Janssen Scientific Affairs, LLC

Statistical Analysis Plan
AMENDMENT 1

Protocol Title: A Phase 4, Randomized, Active-Controlled, Open-label Study to Evaluate the 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 800mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir alafenamide 10 mg)

Status:	Approved
Date:	24 March 2023
Prepared by:	Janssen Scientific Affairs, LLC
Document No.:	EDMS-RIM-989506

Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

TABLE OF CONTENTS

AMENDMENT HISTORY

Status and Version	Release Date	Change Description	Reason/Comment
Final Version 1.0	08-Dec-2020		
Amendment 1	09-Feb-2022	• Change of inclusion criteria #4 definition. 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. • Treatment phase end date was changed from visit date +1 day to visit date + 7 days for ongoing and early withdrawal subjects • Some Demographic and baseline characteristic label modification and additional information	• To account for new data, investigator feedback and protocol amendment. The window was extended from 12 month to 12-to-36 month. • Clinical feedback from interim analysis outputs
	24-Feb-2023	• Description of Primary analysis and Final Analysis • Scope of subgroup analysis • Table of visit window • Table of trial phase • Removal of tipping point analysis • Genotype/phenotype session	• Clarify the range of data for Primary Analysis and Final Analysis • Study team feedback • Formatting • To account for scrambled data • Not applicable • According to data availability

ABBREVIATIONS

ACC	American College of Cardiology
ADR	Adverse Drug Reaction
AE	adverse event
AEOI	Adverse events of interest
ALP	Alkaline phosphatase
ALT/SGPT	alanine aminotransferase
ANCOVA	analysis of covariance
ART	antiretroviral therapy
ARV	antiretroviral
AST/SGOT	aspartate aminotransferase
ATC	anatomic and therapeutic Class
BCO	biological cut-off
BMI	body mass index
BSA	body surface area
BSQ	body shape questionnaire
CBC	complete blood count
CCO	clinical cut-off
CD4	cluster of differentiation 4
CD8	cluster of differentiation 8
CDC	Centers for Disease Control and Prevention
CI	confidence interval
COBI	cobicistat
CRF	case report form
CSR	Clinical Study Report
D/C/F/TAF	darunavir/cobicistat/emtricitabine/tenofovir alafenamide
DAIDS	Division of AIDS
DBP	diastolic blood pressure
DEXA	dual- energy X-ray absorptiometry
DMC	Data Monitoring Committee
DPS	Data Presentation Specifications
DRC	Data Review Committee
DRV	darunavir
EAS	Efficacy analysis set
EC_{50}	50% effective concentration
ECG	electrocardiogram
eCRF	electronic case report form
eGFRcr	creatinine-based estimated glomerular filtration rate
EOI	events of interest
ESID	Early Study Intervention Discontinuation
ES	effect size
FC	fold change
FDA	Food and Drug Administration
FDC	Fixed-dose Combination
FU	Follow up
HAIR	hypertension, age, insulin, resistance
HbA1c	Hemoglobin A1c
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL	high density lipoprotein
HIV-1	Human Immunodeficiency Virus Type 1
HIV-SI	HIV-Symptom Index
HOMA-IR	homeostatic model assessment of insulin resistance

IA	interim analysis
INI	Integrase inhibitor
IN	Integrase
ITT	intent-to-treat
IWRS	interactive web response system
LDL	low-density lipoprotein
LME	linear mixed- effects
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MMRM	mixed model for repeated measures
MSM	men who have **sex** with men
NAFLD	non-alcoholic fatty liver disease
NNRTI	Non- Nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
PGIC	patient global impression of change
PGIC-S	patient global impression of change for satiety
PI	protease inhibitor
PK	pharmacokinetic(s)
PP	per protocol
PR	protease
PRO	patient report outcome
RAM	Resistance-Associated Mutation
RNA	Ribonucleic acid
RPV	rilpivirine
RT	reverse transcriptase
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SD	standard deviation
SoA	Schedule of Activities
SOC	System organ class
SSR	sample size re-estimation
T2DM	Type 2 diabetes mellitus
TEAE	treatment-emergent adverse event
VAT	Visceral Adipose Tissue
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

1. INTRODUCTION

This statistical analysis plan (SAP) contains definitions of analysis sets, derived variables and statistical methods for the analysis of metabolic (the percent change in body weight), efficacy and safety.

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 US Food and Drug Administration as a complete regimen for the treatment of HIV-1 infection in adults and pediatric patients weighing ≥40 kg 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 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 ARV regimen in this study will be comprised of an INI + TAF/FTC ARV regimen.

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 3)

- 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 5.2.3). In this analysis, primary and other endpoints up to week 24 will be presented. Additionally, patient data collected beyond week 24 at this time, including metabolic, adverse events (AEs) and other pertinent data, will be descriptively summarized

- The Week 48 analysis: once all participants have completed the Week 48 assessments or discontinued earlier. Descriptive statistics will be conducted

1.1. Trial Objectives

1.1.1. Primary Objective

The primary objective of this study is to assess the percent change in body weight at Week 24 from Baseline 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.

1.1.2. Secondary Objectives

1.1.2.1. Week 24 Objectives

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)
- 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)
- 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)
- 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)
- 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)
- 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)

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)

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)
- 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)

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)

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)
- 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)

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)

Exploratory:

Exploratory clinical biomarker: Alpha melanocyte stimulating hormone • 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)
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)
• 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)

1.1.2.2. Week 48 Secondary Objectives

Metabolic:

• To assess the percent change in body weight when switching to D/C/F/TAF FDC (Immediate Switch Arm)
• To assess changes in body weight when switching to D/C/F/TAF FDC (Immediate Switch Arm)
• To assess changes in body composition when switching to D/C/F/TAF FDC (Immediate Switch Arm)
• To assess change in blood pressure when switching to D/C/F/TAF FDC (Immediate Switch Arm)
• To assess changes in clinical laboratory tests when switching to D/C/F/TAF FDC (Immediate Switch Arm)
• To assess changes in liver biomarkers when switching to D/C/F/TAF FDC (Immediate Switch Arm)
• 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)

Safety:

• To evaluate the safety of switching to D/C/F/TAF FDC (Immediate Switch Arm)

Efficacy:

• To evaluate the virologic outcomes when switching to D/C/F/TAF FDC (Immediate Switch Arm)
• To evaluate immunological changes when switching to D/C/F/TAF FDC (Immediate Switch Arm)

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)

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)
• To describe responses on the PGIC in participants switching to D/C/F/TAF FDC (Immediate Switch Arm)

Adherence:

• To evaluate adherence in participants switching to D/C/F/TAF FDC (Immediate Switch Arm)

Exploratory:

Exploratory clinical biomarker: Alpha melanocyte stimulating hormone • To assess changes in alpha-melanocyte stimulating hormone when switching to D/C/F/TAF FDC (Immediate Switch Arm)
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)
• To assess changes in concerns about body shape for participants switching to D/C/F/TAF FDC (Immediate Switch Arm)

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

Metabolic:

• To assess consistency of effect in changes in body weight in participants switching to D/C/F/TAF FDC (Immediate Switch Arm) compared to participants switching to D/C/F/TAF FDC after 24 weeks on INI + TAF/FTC ARV regimen (Delayed Switch Arm)
• To assess consistency of effect in body composition changes when switching to D/C/F/TAF FDC (Immediate Switch Arm) compared to participants switching to D/C/F/TAF FDC after 24 weeks on INI + TAF/FTC ARV regimen (Delayed Switch Arm)
• To assess consistency of effect in change in blood pressure when switching to D/C/F/TAF FDC (Immediate Switch Arm) compared to participants switching to D/C/F/TAF FDC after 24 weeks on INI + TAF/FTC ARV regimen (Delayed Switch Arm)
• To assess changes in clinical laboratory tests when switching to D/C/F/TAF FDC (Immediate Switch Arm) compared to participants switching to D/C/F/TAF FDC after 24 weeks on INI + TAF/FTC ARV regimen (Delayed Switch Arm)
• To assess changes in liver biomarkers when switching to D/C/F/TAF FDC (Immediate Switch Arm) compared to participants switching to D/C/F/TAF FDC after 24 weeks on INI + TAF/FTC ARV regimen (Delayed Switch Arm)
• To assess consistency of effect in change of concomitant medications of interest when switching to D/C/F/TAF FDC (Immediate Switch Arm) (including anti-hypertensive, anti-hyperglycemic, and lipid lowering agents) compared to participants switching to D/C/F/TAF FDC after 24 weeks on INI + TAF/FTC ARV Regimen (Delayed Switch Arm)

Safety:

• To evaluate the safety of switching to D/C/F/TAF FDC (Immediate Switch Arm) compared to participants switching to D/C/F/TAF FDC after 24 weeks on INI + TAF/FTC ARV regimen (Delayed Switch Arm)

Efficacy:

• To evaluate the virologic outcomes when switching to D/C/F/TAF FDC (Immediate Switch Arm) compared to participants switching to D/C/F/TAF FDC after 24 weeks on INI + TAF/FTC ARV regimen (Delayed Switch Arm)

• To evaluate immunological changes when switching to D/C/F/TAF FDC (Immediate Switch Arm) compared to participants switching to D/C/F/TAF FDC after 24 weeks on INI + TAF/FTC ARV regimen (Delayed Switch Arm)

Resistance:

• To assess viral resistance in participants with confirmed HIV-1 RNA rebound when switching to D/C/F/TAF FDC compared to participants switching to D/C/F/TAF FDC after 24 weeks on INI + TAF/FTC ARV regimen (Delayed Switch Arm)

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 participants switching to D/C/F/TAF FDC after 24 weeks on INI + TAF/FTC ARV regimen (Delayed Switch Arm)
• To describe responses on the PGIC in participants switching to D/C/F/TAF FDC (Immediate Switch Arm) and in participants switching to D/C/TAF FDC after 24 weeks on INI + TAF/FTC ARV regimen (Delayed Switch Arm)

Adherence:

