI' was corrected from 'basal metabolic rate' and 'body metabolic index' to 'body mass index'.	
Appendix 14 (now Appendix 13)	The text '~~and bring back study medication for pill count~~' was deleted. The word 'counsellation' was replaced by 'counseling' in the following statement 'Contact the patient within 48 hours, assess potential causes and provide adherence counseling as appropriate or take any other action as deemed appropriate'.	

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3. Bhaduri S, Roberts. M. "Weight gain in patients using integrase inhibitors: An emerging class side effect." HIV Medicine. 2017;18(Supplement 1):48.
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INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

Institution: Janssen Scientific Affairs, LLC

Signature: [electronic signature appended at the end of the protocol] Date: _____
(Day Month Year)

Note: If the address or telephone number of the investigator changes during the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

Signature

User	Date	Reason
PPD	29-Apr-2022 14:04:07 (GMT)	Document Approval

Janssen Scientific Affairs

Clinical Protocol

COVID-19 Appendix

Protocol Title

A Phase 4, Randomized, Active-Controlled, Open-label Study to Evaluate the Safety and Tolerability of Switching to Once-Daily Darunavir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (D/C/F/TAF) Fixed-dose Combination (FDC) Regimen in Virologically-suppressed Human Immunodeficiency Virus Type 1 (HIV-1) Infected Participants Experiencing Rapid Weight Gain with an INI + TAF/FTC ARV Regimen

DEFINE

D/C/F/TAF FDC Evaluated as a Fixed Dose Combination Regimen in Participants Switching from an Integrase Inhibitor who have Experienced Rapid Weight Gain

Protocol TMC114FD2HTX4004; Phase 4

TMC114+JNJ-48763364-AAA+JNJ-35807551-AAA+JNJ-63625328-ZCA (darunavir 800 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir alafenamide 10 mg)

United States (US) sites of this study will be conducted under US Food & Drug Administration Investigational New Drug (IND) regulations (21 CFR Part 312).

Status: Approved
Date: 03 June 2020
Prepared by: Janssen Scientific Affairs, LLC
EDMS number: EDMS-RIM-75905, 1.0

THIS APPENDIX APPLIES TO ALL CURRENT APPROVED VERSIONS OF PROTOCOL

GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

COVID-19 APPENDIX

GUIDANCE ON STUDY CONDUCT DURING THE COVID-19 PANDEMIC

It is recognized that the Coronavirus Disease 2019 (COVID-19) pandemic may have an impact on the conduct of this clinical study due to, for example, self-isolation/quarantine by participants and study-site personnel; travel restrictions/limited access to public places, including hospitals; study-site personnel being reassigned to critical tasks.

In alignment with recent health authority guidance, the sponsor is providing options for study related participant management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government requirements or the clinical judgment of the investigator to protect the health and well-being of participants and site staff. If, at any time, a participant's safety is considered to be at risk, study intervention will be discontinued, and study follow-up will be conducted.

Scheduled visits that cannot be conducted in person at the study site will be performed to the extent possible remotely/virtually or delayed until such time that on-site visits can be resumed. At each contact, participants will be interviewed to collect safety data. Key metabolic and efficacy endpoint assessments should be performed if required and as feasible. Participants will also be questioned regarding general health status to fulfill any physical examination requirement.

Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow-up. **Modifications to protocol-required assessments may be permitted via COVID-19 Appendix after consultation with the participant, investigator, and the sponsor.** Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations of study interventions and withdrawal from the study should be documented with the prefix "COVID-19-related" in the case report form (CRF).

The sponsor will continue to monitor the conduct and progress of the clinical study, and any changes will be communicated to the sites and to the health authorities according to local guidance. If a participant has tested positive for COVID-19, the investigator should contact the sponsor's responsible medical officer to discuss plans for study intervention and follow-up. Modifications made to the study conduct as a result of the COVID-19 pandemic should be summarized in the clinical study report.

The below emergency provisions are meant to ensure participant safety on study while site capabilities are compromised by COVID-19-related restrictions. As restrictions are lifted and the acute phase of the COVID-19 pandemic resolves, sites should revert to original protocol conduct as soon as feasible. If at any time during the course of the study the status of the pandemic resurges these provisions may need to be enacted again.

- To safely maintain participants on study intervention while site capabilities are compromised by COVID-19-related restrictions, participants for whom there is no safety concern may have tele-health contacts (conducted via phone or video conversation as per local regulation) for

the study visits at Weeks 4, 12, 28 and 36 until such time that on-site visits can be resumed. Whenever possible, the study visits at Weeks 24 and 48 should be on-site visits, conducted within the protocol window of ± 7 days; if on-site visits are not possible, tele-health contacts can be used. Normal study procedures should be followed for the applicable study visits as closely as possible. The reasons for visits and/or procedures not being conducted should be entered in the CRF. The CRF completion guidelines should be consulted for details.

