Approvals

ACTG A5371 (SLIM LIVER)

Primary Statistical Analysis Plan

Version 2.0

June 23, 2023

A Single-Arm, Open-Label, Pilot Study of Semaglutide for Non-Alcoholic Fatty Liver Disease (NAFLD), a Metabolic Syndrome with Insulin Resistance, Increased Hepatic Lipids, and Increased Cardiovascular Disease Risk

ClinicalTrials.gov Identifier: NCT04216589

A5371 Version 2.0 (CM #1, CM #2, LOA #1)

This is the ACTG A5371 SAP Version 2.0 with names of authors, names of publication writing team members and analysis timeline redacted.

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Version History

Version	Changes Made	Date Finalized
1	Original Version	11/10/2020
1.1	A review occurred for LOA #1 with no changes needed. The SAP authors and the document header were updated.	06/14/2022
2.0	Added all protocol-specified primary, secondary and exploratory objectives and associated analyses. Added primary and secondary estimands. Adjusted analysis visit windows. Finalized subgroup analyses and metabolic syndrome definition. Removed analysis timelines as these will be tracked and maintained by the CTS.	06/23/2023

1 Introduction

1.1 Purpose

This Primary Statistical Analysis Plan (SAP) describes the primary estimand and secondary and other outcome measures that will address specific study objectives of the A5371 study. The Primary SAP includes general analytic approaches for the estimand and outcome measures in the primary manuscript or submitted to ClinicalTrials.gov (regardless of the reporting timeline). The Primary SAP facilitates discussion of the statistical analysis components among the lead study investigators and statisticians, helping them agree on the statistical analyses to be performed and presented in the primary and secondary analysis reports.

The Analysis Implementation Plan (AIP) provides outlines of tables, figures, and possibly coding descriptions.

1.2 Version History

Version 2.0 of the SAP contains all analyses associated with protocol-specified primary, secondary and exploratory objectives.

Major modifications include the addition al primary and secondary estimands and specific outcome measures for all objectives.

2 Study Overview

2.1 Overview of Study Design

A5371 is a single-arm, open-label, pilot study of the effects of semaglutide on intra-hepatic triglyceride (IHTG) content in adults living with HIV, central adiposity, insulin resistance or pre-diabetes, and hepatic steatosis. Eligible participants will receive semaglutide subcutaneously once weekly for 24 weeks; IHTG will quantified by magnetic resonance imaging-proton density fat fraction (MRI-PDFF) prior to starting treatment (pre-entry) and at week 24.

The study aims to enroll 50 participants, targeting at least 40% persons currently identifying as cisgender or transgender women and 50% non-white.

The study population consists of adults (≥ 18 years of age) with HIV not meeting criteria for diabetes who:

- Have central adiposity (minimum waist circumference ≥ 95cm for individual assigned male sex at birth or ≥ 94 cm for individuals assigned female sex at birth)
- Have ≥ 5% IHTG content
- Have at least one of the following insulin resistance or pre-diabetes indicators: fasting plasma glucose 100-125 mg/dL, HbA1c between 5.7 and <6.5%, or HOMA-IR > 3.0
- Have had stable body weight (no gains or losses of >5%) within 12 weeks prior to entry
- Have CD4+ T-cell count ≥ 200 cells/mm^3 within 30 days prior to pre-entry
- Have no changed ART in the 24 weeks prior to entry

- Have two separate reports of HIV-1 RNA < 50 copies/mL, and no > 500 copies/mL during 48 weeks prior to entry

The primary analysis will commence once all primary outcome measures have been read and recorded in the central database. This analysis will also address all secondary and exploratory objectives through study week 24. All secondary and exploratory objectives through study week 48 will be included in a secondary analysis.

2.2 Hypotheses

2.2.1 Primary Hypothesis

Among antiretroviral therapy (ART)-treated, virologically suppressed adults with HIV, hepatic steatosis, central adiposity, and insulin resistance, 24 weeks of semaglutide will result in reductions in intra-hepatic triglyceride (IHTG) content, as quantified by magnetic resonance imaging-proton density fat fraction (MRI-PDFF).

2.2.2 Secondary Hypotheses

1) Semaglutide will be safe and well tolerated.