• To evaluate adherence in participants switching to D/C/F/TAF FDC (Immediate Switch Arm) compared to participants switching to D/C/F/TAF FDC after 24 weeks on INI + TAF/FTC ARV regimen (Delayed Switch Arm)

Exploratory:

Exploratory clinical biomarker: Alpha melanocyte stimulating hormone
• To assess changes in alpha melanocyte stimulating hormone when switching to D/C/F/TAF FDC (Immediate Switch Arm) after 24 weeks compared to participants switching to D/C/F/TAF FDC after 24 weeks on INI + TAF/FTC ARV regimen (Delayed Switch Arm)
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 participants switching to D/C/F/TAF FDC after 24 weeks on INI + TAF/FTC ARV regimen (Delayed Switch Arm)
• To assess changes in concerns about body shape for participants switching to D/C/F/TAF FDC (Immediate Switch Arm) compared to participants switching to D/C/F/TAF FDC after 24 weeks on INI + TAF/FTC ARV regimen (Delayed Switch Arm)

1.2. Hypothesis

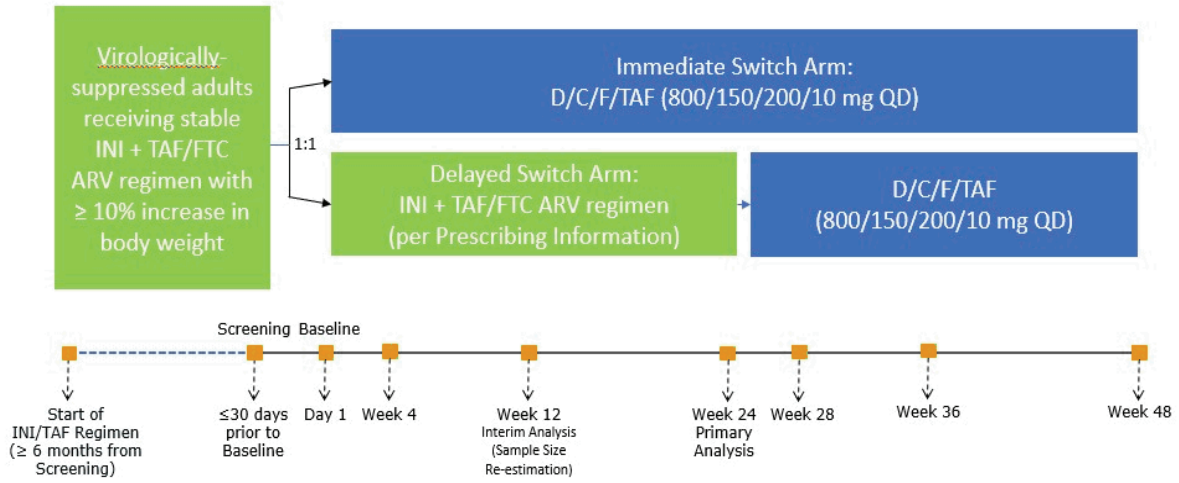
Based on the primary endpoint, the percent change in body weight at Week 24 from Baseline in the Immediate Switch Arm (D/C/F/TAF FDC) is less than that of the Delayed Switch Arm (INI + TAF/FTC ARV).

1.3. Trial Design

This is a randomized, 48 week, active-controlled, open-label, prospective, multicenter, Phase 4 study to evaluate the 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. Figure 1 described three phases conducted in this study: 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).

Figure 1: Schematic Overview of the Study



Approximately 110 subjects will participate 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.

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 one of the following two 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.

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 12-to-36 month time period 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 three 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 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 one of the following two 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 be given the option to receive the D/C/F/TAF tablet and will be followed for an additional 24 weeks.

- **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 will return for study visits at Weeks 4, 12, 24, 36, and 48. Additionally, participants randomized to the Delayed Switch Arm will have an additional study visit at Week 28 (i.e., 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, if necessary.

Key safety assessments 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.

Patient Reported outcomes (PROs), including body shape questionnaire [BSQ-8D], DAILY EATS, HIV-Symptom Index [HIV-SI], and patient global impression of change [PGIC]), will be completed.

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

HIV-1 genotypic and phenotypic resistance testing (PhenoSense GT® Plus Integrase[1]) 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 an HIV-1 RNA >400 copies/mL at the time of confirmed rebound. 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. Additionally, data collected beyond Week 24 visit, including metabolic data, adverse events and other pertinent data, will also be summarized in the primary analysis. 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).

1.4. Statistical Hypotheses for Trial Objectives

The primary goal of this study is to assess the percent change in body weight at Week 24 from Baseline of D/C/F/TAF FDC (Immediate Switch arm) in HIV-1 infected participant who are virologically-suppressed (HIV-1 RNA <50 copies/mL) and have experienced rapid and significant body weight gain in combination with an INI + TAF/FTC ARV regimen (Delayed Switch arm). 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= percent change in body weight at Week 24 from baseline for treatment D/C/F/TAF (Immediate Switch arm), Dc for the Delayed Switch arm.

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

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

Primary Endpoint Analyses: Percent change in body weight at Week 24 from Baseline. The primary endpoint analyses will be based on the ITT population. It will be evaluated using LME model with participant as random effect adjusted by baseline BMI and stratification factors (sex and race) in a longitudinal data with repeated measures (percent change in body weight measured at multiple visits).

1.5. Sample Size Justification

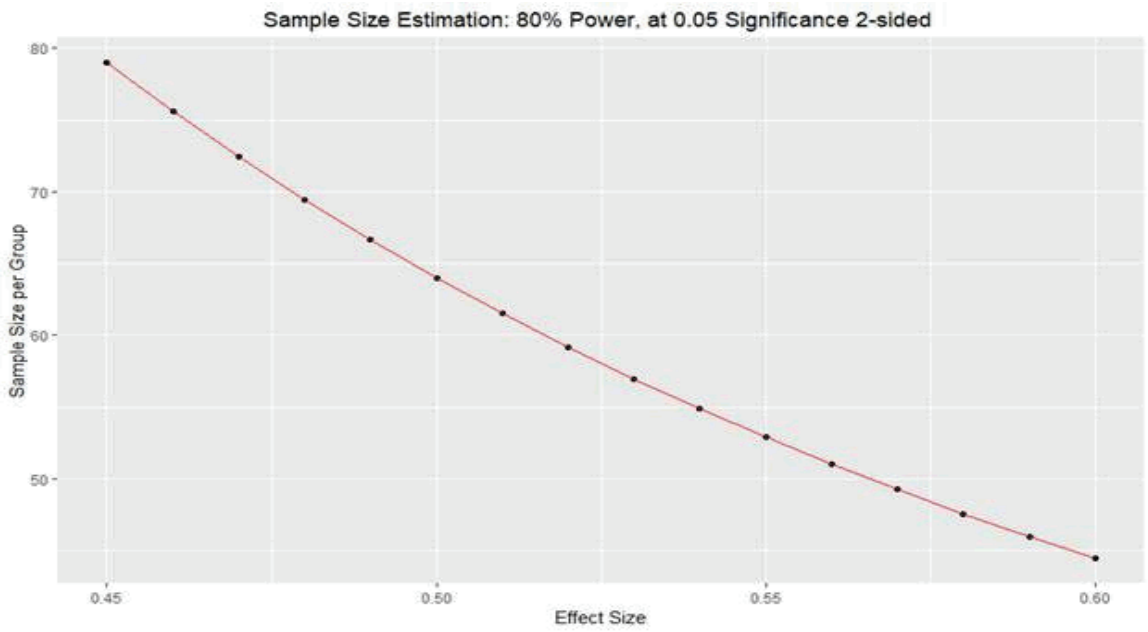
Using a T-test with 80% power to detect a difference of 3% at the significance level of 0.05, 2-sided, the sample size per treatment arm is a simple function of effect size (ES): $n_{arm}=16/(ES)^2$. The effect size is the standardized difference: $ES=\Delta/\sigma$, where Δ is the difference between 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[2, 3] 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 1 and Figure 2), resulting a range of ES and corresponding sample size[3].

Table 2 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)

Figure 2: 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 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.

1.6. Randomization and Blinding

1.6.1. Procedures for Randomization

Participants will be randomly assigned to one of two 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 (sex and race), 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 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 after the screening visit (for further details, see Section 8 in Protocol). 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. Study drug 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 then will give the relevant participant details to uniquely identify the participant.

1.6.2. Blinding

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

2. GENERAL ANALYSIS DEFINITIONS

2.1. Treatment Arms

Following notations for the treatment arms will be used:

- **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.

2.2. Visit Windows

As subjects do not always adhere to the protocol visit schedule, the following rules are applied to assign actual visits to analysis visits. Listed below are the visit windows and the target days for each visit. The reference day is Study Day 1. If a subject has 2 or more actual visits in one visit window, the visit closest to the target day will be used as the protocol visit for that visit window. The other additional visit(s) will not be used in the summaries or analyses, but they can be used for determination of clinically important endpoints. If 2 actual visits are equidistant from the target day within a visit window, the later visit is used.

All assignments will be made in chronological order. Once a visit date is assigned to a visit window, it will no longer be used for a later time point except for the endpoint. Listed below (Table 2) are the analysis time points (week), visit windows and the target days for each visit defined in the protocol during the treatment phase. The time intervals will be used for reporting of metabolic/weight, efficacy, and safety data.

Table 2. Visit Windows

Analysis Time Point [a]	Immediate Switch Arm - Time Interval (Day)	Delayed Switch Arm - Time Interval (Day)	Target Time Point (Day)
Screening	Day-42 - <Day 0	Day-42 - <Day 0	-∞
Baseline [b]	≤Day 1	≤Day 1	1
Week 4	Day 2 – Day 56	Day 2 – Day 56	29
Week 12	Day 57 – Day 126	Day 57 – Day 126	85
Week 24	Day 127 – Day 210	Day 127 – Day 182	169
Week 28	NA	Day 183 – Day 224	197
Week 36	Day 211 – Day 294	Day 225 – Day 294	253
Week 48	Day 295 – Day 378	Day 295 – Day 378	337

[a] For subjects discontinuing treatment early, data collected at that visit will count towards the time interval based on days relative to baseline.