- At each contact, participants will be interviewed to collect safety data. Key metabolic and efficacy endpoint assessments should be performed if required and as feasible. Participants will also be questioned regarding general health status to fulfill any physical examination requirement.
- If home health visits are conducted, arrangements should be made to weigh the participant using the same scale at previous visits at the study site. Each site will be provided with a portable scale that should be used for the duration of the study. Participants should be weighed wearing underwear and a gown; they will be instructed to take off their shoes and to empty their bladders before being weighed.
- Central laboratory testing should be performed according to the current Schedule of Activities (SoA) as outlined in the protocol. If central laboratory tests cannot be performed, the use of a local laboratory is allowed for protocol-specified laboratory assessments. A copy of the local laboratory report should be reviewed for safety by the investigator and retained, along with reference ranges, for source documentation. Results from key metabolic parameters including leptin, adiponectin (if available) and fasting metabolic profile (total, high-density lipoprotein [HDL] and low-density lipoprotein [LDL], cholesterol, triglycerides, glucose) and efficacy parameters (HIV-1 RNA viral load and CD4+ cell counts) from the local laboratory testing for Week 24 and Week 48/ESID will be entered in the CRF. In anticipation of this possibility, study sites should consider proactively adding a local laboratory to the Form FDA 1572 and providing the sponsor with supporting documentation (eg, Clinical Laboratory Improvement Amendments [CLIA], CV of the laboratory head, etc.).
  - If a participant is found to have abnormal laboratory findings, including Grade 3 or 4 abnormalities, suspected virologic rebound (HIV-1 RNA value ≥200 copies/mL), or other laboratory findings that in the judgment of the investigator warrant confirmation, a concerted effort should be made to have the participant seen at an unscheduled visit at the study site or in person home visit for examination and applicable laboratory testing using the central laboratory.
- At Weeks 24 and 48, the PROs (BSQ-8D, HIV-SI, PGIC and PGIC-S) should be completed by the participant during the on-site study visit using the sponsor-provided electronic device. If the Week-24 or Week 48-visit is conducted remotely, the PROs will be collected using the sponsor-provided electronic device, if possible. If remote completion of the PROs is not possible, the PRO assessments will not collected at these visits and the reason recorded in the CRF.
- The SoA window for the completion of the DEXA scan at Week 24 and 48/ESID is ±10 days. If the DEXA scan cannot be performed within this window due to COVID-19 related restrictions, this should be documented as a deviation related to COVID-19 and should be conducted as soon as possible.

- Study intervention should be continued if, in the assessment of the investigator, it does not result in risk to the participant. Remote medical consultation and clinical safety laboratory assessments (including home health visits) will allow continued study participation for participants in this trial. If at any time a participant's safety is considered to be at risk due to study intervention, study intervention will be temporarily or permanently discontinued, while every effort should be made to maintain follow-up on study.
- The benefit of continuing study intervention should be considered by the investigator for each individual participant, considering the potential impact of reduced direct clinical supervision on participant safety. A temporary interruption of study intervention might be considered based on investigator´s discretion and documented.
- If study procedures cannot be performed per study protocol and are delayed, participants should stay on the assigned study intervention until these procedures can be performed.
- If a participant develops SARS-CoV-2 infection or related disease, the investigator should contact the sponsor to discuss plans for study intervention and follow-up. An interruption of study intervention should be considered by the investigator, depending on symptoms and concomitant medication used for the treatment of COVID-19. Treatment must be interrupted if prohibited medication is used. Standard Adverse Event/Serious Adverse Event reporting requirements apply.
- When a participant, for whom study intervention has been interrupted, recovers from suspected or confirmed SARS-CoV-2 infection or related disease and all toxicities improve to Grade ≤1, the investigator should discuss with the sponsor about resuming study intervention. If the study intervention has been interrupted for more than 4 weeks, the participant should be withdrawn from the study.
- Dispensing of D/C/F/TAF:
  - For participants unable to visit the study site, handover to a caregiver or delegate of D/C/F/TAF or direct-to-participant (DTP) shipment may be implemented, where allowed per local regulations and if requested by the principal investigator. Where handover to delegates or DTP shipments are deemed necessary, the process must be coordinated between the site staff and sponsor following standard DTP procedures for arranging shipment and adhering to associated approvals and documentation requirements.
  - For participants who are able to visit the study site, but who request to reduce visit frequency or for whom limited access to the site is expected, an additional supply of D/C/F/TAF can be provided using an Unscheduled Visit in the IWRS system.
- In the unlikely event that there is a need to communicate new important safety information to the participant during the study, participants will be reconsented at the next on-site or home visit.

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): _____

Institution: Janssen Scientific Affairs, LLC

Signature: electronic signature appended at the end of the protocol Date: _____

(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

Signature

User	Date	Reason
PPD	03-Jun-2020 17:59:41 (GMT)	Document Approval