2) Semaglutide will improve cardiometabolic parameters central to the pathogenesis of atherosclerosis and increased cardiovascular risks.

2.3 Study Objectives

This Primary SAP addresses the following primary, secondary and exploratory objectives in the study protocol with the corresponding protocol numbering shown in brackets.

Analysis of the study objectives below will be analyzed under an “any effect” framework (i.e., identify effects different than zero). These analyses will be finalized once the last participant has completed the Week 24 (for primary analysis report) or Week 48 (for secondary analysis report) study visit, all queries have been resolved, and the study database closure/data lock has been completed (applicable to secondary analysis report only).

2.3.1 Primary Objective

To evaluate whether semaglutide will reduce IHTG content, as quantified by MRI-PDFF, among ART-treated adults with HIV, hepatic steatosis, central adiposity, and insulin resistance or pre-diabetes [Protocol Objective 1.2].

2.3.2 Secondary Objectives

1) To evaluate the safety and tolerability of semaglutide in adults with HIV, hepatic steatosis, central adiposity, and insulin resistance or pre-diabetes [Protocol Objective 1.3.1].

2) To evaluate the effects of semaglutide on weight, minimum waist circumference (WC), and body mass index (BMI) [Protocol Objective 1.3.2].

3) To evaluate the effects of semaglutide on insulin resistance or pre-diabetes, lipid profiles, and the prevalence of metabolic syndrome [Protocol Objective 1.3.3].

4) To evaluate relationships between observed changes in IHTG and changes in metabolic parameters. [Protocol Objective 1.3.4].

2.3.3 Exploratory Objectives

1) To evaluate the durability of semaglutide on weight, minimum WC, and BMI after cessation of study therapy [Protocol Objective 1.4.1].

2) To evaluate the relationships between systemic measures of carbohydrate and lipid metabolism and a) IHTG and b) visceral adipose tissue (VAT) area in participants treated with semaglutide [protocol Objective 1.4.2].

3) To evaluate the effects of semaglutide on MRI-quantified VAT and abdominal subcutaneous adipose tissue (SAT) area and density [Protocol Objective 1.4.3].

4) To evaluate the effects of semaglutide on circulating inflammatory biomarker and adipocytokine levels [Protocol Objective 1.4.4].

5) To evaluate the effects of semaglutide on muscle function and muscle fat [Protocol Objective 1.4.5].

6) To evaluate the effects of semaglutide adherence on primary and secondary outcomes [Protocol Objective 1.4.6].

7) To evaluate the effects of semaglutide on self-reported quality of life [Protocol Objective 1.4.7].

8) To evaluate the effects of semaglutide on the gut microbiome [Protocol Objective 1.4.8].

9) To evaluate relationships between changes in IHTG content and changes in VAT and SAT area and muscle fat quantity [Protocol Objective 1.4.9].

10) To evaluate the effects of semaglutide on circulating immune cell profiles [Protocol Objective 1.4.10].

2.4 Overview of Sample Size Considerations

The study is designed to evaluate whether 24 weeks of semaglutide will improve IHTG in ART-treated, adults with HIV, hepatic steatosis, central obesity, and insulin resistance or pre-diabetes. The primary comparison will examine the absolute change in IHTG from pre-entry to week 24.

The sample size is based on a two-sided, one-sample t-test with 5% significance level and 90% statistical power, and assumes, based on published literature, that semaglutide will reduce (improve) IHTG. Assuming a 9% SD, with 37 participants, there is 90% statistical power to identify a significant change in IHTG, under the assumption that the true change is 5% over 24 weeks. Inflating the sample size to account for 25% loss to follow-up and premature treatment discontinuation, yields a total sample size of 50 participants.

2.5 Overview of Formal Interim Monitoring

The study will be monitored by an independent ACTG-appointed Study Monitoring Committee (SMC). The SMC will review the study at least annually, with the first review occurring approximately 6 months (and no later than 1 year) after the first participant enrolls; interim reviews may also be convened if a concern is identified. The SMC will review summaries of accrual, baseline characteristics, study conduct (including premature treatment and study discontinuations), and adverse events. Summaries of primary efficacy will not be provided during interim reviews and there are no pre-specified stopping guidelines.