[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.

Note: Target Time Point (Day)=Week x×7 +1; Time Interval (Day), for example, Start day=127=(85+169)/2 and then obtain the previous interval End day=127-1=126. Similarly, for other intervals' Start day and End day.

Phases will be constructed for each subject as follows for adverse events, concomitant therapies, and for the determination of the worst-case/toxicity/change in the cross-tabulations.

Trial phase	Start date	End date
Screening	Minimum of date of signing the informed consent and date of the screening visit, no early than Day -42	1 day before start of treatment or day 1 of treatment whichever the last before first dose.
Treatment Phase I	Date of the first intake (after randomization)	For ongoing/completed subjects, in order of priority: – For delayed switched arm, use first D/C/F/TAF intake date – 1; – For immediate switch arm, use Week 24 visit date; if missing then – Projected Week 24 visit date Projected Week 24 visit date = first dose date + (7×24). <u>In case of withdrawal before Week 24 visit</u>: Date of last intake +7 days. If the last dose date is missing, use the following date in order of priority: – The date of treatment termination + 7 days; – The first available follow-up visit date-1 day; – The earlier of projected Week 24 visit date +7 and Trial discontinuation date + 7, where projected Week 24 visit date = first dose date + (7×24).
Treatment Phase II	Treatment Phase I end date +1 day	For ongoing/completed subjects, in order of priority: – Week 48 visit date + 7; if missing then – Projected Week 48 visit date +7, where projected Week 48 visit date = first dose date + (7×48). <u>In case of withdrawal after Week 24 visit</u>: Date of last intake +7 days. If the last intake date is missing, use the following date in order of priority: – The date of withdrawal + 7 days; – The first available follow-up visit date-1 day; – The earlier of projected Week 48 visit date +7 and trial discontinuation date + 7, where projected Week 48 visit date = first dose date + (7×48).
***Follow-up**	End of the last treatment phase +1 day	Trial termination date for all groups (date of last contact)

*30 day follow-up visit required for any subject who has ongoing AE or SAE at the time of his last study visit.

2.3. Pooling Algorithm for Analysis Centers

Not applicable.

2.4. Analysis Sets

2.4.1. All Subjects

All subject analysis set population includes subjects who were screened.

2.4.1.1. Intent-to-Treat Analysis Set

The intent-to-treat (ITT) analysis set will include all the subjects who were randomized and received at least 1 dose of treatment subsequent to randomization in the study. Subjects will be grouped according to the treatment arm (D/C/F/TAF FDC or Active-Control) to which they were randomized.

The ITT analysis set is the primary analysis set for primary endpoint (percent change in body weight) analysis. The ITT analysis set is also used for efficacy analysis. Efficacy data up to the last dose date of the randomized study treatment will be included.

2.4.1.2. Per-Protocol Analysis Set

Since an analysis on the ITT population may not be conservative in certain analysis settings, an analysis based on the per-protocol (PP) population will also be performed to investigate the impact of excluding subjects with major protocol violations and to evaluate the robustness of the primary and major secondary analysis results.

2.4.2. Safety Analysis Set

The safety analysis set includes all randomized subjects who received at least 1 dose of study intervention (i.e., ITT analysis set). The safety analysis (including all data collected up to 30-day follow-up visit) is also performed on the ITT analysis set. Participants will be assessed according to the actual intervention they received.

2.5. Definition of Subgroups

The pre-specified subgroups are summarized in the table below. Selected subgroup analyses will be performed for baseline and demographic characteristics tables. Additional subgroup analyses may be performed, if requested and deemed necessary.

Subgroup	Definition
Race [a*]	• Black/African American • Non-Black/African American
Sex*	• Female • Male
Race:Sex*	• Black/African American Female • Black/African American Male

Subgroup	Definition
	• Non-Black/African American Female • Non-Black/African American Male
Ethnicity*	• Hispanic or Latino • Non-Hispanic or Latino • Others (Unknown/Not Reported)
Race/Ethnicity	• Black/African American Hispanic or Latino • Black/African American Non-Hispanic or Latino • Non-Black/African American Hispanic or Latino • Non-Black/African American Non-Hispanic or Latino
Baseline CD4+ categories	• >200 • ≤ 200
Age Group*	**Adults** • 18-25 • 26-50 • 51-64 • ≥65
BMI*	• normal 18 - <25 kg/m^2 • overweight 25 - <30 kg/m^2 • obese ≥30 kg/m^2
Waist circumference (inch) *	• Male WC ≥ 40” • Males WC < 40” • Female WC ≥ 35” • Female WC < 35”
ARV Treatment Regimen at Time of Screening	• BIC/FTC/TAF • DTG + FTC/TAF • RAL + FTC/TAF • EVG/C/FTC/TAF
Delayed Switch Regimen	• DTG+FTC/TAF vs SYM • BIC/FTC/TAF vs SYM • RAL+FTC/TAF vs SYM • EVG/C/FTC/TAF vs SYM
Presence of one or more primary and/or DRV Resistance-Associated Mutation (RAMs),	• Yes/No
Presence of one or more NRTI RAMs	• Yes/No
Presence of one or more NNRTI RAMs	• Yes/No
Presence of one or more Primary INI RAMs	• Yes/No
Presence of one or more Secondary INI RAMs	• Yes/No
HIV Acquisition Risk Factor [b]*	• Heterosexual contact • MSM • Others

Subgroup	Definition
NAFLD fibrosis score*	• F0-F2 • Indeterminate • F3-F4
HAIR scores *	• >=2 • <2
Baseline Co-morbid conditions (defined by Medical History)	• Diabetes Y/N • HTN Y/N • Hyperlipidemia Y/N

[a] Non-Black/African American=White, American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, Multiple, Other, Unknown, and Not reported.

[b] Others= Intravenously injectable drug use, Blood transfusion, Hemophilia-associated injections, Occupational exposure, Mother to child transmission and other.

* Subgroup analyses will be performed for these subgroups only

2.6. Study Day and Relative Day

Study Day 1 or Day 1 refers to the start of the first study agent administration or randomization date. If subjects start medication a day after baseline/screening visit, actual treatment administration date will be used as Day 1 instead of screening/baseline visit date.

All metabolic, efficacy and safety assessments at all visits will be assigned a day relative to this date.

2.7. Baseline and Endpoint

Baseline is defined as the last observation prior to the start of the first study agent administration or randomization date.

Endpoint is defined as the last available postbaseline result within the analysis period. Unscheduled visit results are included in this definition and will be considered as the endpoint value if the unscheduled visit result is the last postbaseline result available within the analysis period.

2.8. Imputation Rules for Missing AE Date of Onset/Resolution

Partial AE onset dates will be imputed as follows:

- If the onset date of an adverse event is missing day only, it will be set to:
  - First day of the month that the AE occurred, if month/year of the onset of AE is different than the month/year of the study treatment start.
  - The day of the study treatment start, if the month/year of the onset of AE is the same as month/year of the study treatment start and month/year of the AE resolution date is different
  - The day of the study treatment start or day of AE resolution date, whichever is earliest, if month/year of the onset of AE and month/year of the study treatment start and month/year of the AE resolution date are same
- If the onset date of an adverse event is missing both day and month, it will be set to the earliest of:

  - January 1 of the year of onset, as long as this date is on or after the study treatment start date
  - Month and day of the study treatment start date, if this date is the same year that the AE occurred
  - Last day of the year if the year of the AE onset is prior to the year of the study treatment start date,
  - The AE resolution date.
- Completely missing onset dates will not be imputed.

Partial AE resolution dates not marked as ongoing will be imputed as follows:

- If the resolution date of an adverse event is missing day only, it will be set to the earliest of the last day of the month of occurrence of resolution or the day of the date of death, if the death occurred in that month.
- If the resolution date of an adverse event is missing both day and month, it will be set to the earliest of December 31 of the year or the day and month of the date of death, if the death occurred in that year.
- Completely missing resolution dates will not be imputed.

3. INTERIM ANALYSIS AND, DATA MONITORING COMMITTEE REVIEW

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 DRC charter for the IA and monitoring. The planned maximum total sample size after SSR is 150 participants. IA contents will be defined in DPS.

The Data Monitoring Committee (DMC) is not applicable. Instead, a data review committee (DRC) is used for the interim analysis. Details are included in the DRC charter.

4. SUBJECT INFORMATION

The number of subjects in each analysis set will be summarized and listed by treatment group, and overall. In addition, the distribution of subjects by site ID will be presented unless otherwise noted.

4.1. Demographics and Baseline Characteristics

Table 3 presents a list of the demographic variables that will be summarized by treatment group, and overall for the ITT, safety, and PP analysis sets. Additionally, baseline disease characteristics data are listed in Table 4. Demographics and baseline disease characteristics will also be summarized and analyzed by study subgroups listed in Section 2.5 using the ITT analysis set.

Table 3: Demographic Variables

Continuous Variables:	**Summary Type**
Age (years)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum])
Weight (kg)/(pounds)	
Percent weight gained on current INI+TAF/FTC regimen at screening	
Duration of virologic suppression on current INI+TAF/FTC regimen (month)	
Duration of infection (month)	
Height (cm)	
Body Mass Index (BMI) (kg/m^2)	
Waist circumference (cm)	
Categorical Variables	
Age (18-25 years, 26-50 years, 51-64 years, and ≥65 years)	Frequency distribution with the number and percentage of subjects in each category.
Baseline history of hypertension (yes/no)	
Baseline history of diabetes (yes/no)	
Baseline history of dyslipidemia (yes/no)	
Baseline active neurologic comorbidities (yes/no)	
Baseline active psychiatric comorbidities (yes/no)	
Number of active neurologic/psychiatric comorbidity (1, 2, 3, 4, >/=5)	
Baseline HbA1c > 6.5% (yes/no)	
Antihypertensives, antihyperglycemic agents or lipid lowering agents (yes/no)	
Sex (male, female)	
Gender (male, female, male-to-female, female-to-male, non-binary/other)	
Race (Black/African American, Non-Black/African American)	
Race:Sex (Black/African American Female, Black/African American Male, Non-Black/African American Female, Non-Black/African American Male)	
Race[a] (Black/African American, White, American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, Other, Unknown, Not reported)	
Ethnicity (Hispanic or Latino, not Hispanic or Latino, Unknown, Not reported)	
BMI (normal 18-<25 kg/m2, overweight 25-<30 kg/m2, obese ≥30 kg/m2)	
Woman of childbearing potential (Of childbearing potential/Permanently Sterilized/ Postmenopausal/ NA)	
Nicotine use (Never used, current user, former user)	
Alcohol consumption (Never used, current user, former user)	
Drug Use (Never used, current user, former user)	
Highest education level (Less than high school, …)	
Marital status (Single- newer married, married, …)	
Employment status (Employed full time for wages, …)	
State belongs to (Alabama, …)	
Social support of the subject (Friend, Family member, …)	
Current housing situation	

[a] If multiple race categories are indicated, the Race is recorded as 'Multiple'

Table 4: Baseline HIV disease characteristics

Continuous Variables:	**Summary Type**
Baseline CD4+ (absolute count and %)	Descriptive statistics (N, mean, standard deviation [SD], median
Baseline-screening eGFRcr[a]	
Baseline HIV-1 viral load (absolute count)	

Duration of INI + TAF/FTC treatment at baseline (years)	and range [minimum and maximum]).
Duration of TAF use (years)	
Duration of ART (years)	
Categorical Variables:	Frequency distribution with the number and percentage of subjects in each category.
Type of INI regimen at baseline	
Number of previous ART regimens	
Switched previous regimens for AE, VF, Convenience and Other	
HIV Acquisition Risk Factor (Heterosexual contact, MSMs, Others [b])	
Baseline viral load (<50, ≥ 50 HIV-1 RNA copies/mL)	
Baseline CD4 cell count (≤200, 200<x≤350, 350< x≤500, >500) cells/mm3)	
HIV-1 subtype (B, Non-B)	
Historical evidence of DRV RAM • yes/no • V11I • V32I • etc.	
Historical evidence of FTC RAM • yes/no • K65R • K65E • etc.	
Historical Evidence of TFV RAM • yes/no • K65N • K70E • etc.	
Historical Evidence of INI RAM • yes/no • T66A • T66I • etc.	

[a] If a participant's actual body weight is greater than 20% over their Ideal Body Weight (IBW), the participant's Adjusted Body Weight (ABW) will be used for eGFRcr (Cockcroft-Gault Formula). IBW(male) = 50kg + 0.9kg x (height(cm) – 152). IBW (female) = 45.5kg + 0.9kg x (height(cm) – 152. ABW= IBW(kg) + 0.4 x (Weight(kg) – IBW(kg)).

[b] Others=Intravenously injectable drug use, Blood transfusion, Hemophilia-associated injections, Occupational exposure, Mother to child transmission, and Other

4.2. Disposition Information

A tabulation of the total number (with percentages) of subjects screened (and reason for screen failures), randomized and not treated, and randomized and treated will be provided.

Tabulation per treatment arm and overall of the number of subjects who have completed the treatment phase, who are ongoing, and who have discontinued the trial before Week 48 visit, with the reason for discontinuation will be provided.

A Kaplan-Meier graph for the time to Discontinuation (any reason) will be included.

The number of subjects in the following disposition categories will be summarized throughout the study:

- Subjects receiving study intervention

- Subjects completing the study
- Subjects who discontinued study intervention
- Reasons for discontinuation of study intervention

The above categories will include summaries. A listing of subjects will be provided for the following categories:

- Subjects who discontinued study intervention

4.3. Treatment Compliance (Adherence)

Treatment adherence defined based on participant self-report using a 4-day recall as collected Drug Adherence page of eCRF for the study will be assessed at all study visits by participant self-report using a 4-day recall.

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.

4.4. Extent of Exposure

The number and percentage of subjects who receive study drug of both D/C/F/TAF FDC arm and active-control arm will be summarized by treatment group.

Descriptive statistics, (N, mean, SD, median, and range (minimum, maximum)), will be tabulated for the duration of treatment of both D/C/F/TAF and control, in weeks, during the respective active treatment phases, up to the Week 48 visit, or in case of early discontinuation, last study medication intake for the ITT analysis set. In addition,

- subject-years of exposure will be shown, derived as mean of treatment duration ((in weeks) x N) x 7 / 365.25..
- subject-weeks of exposure are calculated as (days of exposure)/7. Subject-weeks will be presented.
- treatment duration (in weeks) is defined as follows for each of the two treatment arms:

  (End of phase – start of phase + 1) / 7

  Treatment interruptions will not be taken into account for the above definition.
- total dose days of exposure is defined as the total number of days that study intervention was administered to the subject (excluding days of known study treatment interruption). If dates of study treatment interruptions are not fully known, in terms of start and end date of interruption, these interruptions will not be excluded from total days of exposure.

4.5. Protocol Deviations

In general, the following list of major protocol deviations may have the potential to impact subjects' rights, safety or well-being, or the integrity and/or result of the clinical study. Subjects with major protocol deviations will be identified prior to database lock and the subjects with major protocol deviations will be summarized by category.

- Developed withdrawal criteria but not withdrawn

- Entered but did not satisfy inclusion/exclusion criteria
- Received a disallowed concomitant treatment
- Received incorrect dose
- Other

4.6. Prior and Concomitant Medications

Prior and Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD). Prior medications are defined as any therapy used before the Baseline Day 1. Concomitant medications are defined as any therapy used on or after the same day as the Baseline Day 1.

Summaries of concomitant medications will be presented by treatment group. The proportion of subjects who receive each concomitant medication and the proportion of subjects who receive at least one concomitant medication will be summarized.

Summaries of concomitant medications will be presented by ATC term. A summary of participants with changes in medications of interest at Week 48 will be reported.

Prior and concomitant therapies will be summarized and grouped as follows by treatment group for specific drugs, using a list of dictionary derived terms provided as metadata. These groups will be tabulated (n, %) per treatment group and analysis phase:

- lipid lowering drugs
- antidiabetic drugs
- antihypertensive drugs
- drugs for cardiovascular disease
- antiosteoporotic drugs
- antidepressants
- antipsychotics
- steroids
- thyroid medications

Prior medications will be summarized by ATC term.

4.7. Medical History

Subjects past and/or concomitant diseases will be tabulated by medical history categories, general medical history, and family history, separately by treatment group. Tabulation (n, %) will be done by body system and medical term. Additionally, all medical history will be listed by medical history category.

5. METABOLIC/WEIGHT

5.1. Analysis Specification

In general, continuous variables will be summarized using descriptive statistics including the number of participants, mean, standard deviation (SD), two-sided 95% confidence interval (CI), median, and range. Binary or categorical variables will be summarized using the number and percentage of participants in each category. Descriptive summaries will be provided by stratification factors (sex and race). Graphic displays will also be used to summarize the data.

5.2. Primary Endpoint

5.2.1. Definition

The primary endpoint is defined as the percent change in body weight at Week 24 from Baseline.

5.2.2. Primary Estimand

The main analysis of the primary endpoint will be conducted by using the following estimand attributes:

A) Study Intervention:

- Arm 1: D/C/F/TAF FDC Arm (Immediate Switch)
- Arm 2: Active-Control Arm (Delayed Switch)

B) Study population: Type 1 (HIV-1) infection currently treated subjects with a stable ARV regimen consisting of an INI combined with TAF/FTC for ≥ 6 consecutive months preceding the screening visit and experiencing a ≥10% increase in body weight within 12 months' time period

C) Variable: Percent change in body weight at Week 24 from Baseline

D) Intercurrent events:

- Treatment discontinuation prior to Week 24: if the participant discontinued treatment prior to Week 24 but weight assessments are available at that time point, all data will be used regardless of occurrence of the intercurrent event (treatment policy strategy).
- Major protocol deviations**:** all data are used regardless of the occurrence of major protocol deviations (treatment policy strategy).
- Deaths prior to Week 24: participants who die prior to Week 24 will be included with the weight data available prior death.

E) Population-level summary: Mean difference in %weight change at Week 24 between study intervention arms.

5.2.3. Analysis Methods

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= percent change in body weight at Week 24 from Baseline for D/C/F/TAFFDC (Immediate Switch Arm), Dc = percent change in body weight at Week 24 from Baseline for active control (Delayed Switch Arm).

The statistical hypothesis will be tested using mixed model for repeated measures (MMRM) below.

Y = Baseline BMI + Sex + Race + Time + Treatment + Treatment*Time + Subject + Ɛ

In this model, Y is the %change in body weight from baseline at time week 4, week 12, and week 24; baseline BMI, sex, race, time, treatment and treatment*time are fixed effects; subject is a random effect; and Ɛ is the random error. Subject is treated as a random effect to incorporate the variability and correlation among repeated measures (time).

The statistical hypothesis will be tested by estimating the treatment LSmeans for the %change in body weight corresponding to the time measurement at week 24. The significance level p-value and 95% confidence interval for the difference will be provided.

To control for the overall Type I error rate at the 2-sided 0.05 significance level, the weighted inverse-normal p-value combination test will be used to combine p-values from interim stage and primary analysis stage[4] . The overall p value will be calculated by the combination statistic below

$Z(p_1, p_2) = w1\ \Phi^{-1}(1-p_1) + w2\ \Phi^{-1}(1-p_2)$

where $w_1=\sqrt{(n_1/N)}$, $w_2=\sqrt{(n_2/N)}$, n_1 and n_2 are number of subjects in IA stage and remaining primary stage.

All available data from randomized participants that have received at least one dose is included (ITT analysis set) will be used for the analysis, regardless of the occurrence of intercurrent events.

Missing Data for body weight is assumed as Missing At Random (MAR). In addition, as a sensitivity analysis, a control-based multiple imputation will be applied to the MMRM model, assuming weight data is not missing at random.