Study enrollment will be paused and the SMC will convene an emergency meeting to review all study AEs, in collaboration with the DAIDS clinical representative, in the event any of the following are observed:

(1) Three participants with the same Grade 3 (or higher) events attributable to semaglutide;
(2) Two participants with Grade 4 events attributable to semaglutide;
(3) Two participants with hepatoxicity events leading to semaglutide being held or permanently discontinued (see protocol section 8);
(4) Death.

3 Outcome Measures

Only outcome measures addressed in this SAP are included below, see protocol section 10.2 for additional measures. Other Outcome Measures, defined in the protocol, which address changes in biomarkers, the microbiome, physical activity/diet, or outcomes listed below through week 48, will be outlined in future SAPs.

3.1 Primary Outcome Measure

1) Change (absolute) in IHTG (%) from pre-entry to week 24.
[For Primary Objective, Secondary Objective 4, and Exploratory Objectives 2 and 9]

3.2 Secondary Outcome Measures

1) Change (percent) in IHTG (%) from pre-entry to week 24.
   [For Primary Objective, Secondary Objective 4, and Exploratory Objectives 2 and 9]

2) Level of IHTG (%) at week 24.
   [For Primary Objective]

3) Occurrence of premature discontinuation of study treatment, including reasons for discontinuation.
   [For Secondary Objective 1]

4) Occurrence of new Grade ≥3 adverse event that are related to study treatment.
   [For Secondary Objective 1]

5) Change (absolute) in body mass index (BMI), body weight, and minimum waist circumference (WC) from week 0 to weeks 12 and 24.
   [For Secondary Objectives 2 and 4]

6) Changes (absolute) in insulin resistance (HOMA-IR), HbA1c and glucose from week 0 to week 24.
   [For Secondary Objectives 3 and 4, and Exploratory Objective 2]

7) Change (absolute) in lipid profiles (triglycerides, HDL cholesterol, LDL cholesterol, total cholesterol) from week 0 to weeks 12 and 24.
   [For Secondary Objectives 3 and 4, and Exploratory Objective 2]

8) Presence of metabolic syndrome at weeks 0, 12, and 24.
   [For Secondary Objective 3]

3.3 Other Outcome Measures

1) Number of empty cartridge pen counts at weeks 4, 12, and 24.
   [For Exploratory Objective 6]

2) Self-reported adherence of semaglutide injections at weeks 4, 12, and 24.
   [For Exploratory Objective 6]

3) Changes (absolute) in chair rise rate from week 0 to week 24 defined as time in seconds to rise 5 times and 10 times.
   [For Exploratory Objective 5]

4) Change in presence of slow gait speed from week 0 to week 24, defined as ≥1 m/sec.
   [For Exploratory Objective 5]

5) Change (absolute) in gait speed (m/sec) from week 0 to week 24
[For Exploratory Objective 5]

6) Change (absolute) in total psoas muscle fat percent as measured by MRI from pre-entry to week 24.
[For Exploratory Objectives 5 and 9]

7) Quality of life measures (general health, poor physical health, poor mental health, impairment) at weeks 0 and 24.
[For Exploratory Objective 7]

8) Change (absolute) in adipose tissue (VAT and SAT) volume as measured by MRI from pre-entry to week 24.
[For Exploratory Objectives 2, 3, and 9]

9) Change (absolute) in BMI, body weight, and WC from week 24 to week 48.
[For Exploratory Objective 1]

10) Change (absolute) in circulating inflammatory biomarkers (sCD14, IL-6, sCD163, CRP, IP-10, MCP-1, CD40L, oxidized LDL, and FABP-4) and adipocytokine levels (adiponectin and GLP-1) from week 0 to weeks 12, 24 and 48. [For Exploratory Objective 4]

11) Change (absolute) in gut microbiome from week 0 to week 24. [For Exploratory Objective 8, analyzed outside of SDAC]

12) Change (absolute) in circulating immune cell profiles (Activated (HLA-DR+/CD38+) CD4+ and CD8+ T lymphocytes; Monocyte (CD14/CD16/CCR2/CX3CR1/CD36/CD11c) subsets; Invariant natural killer (6B11/CD69) and mucosal associated invariant (Vα7.2/CD161) T lymphocytes) from week 0 to week 24. [For Exploratory Objective 10]

4 General Considerations

The following analysis populations are defined for A5371:

- Screened Population: All participants who were screened for enrollment into the study.