5.2.4. Sensitivity Estimator

A sensitivity analysis will be performed for primary endpoint (percent change in body weight Week 24) analysis based on modified ITT population (mITT) which will exclude those ITT subjects who are impacted specifically by COVID-19 with missing important study visits and/or discontinuation. The mITT analysis set will be pre-specified before the database lock.

A second sensitivity analysis will be performed to evaluate outlier effect on the primary endpoint. Outliers of percent weight change, which is defined as more than three standard deviations from the mean percent change in body weight from baseline at Week 24, will be excluded from modified ITT population 2 (mITT2) for this analysis.

The same MMRM model described in methods for the primary estimand will be used for the sensitivity analyses described above.

6. EFFICACY/VIROLOGY

6.1. Analysis Specifications

6.1.1. Data Handling Rules

Plasma viral load will be measured using a validated assay at a central laboratory.

Imputation of left censored HIV-1 RNA values: viral load results recorded as "< 20 copies/mL HIV RNA detected", "< 20 copies/mL HIV RNA copies/mL Not Detected" and "NO HIV-1 RNA DETECTED" will be scored at 19.

If there are retesting, repeating the same analysis from same collected sample, last or retested results will be used in analysis.

6.1.2. Virologic Response Definitions

The following imputation methods will be used to calculate virologic response at a given time point addition with applying 50/200 copies/mL as threshold.

Two imputation mechanisms are considered:

1. Observed
2. FDA Snapshot

The first mechanism, Observed, does not require an imputation procedure. Subjects with a missing value are disregarded in the analysis for that time point.

The second mechanism FDA snapshot approach**:** The snapshot mechanism is based on the last available plasma HIV-1 RNA level within the window of an analysis time point. This does not necessarily coincide with the HIV-1 RNA assessment with USE = 'Y'.

The snapshot approach will classify subjects into 3 outcome categories: "virologic response", "virologic failure", or "no viral load data in the Week 24 and Week 48 visit windows". Several subcategories of the outcome will also be presented in the analysis and are shown below. The categories below are mutually exclusive such that a subject will be included in one category. If a subject discontinues in the time window

but also has an HIV-RNA value in the time window, then the viral load data will be used to classify the subject's category.

- Virologic response:
  - HIV RNA <50/200 copies/mL in the Week 24 visit window (Week 18-30) and Week 48 visit window (Week 42-54)
- Virologic failure:
  - HIV RNA ≥50/200 copies/mL in the Week 24 visit window (Week 18-30) and Week 48 visit window (Week 42-54)
  - Virologic failure leading to discontinuation
  - Discontinued due to other reason (i.e., other than AE/death or virologic failure) and last available HIV RNA ≥50/200 copies/mL
- No viral load data in the Week 24 visit window (Week 18-30) and Week 48 visit window (Week 42-54):
  - Discontinued due to AE/death (subjects will be classified in this category if discontinued prior to Week 24 visit window and Week 48 visit window regardless of HIV RNA level).
  - Discontinued due to other reason (i.e., other than AE/death or virologic failure) and the last available HIV RNA <50/200 copies/mL (or missing)
  - Missing data during the Week 24 visit window and Week 48 visit window but on study.

Virologic failure leading to discontinuation will be determined by a medical assessment of the comment fields and other specification reasons for discontinuation to determine if anyone discontinued the trial due to lack of efficacy reasons. Upon further clinical evaluation additional comments or other specification reasons might need to be added, and these will be documented in the DPS. An identified subject will be classified to the snapshot categories as follows:

- Data within window: If an identified subject has HIV RNA data within the window, the HIV RNA data will be used to classify the subject as either at or above the threshold or below the threshold.
- No data within window: If an identified subject does not have HIV RNA data in window, then regardless of the last HIV RNA value the subject will be classified as "Virologic failure leading to discontinuation".

Virologic response will then be categorized as follows: Yes (virologic response), or No (virologic failure and no viral load data in the Week 24 visit window and Week 48 visit window).

The snapshot approach will also be displayed over time by analysis time points and will follow the same logic as defined above weeks 24 and 48 time point. (Please see Section 2.2. Visit Windows for visit intervals).

Subjects will also be classified as confirmed virologic rebounds if they meet the criteria below:

- Two consecutive HIV RNA ≥200 copies/mL at a scheduled or unscheduled visit after maintaining HIV-1 RNA <50 copies/mL).

6.2. Secondary Endpoints and Analysis Methods

6.2.1. Weeks 24 and 48 Endpoints

In the following, the secondary endpoints at Week 24 are defined for D/C/F/TAF FDC regimen (Immediate Switch Arm) versus INI + TAF/FTC ARV regimen (Delayed Switch Arm), while the secondary endpoints at Week 48 are related to D/C/F/TAF FDC (Immediate Switch Arm) only.

Metabolic:

- Change from Baseline in absolute body weight over time
- Proportion of participants with % change from baseline in body weight >5% over time.
- Proportion of participants with % change from baseline in body weight >3% over time.
- Change from Baseline in BMI over time.
- Change from Baseline in body composition as measured by DEXA scan at Week 24 and Week 48, respectively.
- Change from Baseline in waist circumference over time.
- Change in SBP and DBP from Baseline over time.
- Change from Baseline in fasting lipids over time.
- Change from Baseline in fasting glucose over time.
- Change from Baseline in HOMA-IR at Week 24 and Week 48, respectively.
- Change from Baseline in HbA1c at Week 24 and Week 48, respectively.
- Change from Baseline in leptin and adiponectin at Week 24 and Week 48, respectively.
- Change from Baseline in the proportion of participants with advanced fibrosis according to the NAFLD fibrosis score at Week 24 and Week 48, respectively.
- Change from Baseline in the proportion of participants at high risk of NASH according to the HAIR score at Week 24 and Week 48, respectively.
- 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 24 and Week 48, respectively 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 from Baseline to Week 24 and Week 48, respectively or Delayed Switch Arm from Baseline to Week 24.

Safety:

- Incidence of any Grade AEs (related and not related) through Week 24 and Week 48, respectively.
- Incidence of Grade 3 and 4 AEs (related and not related) through Week 24 and Week 48,

respectively.
- Incidence of discontinuations due to AEs through Week 24 and Week 48, respectively.
- Incidence of SAEs (related and not related) through Week 24 and Week 48, respectively.
- Change from Baseline in clinical laboratory tests over time .
- Incidence of Grade 3 and 4 laboratory abnormalities over time .

Efficacy:

- Proportion of participants with confirmed virologic rebound through Week 24 and Week 48, respectively.
- Proportion of participants with virologic response (HIV-1 RNA<50 copies/mL) at Week 24 and Week 48, respectively, according to the FDA snapshot algorithm
- Proportion of participants with virologic failure (HIV-1 RNA ≥50 copies/mL) at Week 24 and Week 48, respectively, according to the FDA snapshot algorithm
- Proportion of participants having virologic response (HIV-1 RNA<200 copies/mL) at Week 24 and Week 48, respectively, according to the FDA snapshot algorithm
- Proportion of participants having virologic failure (HIV-1 RNA ≥200 copies/mL) at Week 24 and Week 48, respectively, according to the FDA snapshot algorithm
- Change from Baseline in CD4+ cell count at Week 24 and Week 48 respectively.

Resistance:

- Proportion of participants with baseline DRV, FTC, TFV and INI resistance-associated mutations (RAMs) based on historical genotypes .
- Incidence of observed genotypic and phenotypic ARV resistance for participants meeting HIV-1 RNA rebound criteria through Weeks 24 and 48, respectively.
- 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 Weeks 24 and 48, respectively.

PROs:

- 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 and Week 48, respectively.
- 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 and Week 48, respectively.
- Association between treatment arm and each bothersome symptom of the HIV-SI adjusting for Baseline variables at Week 24 and Week 48, respectively.
- PGIC and PGIC-S at Week 24 and Week 48, respectively.

Adherence:

- Adherence rates by participant self-report using 4-day recall at Weeks 4, 12, 24, 36 and 48, respectively.

Exploratory:

Exploratory clinical biomarker:

- Change from Baseline in alpha melanocyte-stimulating hormone at Week 24 and Week 48, respectively.

Exploratory PROs:

- Change from Baseline in the scores on the DAILY EATS at Week 24 and Week 48, respectively.
- Change from Baseline in the scores on the BSQ-8D at Week 24 and Week 48, respectively.
- 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 24 and Week 48, respectively.

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

Metabolic:

- Change in absolute body weight from Baseline to Week 24 (Immediate Switch Arm) compared to the change in absolute body weight from Week 24 to Week 48 (Delayed Switch Arm)
- The proportion of participants having a >5% change in body weight from Baseline to Week 24 (Immediate Switch Arm) compared to the proportion of participants having a >5% change in body weight from Week 24 to Week 48 (Delayed Switch Arm)
- The proportion of participants having a >3% change in body weight from Baseline to Week 24 (Immediate Switch Arm) compared to the proportion of participants having a >3% change in body weight from Week 24 to Week 48 (Delayed Switch Arm)
- Change in BMI from Baseline through Week 24 (Immediate Switch Arm) compared to the change in BMI from Week 24 through Week 48 (Delayed Switch Arm)
- Change in BMI categories from Baseline through Week 24 (Immediate Switch Arm) compared to the change in BMI categories from Week 24 through Week 48 (Delayed Switch Arm)
- Percent change in body weight from Baseline to Week 24 (Immediate Switch Arm) compared to the percent change in body weight from Week 24 to Week 48 (Delayed Switch Arm).
- Percent change in Visceral Adipose Tissue from Baseline to Week 24 (Immediate Switch Arm) compared to the percent change in Visceral Adipose Tissue from Week 24 to Week 48 (Delayed Switch Arm).
- Change in body composition as measured by DEXA from Baseline through Week 24 (Immediate Switch Arm) compared to the change in body composition from Week 24 through Week 48 (Delayed Switch Arm)
- Change in waist circumference from Baseline to Week 24 (Immediate Switch Arm) compared to the change in waist circumference from Week 24 to Week 48 (Delayed Switch Arm)
- The proportion of participants having a waist circumference of > 40 inches for men and > 35 inches for women at Week 24 (Immediate Switch Arm) compared to the proportion of participants having waist circumference of > 40 inches for men and > 35 inches for women at Week 48 (Delayed Switch Arm)
- Change in SBP and DBP from Baseline to Week 24 (Immediate Switch Arm) compared to the change in SBP and DBP from Week 24 to Week 48 (Delayed Switch Arm)
- Change in fasting lipids from Baseline to Week 24 (Immediate Switch Arm) compared to the change in fasting lipids from Week 24 to Week 48 (Delayed Switch Arm)
- Change in fasting glucose from Baseline to Week 24 (Immediate Switch Arm) compared to the change in fasting glucose from Week 24 to Week 48 (Delayed Switch Arm)