- Randomized Population: All participants who were enrolled to the study (this is an intent-to-treat [ITT] population).

- Treated Population: All participants who received at least one dose of study treatment (this is a modified ITT population or “Safety Set”).

- Evaluable Population: All participants who remained on study treatment

until 28 days prior to the Week 24 MRI, who did not have any eligibility violations, and who did not start prohibited medications known to cause changes in weight prior to the Week 24 MRI (this is a per protocol [PP] population or "Efficacy Set").

Note: All concomitant medications will be reviewed by the study chairs in a blinded fashion prior to final analysis to flag prohibited medications known to cause changes in weight.

Study week windows are as defined in the protocol.

For all analyses, the following visit windows will be used (based on days from study entry):

- Screening: evaluations completed within 30 days of pre-entry.
- Pre-Entry: ≥1 day after screening and within 14 days prior to entry.
- Entry (week 0): entry evaluations must occur on/after randomization and on/prior to treatment initiation.
- On-treatment evaluations:
    - Week 4: weeks [2, 6] / days [14, 42]
    - Week 12: weeks [8, 16] / days [56, 112]
    - Week 24: weeks [20, 29] / days [140, 203]
- Week 48: post-treatment evaluation scheduled within a week [44, 52] / day [308, 364] window.

If multiple results are available within a visit window priority will first be given to data collected while on treatment and second to data closest to the scheduled visit.

If participants start prohibited medications known to cause changes in weight after the Week 24 MRI, data collected after this initiation will be excluded from analyses.

Key study visits occur at pre-entry, entry, week 24 and week 48.

Pre-entry: Occurs after screening, but within 14 days of study entry (week 0). First MRI-PDFF to measure IHTG.

Entry (week 0): First dose of study treatment occurs.

Week 24: Last on-treatment study visit; second MRI-PDFF to measure IHTG.

Week 48: Last on-study visit.

Analysis of primary and secondary outcomes will not adjust for multiple comparisons. Continuous variables will be summarized using mean, standard deviation, median, interquartile range (Q1 and Q3), 10^{th} and 90^{th} percentile, and min and max; categorical variables will be summarized using frequency and percentage. Non-normal continuous data will be log-transformed to the log-10 scale for analysis; it is anticipated that biomarkers such as HOMA-IR will be log-transformed.

All statistical tests will be evaluated using a 5% alpha.

4.1 Definitions

New Grade 3 or higher AE is defined as Grade 3 or higher event that was new in onset or aggravated in severity from the baseline condition (i.e., Grade 1 or 2 at baseline escalates to Grade 3 or higher, or Grade 3 at baseline escalates to Grade 4 or higher), following the start of study treatment.

Metabolic syndrome is defined as having 3 or more of the following: increased minimum WC (≥40 inches men, ≥35 inches women), high triglyceride level (>150 mg/dL or taking lipid-lowering medication), reduced HDL cholesterol (<40 mg/dL men, <50 mg/dL women), increased blood pressure (≥130/85 mm Hg or taking blood pressure medication), and elevated fasting blood glucose (>100 mg/dL or taking glucose-lowering medication), based on current guidelines.

Factors for subgroup analyses:

1. Sex at birth (male sex at birth, female sex at birth)
2. Gender (cisgender or transgender female, cisgender or transgender male)
3. Race/ethnicity (White non-Hispanic and Other, White Hispanic, Black [regardless of ethnicity])
4. Age (<40, 40-60, >60)
5. IHTG % at pre-entry (<5%, 5%-<15%, 15%-<25%, ≥25%)
6. VAT at pre-entry (<sex-specific median, ≥sex-specific median)
7. Semaglutide doses received (100%, <100%)