- Change in in HOMA-IR from Baseline to Week 24 (Immediate Switch Arm) compared to the change in HOMA-IR from Week 24 to Week 48 (Delayed Switch Arm)
- Change in HbA1c from Baseline to Week 24 (Immediate Switch Arm) compared to the change in HbA1c from Week 24 to Week 48 (Delayed Switch Arm)
- Change in leptin and adiponectin from Baseline to Week 24 (Immediate Switch Arm) compared to the change in leptin and adiponectin from Week 24 to Week 48 (Delayed Switch Arm)
- Change in the proportion of participants from Baseline to Week 24 with advanced fibrosis according to the NAFLD fibrosis score (F0-F1, Indeterminate, and F3-F4) (Immediate Switch Arm) compared to the change in the proportion of participants from Week 24 to Week 48 with advanced fibrosis according to the NAFLD fibrosis score (Delayed Switch Arm)
- Change in the proportion of participants from Baseline to Week 24 at high risk of NASH according to the HAIR score (<2 and ≥2) (Immediate Switch Arm) compared to the change in the proportion of participants from Week 24 to Week 48 at high risk of NASH according to the HAIR score (Delayed Switch Arm)
- Proportion of participants having a dose-reduction or complete withdrawal of anti-hypertensive, anti- hyperglycemic, or lipid lowering agents from Baseline to Week 24 (Immediate Switch Arm) compared to Week 24 to Week 48 (Delayed Switch Arm)
- Proportion of participants starting an anti- hypertensive, anti-hyperglycemic, or lipid lowering agent from Baseline to Week 24 (Immediate Switch Arm) compared to Weeks 24 to Week 48 (Delayed Switch Arm)

Safety:

- Incidence of any Grade AEs (related and not related) through Week 24 (Immediate Switch Arm) compared to the incidence of any grade AEs (related and not related) through Week 48 (Delayed Switch Arm)
- Incidence of Grade 3 and 4 AEs (related and not related) through Week 24 (Immediate Switch Arm) compared to the incidence of Grade 3 and 4 AEs (related and not related) through Week 48 (Delayed Switch Arm)
- Incidence of discontinuations due to AEs through Week 24 (Immediate Switch Arm) compared to discontinuations due to AEs through Week 48 (Delayed Switch Arm)
- Incidence of SAEs (related and not related) through Week 24 (Immediate Switch Arm) compared to Incidence of SAEs (related and not related) through Week 48 (Delayed Switch Arm)
- Change in clinical laboratory tests over time (Baseline to Week 24 for Immediate Switch Arm) compared to the change in clinical laboratory tests over time (Week 24 to Week 48 (Delayed Switch Arm)
- Incidence of Grade 3 and 4 laboratory abnormalities through Week 24 (Immediate Switch Arm) compared to Grade 3 and 4 laboratory abnormalities through Week 48 (Delayed Switch Arm)

Efficacy:

- The proportion of participants with confirmed virologic rebound at Week 24 (Immediate Switch Arm) compared to the proportion of participants with confirmed virologic rebound from Week 24 to Week 48 (Delayed Switch Arm)

- The proportion of participants with virologic response (HIV-1 RNA<50 copies/mL) at Week 24 according to the FDA snapshot algorithm (Immediate Switch Arm) compared to the proportion of participants with virologic response (HIV-1 RNA<50 copies/mL) at Week 48 according to the FDA snapshot algorithm (Delayed Switch Arm)
- The proportion of participants with virologic failure (HIV-1 RNA ≥50 copies/mL) at Week 24 according to the FDA snapshot algorithm (Immediate Switch Arm) compared to the proportion of participants with virologic failure (HIV-1 RNA ≥50 copies/mL) at Week 48 according to the FDA snapshot algorithm (Delayed Switch Arm)
- The proportion of participants having virologic response (HIV-1 RNA<200 copies/mL) at Week 24 according to the FDA snapshot algorithm (Immediate Switch Arm) compared to the proportion of participants having virologic response (HIV-1 RNA<200 copies/mL) at Week 48 according to the FDA snapshot algorithm (Delayed Switch Arm)
- The proportion of participants having virologic failure (HIV-1 RNA ≥200 copies/mL) at Week 24 according to the FDA snapshot algorithm (Immediate Switch Arm) compared to the proportion of participants having virologic failure (HIV-1 RNA ≥200 copies/mL) at Week 48 according to the FDA snapshot algorithm (Delayed Switch Arm)
- Change in CD4+ cell count from Baseline to Week 24 (Immediate Switch Arm) compared to the change in CD4+ cell count from Week 24 to Week 48 (Delayed Switch Arm)

Resistance:

- Incidence of observed genotypic and phenotypic resistance for participants meeting HIV-1 RNA rebound criteria at Week 24 (Immediate Switch Arm) compared to the incidence of observed genotypic and phenotypic resistance for participants meeting HIV-1 RNA rebound criteria from Week 24 to Week 48 (Delayed Switch Arm)
- Proportion of participants with baseline DRV, FTC, TFV and INI RAMs based on historical genotypes
- Proportion of participant with identified post-baseline RAMs and loss of phenotypic susceptibility, when available, upon meeting confirmed virologic rebound at Week 24 (Immediate Switch Arm) compared to proportion of participant with identified post-baseline RAMs and loss of phenotypic susceptibility, when available, upon meeting confirmed virologic rebound from Week 24 to Week 48 (Delayed Switch Arm)

PROs:

- Change in the proportion of participants who have bothersome symptoms (scores of 2, 3 or 4) across all items of the HIV-SI from Baseline to Week 24 (Immediate Switch Arm) compared to the Change in the proportion of participants who have bothersome symptoms (scores of 2, 3 or 4) across all items of the HIV-SI from Week 24 to Week 48 (Delayed Switch Arm)
- Change in the proportion of participants who have any symptoms (scores of 1, 2, 3 or 4) across all items of the HIV-SI from Baseline to Week 24 (Immediate Switch Arm) compared to the change in the proportion of participants who have any symptoms (scores of 1, 2, 3 or 4) across all items of the HIV-SI from Week 24 to Week 48 (Delayed Switch Arm)
- PGIC and PGIC-S at Week 24 (Immediate Switch Arm) and PGIC and PGIC-S at Week 48 (Delayed Switch Arm)

Adherence:

- Adherence rates by participant self-report using 4-day recall at Weeks 12 and 24 (Immediate

Switch Arm) compared to the Adherence rates by participant self- report using 4-day recall at Weeks 36 and 48 (Delayed Switch Arm).

Exploratory:

Exploratory clinical biomarker:

- Change in alpha stimulating-melanocyte hormone from Baseline to Week 24 (Immediate Switch Arm) compared to the change in alpha stimulating melanocyte hormone from Week 24 to Week 48 (Delayed Switch Arm).

Exploratory PROs:

- Change in the scores on the DAILY EATS from Baseline to Week 24 (Immediate Switch Arm) compared to the change in the scores on the DAILY EATS from Week 24 to Week 48 (Delayed Switch Arm)
- Change in the scores on the BSQ-8D from Baseline to Week 24 (Immediate Switch Arm) compared to the change in the scores on the BSQ-8D from Week 24 to Week 48 (Delayed Switch Arm)
- Change 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 from Baseline to Week 24 (Immediate Switch Arm) compared to the change 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 from Week 24 to Week 48 (Delayed Switch Arm).

6.2.2. Secondary Analysis Methods

6.2.2.1. Metabolic Analyses

Secondary metabolic endpoints will be analyzed using descriptive statistics and frequency tabulations.

6.2.2.2. Efficacy Analyses

Tabulations (numbers and proportions) per time point will be provided for the categorical parameters (virologic rebounders, responses, FDA snapshot response outcomes) for secondary endpoints at Weeks 24 and 48, respectively. The treatment arms will be compared by 2-sided 95% CIs constructed using Clopper-Pearson method.

Descriptive statistics (n, mean (SD), median, and ranges) per time point will be provided for the continuous parameters, CD4 cell count actual values and the change from baseline in $CD4^+$ cell count at Weeks 24 and 48. 95% CIs for the means and mean changes will be calculated.

6.2.2.2.1. Genotype and Phenotype

As all patients are expected to be virologically suppressed at time of study entry, standard resistance testing will not be performed. Historical genotypic testing results will be collected and tabulated if available prior to study entry.

For subjects 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 (using PhenoSense GT® Plus Integrase[1]) 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. The analysis method is described in Section 6.2.1.

6.2.2.3. Adherence Analyses

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.

Treatment adherence based on participant self-report using a 4-day recall will be summarized descriptively and frequency tabulations for both D/C/F/TAF FDC and the INI + TAF/FTC ARV regimen. Cumulative treatment adherence through Week 48 will be determined. Additionally, all self-reported adherence will be listed.

6.2.2.4. Exploratory Analyses

Descriptive statistics and frequency tabulations, when available, will be presented for all exploratory endpoints.

In addition, for the Alpha melanocyte stimulating hormone, the association analysis whether increases in concentrations of alpha melanocyte stimulating hormone induce a satiety response will be conducted.

7. SAFETY

7.1. Adverse Events

7.1.1. Definitions

Reported AE parameters and grades are based on the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events ("DAIDS AE grading table"). All AEs will be coded using MedDRA version 25.0.