5 Estimands and Analysis

5.1 Primary Estimand and Analysis

Primary Objective 1: To evaluate whether semaglutide will reduce IHTG content, as quantified by MRI-PDFF, among ART-treated adults with HIV, hepatic steatosis, central adiposity, and insulin resistance or pre-diabetes	
Estimand	Absolute change in IHTG (%) 24 weeks after initiating semaglutide, among HIV-infected adults with NAFLD who remain on study treatment without use of prohibited medications.
Treatment	Semaglutide

Target population	Analysis set
Adults ≥18 years of age with HIV, central adiposity, insulin resistance or pre-diabetes, and hepatic steatosis, with HIV RNA suppression for at least the prior 48 weeks on ART.	Efficacy set (Participants who remained on study treatment for 24 weeks and did not receive prohibited medications during this time period)
Variable(s)	**Outcome measure(s)**
Change in IHTG 24 weeks after initiating semaglutide.	Absolute change from pre-entry to Week 24 in IHTG (%).
Handling of intercurrent events	**Handling of missing data**

The following intercurrent events are relevant to the estimand: 1. Death: Excluded (principal stratum) 2. Change in background ART regimen: ignored (treatment policy) 3. Use of prohibited medications: excluded (principal stratum) 4. Treatment discontinuation prior to week 24: excluded (principal stratum) 5. Pregnancy: excluded (principal stratum)	The analysis will be performed on the efficacy set and subset to intercurrent events (principal stratum). Missing data in this population will be assumed to be missing completely at random and thus ignored. Sensitivity analysis: If >10% of participants in the efficacy set are missing outcomes the analysis will be repeated using multiple imputation for the missing values.
Population-level summary measure	Analysis approach
The average absolute change in IHTG (%) 24 weeks after initiating semaglutide.	Linear regression of absolute IHTG change (%) on treatment arm without a model intercept. The estimated treatment arm effect, 95% CI and associated p-value will be provided.

5.2 Secondary Estimands and Analyses

5.2.1 First Secondary Estimand

Secondary Objective 1: To evaluate the safety and tolerability of semaglutide in adults with HIV, hepatic steatosis, central adiposity, and insulin resistance or pre-diabetes	
Estimand	Probability of new Grade ≥3 adverse events related to study treatment among HIV-infected adults with NAFLD who initiated study treatment.
Treatment	Semaglutide

Target population	Analysis set
Adults ≥18 years of age with HIV, central adiposity, insulin resistance or pre-diabetes, and hepatic steatosis, with HIV RNA suppression for at least the prior 48 weeks on ART.	Safety set (Participants who received at least one dose of study treatment)
Variable(s)	**Outcome measure(s)**
Occurrence of new Grade ≥3 adverse event related to study treatment.after initiating semaglutide.	Outcome measure as defined by the Variable.
Handling of intercurrent events	**Handling of missing data**
The following intercurrent events are relevant to the estimand: 1. Non-treatment-related death: ignored (treatment policy) 2. Change in background ART regimen: ignored (treatment policy) 3. Use of prohibited medications: excluded ignored (treatment policy) 4. Treatment discontinuation prior to week 24: ignored (treatment policy)	Participants who discontinue follow-up before prematurely will have their outcome determined based on data available until the time of discontinuation (i.e., a participant who discontinued follow-up without a prior AE is assumed not to have an AE had they been observed for the intended duration [48 weeks]). Sensitivity analysis: If >10% of participants in the safety set are prematurely discontinued, the Kaplan-Meier estimator of time to first

5. Pregnancy: ignored (treatment policy)	Grade ≥3 treatment-related AE with participants censored at the time of study discontinuation will be estimated.
Population-level summary measure	Analysis approach
The probability of a Grade ≥3 adverse event related to semaglutide.	The observed proportion will be provided.