Adverse Drug Reaction (ADR)

ADRs will be presented. A current list of all ADRs is in Attachment 1, and upon further clinical evaluation, additional (grouped) terms might need to be added. The medical assessment of the safety data will be performed according to a pre-specified algorithm (attached to the DPS) and will lead to the final list of ADRs. In case multiple lists are available (US definition), ADRs will be tabulated separately per list.

Events of interest

The events of interest (EOI) groups include a broad list of terms to identify potential cases. The preferred terms belonging to each adverse events of interest (AEOI) group will be coded using MedDRA version 25.0.

Since many of the terms used to identify potential cases are clinically non-specific, only those retrieved cases that upon medical review are specifically suggestive of /compatible with the AEs of special interest will be commented on in the CSR.

AEOI groups used for the safety analyses are listed as follows.

- Severe skin reactions
- Rash
- Hepatotoxicity
- Hyperglycaemia
- Lipid abnormalities
- Coronary artery events
- Renal toxicity
- Bone events due to potential PRT/loss of BMD
- Ocular effects (posterior uveitis)
- Lipodystrophy

Incidence of treatment-emergent adverse events (TEAEs) of interest will be summarized as AE summary tables.

A listing of subjects who died will be provided.

7.1.2. Analysis Methods

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

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Any AE occurring at or after the initial administration of study drug through the day of last dose plus 7 day is considered to be treatment emergent. If the event occurs on the day of the initial administration of study drug, then the event will be assumed to be treatment emergent. If the event date is recorded as partial or completely missing, then the event will be considered to be treatment emergent unless it is known to be prior to the first administration of study drug based on partial onset date or resolution date. All reported treatment-emergent adverse events will be included in the analysis. For each adverse event, the number and percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group. In addition, comparisons between treatment groups will be provided.

A summary will be provided for the following TEAEs:

- any adverse events,
- serious adverse events,

- deaths due to AE,
- adverse events by toxicity grade (as well as AEs with toxicity grade at least 2 and AEs with toxicity grades 3 or 4),
- AEs at least possibly related to study medication,
- AEs for which the medication was temporarily/permanently stopped,
- serious adverse events that were at least possibly related to the medication.

Incidences of AEs for above mentioned analyses will also be presented by SOC and preferred term. A listing of all AEs will be provided. There will be no formal statistical testing.

Summary of adverse events and incidence tabulations for individual AE will be provided for AEOIs and ADRs.

AIDS defining illness based on WHO clinical staging will be tabulated.

AE listings will be provided for subjects who

- had SAEs
- had AEs leading to discontinuation of study drug.
- had grade 3 or 4 AE
- had each AEOI category?

7.2. Clinical Laboratory Tests

7.2.1. Definitions

All clinical laboratory tests will be displayed for the subjects included in the ITT analysis set. Laboratory parameters of the lab subcategories and calculations are listed in Attachment 2.

Number and percentage of subjects with postbaseline clinically important laboratory values and/or markedly abnormal postbaseline values will be presented by treatment group.

7.2.2. Analysis Methods

Descriptive statistics will be presented for all chemistry, hematology, and urinalysis laboratory tests at scheduled time points. If there are retesting, repeating the same analyze from same collected sample, last or retested results will be used in analysis.

Change from baseline to each scheduled time points will be summarized descriptively for chemistry, hematology, and urinalysis (pH, and specific gravity) tests. A box plot of change from baseline to analysis timepoints will be provided for the following laboratory tests: eGFR, ALT and AST.

Cross-tabulations for the worst toxicity grades through Weeks 24 and 48, respectively, versus reference per laboratory test, and cross-tabulations of the worst toxicity grades at Weeks 24 and 48, respectively, versus reference will also be provided if applicable. Subject listings of abnormal laboratory values will be provided.

Descriptive statistics by Division of AIDS (DAIDS) toxicity grade over time will be presented. Shift summaries from baseline DAIDS toxicity grade to the worst on-treatment toxicity grade will also be presented.

If the DAIDS grading is not available, shift tables will be provided summarizing the shift in laboratory values from baseline to weeks 24 and 48 analysis time points with respect to abnormality criteria (low, normal, high).

7.3. Vital Signs and Physical Examination Findings

7.3.1. Definitions

The following vital signs parameters will be analyzed.

- Pulse (bpm)
- Systolic blood pressure, SBP (mmHg)
- Diastolic blood pressure, DBP (mmHg)

A listing of subjects with treatment-emergent clinically important vital signs will be presented, along with a listing of all vital sign measurements.

Table 5: Pulse, SBP and DBP are classified in the following abnormality codes.

Abnormality Code	Pulse (bpm)	DBP[a] (mmHg)	SBP[a] (mmHg)
Abnormally low	≤50	≤50	≤90
Grade 1 or mild	-	>90 - <100	>140 - <160
Grade 2 or moderate	-	≥100 - <110	≥ 160 - <180
Grade 3 or severe	-	≥110	≥180
Abnormally high	≥120	-	-

[a] Classification of adverse events related to hypotension/hypertension should be done according to the DAIDS grading table (Appendix 7 at protocol).

In determining abnormalities, the following rules are applied:

- worst grades/abnormalities are determined over the whole observational period for each trial period separately, including post-reference scheduled *and* unscheduled measurements of that phase.
- The abnormalities ‘abnormally low’ and ‘abnormally high’/grades are considered equally important, i.e. if a subject has as well an abnormally low as an abnormally high or graded value post-reference, both abnormalities are shown in the tables. (This means that the sum of the percentages can be more than 100%).

Definition treatment-emergent:

An abnormality will be considered treatment-emergent in a particular period if it is worse than the reference corresponding to this period. If the reference is missing, the abnormality is always considered as treatment-emergent. A shift from ‘abnormally low’ at reference to ‘abnormally high’ or ‘grade’ post reference (or vice versa) is also treatment-emergent.

7.3.2. Analysis Methods

Continuous vital sign parameters including height, weight, pulse, blood pressure (systolic and diastolic), and Body Mass Index (BMI) will be summarized at each assessment time point by descriptive statistics (mean, standard deviation, median, minimum and maximum) per treatment arm.

Cross-tabulations for the worst abnormalities versus reference per vital signs test will be produced by treatment arm.

Descriptive statistics for the actual values and changes from baseline (including BMI, weight) per timepoint will be presented. The only reference time point that will be used to calculate these changes is the timepoint closest to the first drug intake after randomization.

BMI will be calculated as weight (kg)/(height (m^2)), at each time point that body weight is measured. The height measurement collected at screening will be used in the calculation. The frequency tabulations will be presented for BMI as a categorical variable and the descriptive statistics will be summarized for BMI as a continuous variable.

Physical examination findings and changes from baseline at each scheduled time point will be tabulated per treatment arm. Abnormal physical examination findings will also be listed.

8. PATIENT REPORTED OUTCOMES (PROs)

8.1. PROs

Following PROs will be assessed at the time points indicated in the Schedule of Activities (SoA). Appendix 8 in the Protocol provided all information of PROs questionnaires. Participants will complete the PROs using the sponsor-provided electronic devices.

8.1.1. HIV-SI

The HIV-Symptom Index (HIV-SI) is a validated PRO instrument that assesses the burden of 20 common symptoms associated with HIV treatment or disease.[5] 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.[6]

8.1.2. BSQ-8D

The Body Shape Questionnaire (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".[7, 8] 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.

8.1.3. 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.

8.1.4. PGIC and PGIC-S

The Patient Global Impression of Change (PGIC) is a global index that is used to rate the overall status of the participant related to the participant's 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 1=very much improved, 2=somewhat improved, 3=a little improved, 4=no change, 5=a little worse, 6=somewhat 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 1=much more satisfied, 2=moderately more satisfied, 3=a little more satisfied, 4=no change, 5=a little less satisfied, 6=moderately less satisfied, and 7=much less satisfied, 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. PRO Analysis Methods

Descriptive statistics for absolute values, including total scores, will be calculated for each PRO measure including HIV-SI, BSQ-8D, DAILY EATS, PGIC (PGIC-S) at each timepoint.

The 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 will be summarized by treatment arm; the 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 will be summarized by treatment arm.

The 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 will be summarized.

The changes from baseline in the scores on the DAILY EATS at Weeks 24 and 48 will be summarized. Further, descriptive statistics will be presented for item-level weekly scores on the DAILY EATS, item-level weekly change scores on the DAILY EATS, Eating Drivers Index (EDI) weekly scores, and EDI

weekly change scores, respectively. Item-level weekly scores are computed as the average of the non-missing item-level scores over the 7-day (weekly) diary period. EDI is computed as the average of the item-level weekly scores for Worst Hunger (Item 2), Appetite (Item 3), and Cravings (Item 4).

Change in the proportion of participants who have bothersome symptoms (scores of 2, 3 or 4) across all items of the HIV-SI from Baseline to Week 24 (Immediate Switch Arm) compared to the Change in the proportion of participants who have bothersome symptoms (scores of 2, 3 or 4) across all items of the HIV-SI from Week 24 to Week 48 (Delayed Switch Arm will be summarized descriptively.

Change in the proportion of participants who have any symptoms (scores of 1, 2, 3 or 4) across all items of the HIV-SI from Baseline to Week 24 (Immediate Switch Arm) compared to the change in the proportion of participants who have any symptoms (scores of 1, 2, 3 or 4) across all items of the HIV-SI from Week 24 to Week 48 (Delayed Switch Arm) will be presented

Descriptive statistics for PGIC and PGIC-S at Week 24 (Immediate Switch Arm) and PGIC and PGIC-S at Week 48 (Delayed Switch Arm) will be calculated.

Association between treatment arm and each bothersome symptoms of the HIV-SI adjusting for baseline variables at Weeks 24 will be calculated. For each symptom we can consider using stepwise variable selection criterion to choose statistically significant covariates at baseline. To understand meaningful change in scores on PRO measures, PGIC-S will be used as an anchor to determine meaningful change scores for the DAILY EATS in participants living with HIV.

Association of the specific item of the HIV-SI with body weight loss/wasting at Weeks 24 and 48 will be evaluated. Association between BSQ-8D scores and percent change in body weight and/or >5% in change in weight will be presented.

9. PHARMACOKINETICS/PHARMACODYNAMICS

9.1. Pharmacokinetics

Plasma concentrations of DRV and COBI may be determined in subjects for the Immediate Switch arm experiencing confirmed virologic rebound, using stored blood samples collected throughout the study period at the discretion of the sponsor, if deemed necessary. 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 serum samples. Participant confidentiality will be maintained.

Plasma concentration will be listed if available.

9.1.1. 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).

9.1.2. Pharmacokinetic Parameters and Evaluations

Not applicable.

9.2. Pharmacodynamics

Not applicable.

REFERENCES

1. Pepkowitz SH. PhenoSense GT ^{Plus}Integrase. Monogram Biosciences. 2019. https://www.monogrambio.com/sites/default/files/2019-10/PhenoSenseGT-Plus-INtegrase_watermark.pdf
2. Eron J, Orkin C, Gallant J. et al. A week-48 randomized phase-3 trial of darunavir/cobicistat/emtricitabine/tenofovir alafenamide in treatment-naive HIV-1 patients. AIDS.2018,32:1431–1442.
3. Orkin C, DeJesus E, Khanlou H. et al. Final 192-week efficacy and safety of once-daily darunavir/ritonavir compared with lopinavir/ritonavir in HIV-1-infected treatment-naïve patients in the ARTEMIS trial. HIV Medicine. 2013;14: 49-59.
4. Bretz, F., König, F., Brannath, W., Glimm, E., Posch, M. (2009)., Adaptive designs for confirmatory clinical trials, Statist. Med. 2009; 28:1181–1217
5. Justice A, Holmes W, Giford A. et al. Development and validation of a self-completed HIV symptom index. J Clin Epidemiol. 2001;(54): S77-90.
6. Edelman EJ, Gordon K, Rodriguez-Barradas MC, Justice AC, Vacs Project T. Patient-reported symptoms on the antiretroviral regimen efavirenz/emtricitabine/tenofovir. AIDS Patient Care STDS. 2012; 26:312-319.
7. Cooper PJ, Taylor MJ, Cooper Z, and Fairburn CG. The development and validation of the Body Shape Questionnaire. International Journal of Eating Disorders 1986,6:485-494.
8. Evans C, Dolan B. Body Shape Questionnaire: derivation of shortened "alternate forms. International Journal of Eating Disorders, 1993;13 (3),315-321.

ATTACHMENT 1. ADVERSE DRUG REACTION (ADR)

ADR grouped Terms: AE preferred terms (as available in AE Clinical database) are assigned an Adverse Drug Reaction System Organ Class (ADRSOC) and Adverse Drug Reaction (ADRCAT) according to the table below.

Adverse Drug Reaction System Organ Class	Adverse Drug Reaction	Adverse Event Preferred Term
GASTROINTESTINAL DISORDERS	ABDOMINAL DISTENSION	ABDOMINAL DISTENSION
	ABDOMINAL PAIN	ABDOMINAL PAIN
		ABDOMINAL PAIN LOWER
		ABDOMINAL PAIN UPPER
	DIARRHOEA	DIARRHOEA
		FREQUENT BOWEL MOVEMENTS
	DYSPEPSIA	DYSPEPSIA
	FLATULENCE	FLATULENCE
	NAUSEA	NAUSEA
	PANCREATITIS ACUTE	PANCREATITIS
		PANCREATITIS ACUTE
	VOMITING	VOMITING
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	ASTHENIA	ASTHENIA
	FATIGUE	FATIGUE
HEPATOBILIARY DISORDERS	ACUTE HEPATITIS	HEPATITIS
		HEPATITIS ACUTE
		HEPATOTOXICITY
IMMUNE SYSTEM DISORDERS	(DRUG) HYPERSENSITIVITY	DRUG HYPERSENSITIVITY
		HYPERSENSITIVITY
	IMMUNE RECONSTITUTION SYNDROME	IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME
		IMMUNE RECONSTITUTION SYNDROME
METABOLISM AND NUTRITION DISORDERS	ANOREXIA	DECREASED APPETITE
	DIABETES MELLITUS	DIABETES MELLITUS
		DIABETES MELLITUS INADEQUATE CONTROL
		TYPE 2 DIABETES MELLITUS
		GLUCOSE TOLERANCE IMPAIRED
	LIPODYSTROPHY	FACIAL WASTING
		FAT REDISTRIBUTION
		FAT TISSUE INCREASED
		LIPOATROPHY

Adverse Drug Reaction System Organ Class	Adverse Drug Reaction	Adverse Event Preferred Term
		LIPODYSTROPHY ACQUIRED
		LIPOHYPERTROPHY
		PARTIAL LIPODYSTROPHY
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	MYALGIA	MYALGIA
	OSTEONECROSIS	OSTEONECROSIS
NERVOUS SYSTEM DISORDERS	HEADACHE	HEADACHE
PSYCHIATRIC DISORDERS	ABNORMAL DREAMS	ABNORMAL DREAMS
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	GYNAECOMASTIA	GYNAECOMASTIA
		HYPERTROPHY BREAST
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	ANGIOEDEMA	ALLERGIC OEDEMA
		ANGIOEDEMA
		CIRCUMORAL OEDEMA
		CONJUNCTIVAL OEDEMA
		CORNEAL OEDEMA
		EPIGLOTTIC OEDEMA
		EYE OEDEMA
		EYE SWELLING
		EYELID OEDEMA
		FACE OEDEMA
		GINGIVAL OEDEMA
		GINGIVAL SWELLING
		GLEICH'S SYNDROME
		HEREDITARY ANGIOEDEMA
		LARYNGEAL OEDEMA
		LARYNGOTRACHEAL OEDEMA
		LIP OEDEMA
		LIP SWELLING
		OCULORESPIRATORY SYNDROME
		OEDEMA MOUTH
		OROPHARYNGEAL SWELLING
		PALATAL OEDEMA
		PERIORBITAL OEDEMA

Adverse Drug Reaction System Organ Class	Adverse Drug Reaction	Adverse Event Preferred Term
		PHARYNGEAL OEDEMA
		SCLERAL OEDEMA
		SMALL BOWEL ANGIOEDEMA
		SWELLING FACE
		SWOLLEN TONGUE
		TONGUE OEDEMA
		TRACHEAL OEDEMA
	PRURITUS	PRURIGO
		PRURITUS
		PRURITUS GENERALISED
	RASH	GENERALISED ERYTHEMA
		RASH
		RASH ERYTHEMATOUS
		RASH GENERALISED
		RASH MACULAR
		RASH MACULO-PAPULAR
		RASH MORBILLIFORM
		RASH PAPULAR
		RASH PRURITIC
	STEVENS-JOHNSON SYNDROME	STEVENS-JOHNSON SYNDROME
	TOXIC EPIDERMAL NECROLYSIS	TOXIC EPIDERMAL NECROLYSIS
	URTICARIA	URTICARIA
		URTICARIA CHRONIC
		URTICARIA PAPULAR
		URTICARIA CHOLINERGIC
		IDIOPATHIC URTICARIA
	Acute generalized exanthematous pustulosis	Acute generalized exanthematous pustulosis
	Drug reaction with eosinophilia and systemic symptoms	Drug reaction with eosinophilia and systemic symptoms

ATTACHMENT 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 in Protocol.	

<table>
<tr><td>Routine Urinalysis</td><td><u>Dipstick</u>
Specific gravity
pH
Glucose
Protein
Blood
Ketones
Bilirubin
Urobilinogen
Nitrite
Leukocyte esterase</td><td><u>Urine chemistry panel</u> (only in the setting of a suspected renal adverse event):
Urine Creatinine
Urine Sodium
Urine Phosphate
Urine Glucose
Urine Albumin
Urine Protein
Serum creatinine</td></tr>
<tr><td></td><td colspan="2">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.</td></tr>
<tr><td>Other Screening Tests</td><td colspan="2">●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 outlined in the Schedule of Activities.</td></tr>
<tr><td>Fasting Metabolic Profile</td><td colspan="2">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.</td></tr>
</table>

- Calculations

<table>
<tr><td>Body Mass Index (BMI) (kg/m^2)</td><td>Weight (kg) / [Height (m)]^2</td></tr>
<tr><td>Child Pugh Class</td><td>
<table>
<tr><th>Measure</th><th>1 point</th><th>2 points</th><th>3 points</th></tr>
<tr><td>Total bilirubin, µmol/L (mg/dL)</td><td><34 (<2)</td><td>34–50 (2–3)</td><td>>50 (>3)</td></tr>
<tr><td>Serum albumin, g/dL</td><td>>3.5</td><td>2.8–3.5</td><td><2.8</td></tr>
<tr><td>Prothrombin time, prolongation (s)</td><td><4.0</td><td>4.0–6.0</td><td>> 6.0</td></tr>
<tr><td>INR</td><td><1.7</td><td>1.7–2.3</td><td>> 2.3</td></tr>
<tr><td>Ascites</td><td>None</td><td>Mild (or suppressed with medication)</td><td>Moderate to severe (or refractory)</td></tr>
<tr><td>Hepatic encephalopathy</td><td>None</td><td>Grade I–II</td><td>Grade III–IV</td></tr>
</table>
</td></tr>
<tr><td>eGFRcr (Cockcroft-Gault Formula)</td><td>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 (IBW), the participant’s Adjusted Body Weight (ABW) will be used for eGFRcr (Cockcroft-Gault Formula):
IBW: Male: 50kg + 0.9kg x (height(cm) – 152)
Female: 45.5kg + 0.9kg x (height(cm) – 152)
ABW: IBW(kg) + 0.4 x (Weight(kg) – IBW(kg))</td></tr>
</table>

HOMA-IR (mg/dL)	Fasting insulin x Fasting glucose / 405
Non-Alcoholic Fatty Liver Disease (NAFLD) Fibrosis Score[10]	-1.675 + 0.037 × age (years) + 0.094 × BMI (kg/m2) + 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

	NAFLD Score >0.675 = F3-F4
NASH: HAIR Scores[11]	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.