5.2.2 Second Secondary Estimand

Secondary Objective 2: To evaluate the effects of semaglutide on weight, minimum waist circumference (WC), and body mass index (BMI)	
Estimand	Absolute change in metabolic parameters (weight, WC, BMI) 24 weeks after initiating semaglutide, among HIV-infected adults with NAFLD who remain on study treatment without use of prohibited medications.
Treatment	Semaglutide

Target population	Analysis set
Adults ≥18 years of age with HIV, central adiposity, insulin resistance or pre-diabetes, and hepatic steatosis, with HIV RNA suppression for at least the prior 48 weeks on ART.	Efficacy set (Participants who remained on study treatment for 24 weeks and did not receive prohibited medications during this time period)
Variable(s)	**Outcome measure(s)**
Change in metabolic parameters (weight, WC, BMI) 24 weeks after initiating semaglutide.	Absolute change from entry to Week 24 in metabolic parameters (weight, WC, BMI).
Handling of intercurrent events	**Handling of missing data**
The following intercurrent events are relevant to the estimand: 1. Death: Excluded (principal stratum) 2. Change in background ART regimen: ignored (treatment policy) 3. Use of prohibited medications: excluded (principal stratum) 4. Treatment discontinuation prior to week 24: excluded (principal stratum) 5. Pregnancy: excluded (principal stratum)	The analysis will be performed on the efficacy set and subset to intercurrent events (principal stratum). Missing data in this population will be assumed to be missing completely at random and thus ignored. Sensitivity analysis: Sensitivity analysis: If >10% of participants in the efficacy set are missing outcomes the analysis will be repeated using multiple imputation for the missing values.
Population-level summary measure	**Analysis approach**
The average absolute change in metabolic parameters (weight, WC, BMI) 24 weeks after initiating semaglutide.	Linear regression of absolute metabolic parameter (weight, WC, BMI) change on treatment arm without a model intercept. The estimated treatment arm effect, 95% CI and associated p-value will be provided.

5.2.3 Third Secondary Estimand

Secondary Objective 2: To evaluate the effects of semaglutide on insulin resistance or pre-diabetes, lipid profiles, and the prevalence of metabolic syndrome	
Estimand	Absolute change in HOMA-IR 24 weeks after initiating semaglutide, among HIV-infected adults with NAFLD who remain on study treatment without use of prohibited medications.
Treatment	Semaglutide

Target population	Analysis set
Adults ≥18 years of age with HIV, central adiposity, insulin resistance or pre-diabetes, and hepatic steatosis, with HIV RNA suppression for at least the prior 48 weeks on ART.	Efficacy set (Participants who remained on study treatment for 24 weeks and did not receive prohibited medications during this time period)
Variable(s)	**Outcome measure(s)**
Change in HOMA-IR 24 weeks after initiating semaglutide.	Absolute change from entry to Week 24 in HOMA-IR.
Handling of intercurrent events	**Handling of missing data**
The following intercurrent events are relevant to the estimand: 1. Death: Excluded (principal stratum) 2. Change in background ART regimen: ignored (treatment policy) 3. Use of prohibited medications: excluded (principal stratum) 4. Treatment discontinuation prior to week 24: excluded (principal stratum) 5. Pregnancy: excluded (principal stratum)	The analysis will be performed on the efficacy set and subset to intercurrent events (principal stratum). Missing data in this population will be assumed to be missing completely at random and thus ignored. Sensitivity analysis: Sensitivity analysis: If >10% of participants in the efficacy set are missing outcomes the analysis will be repeated using multiple imputation for the missing values.
Population-level summary measure	**Analysis approach**
The average absolute change in HOMA-IR 24 weeks after initiating semaglutide.	Linear regression of absolute HOMA-IR change on treatment arm without a model intercept. The estimated treatment arm effect, 95% CI and associated p-value will be provided.

6 Analysis of Objectives

6.1 Primary Analysis

1. IHTG (%)
    a. Using the PP population, the average absolute change in IHTG (%) from Pre-Entry to Week 24 will be estimated by a linear regression model without an intercept term (as this is a single arm study). Each participant will have a single outcome measure of IHTG (%) absolute change from pre-entry to Week 24. Study arm will be the only covariate in the model.

b. Using the PP population, the above analysis (a) will be repeated with the model being adjusted for baseline covariates found to differ between participants with and without IHTG (%) change outcomes.
c. Using the mITT population, the average absolute change in IHTG (%) from Pre-Entry to final MRI will be estimated by a linear regression model without an intercept term (as this is a single arm study). Each participant will have a single outcome measure of IHTG (%) absolute change from pre-entry to final MRI. Study arm will be the only covariate in the model. [NOTE: this analysis will only be conducted if >10% of the mITT population is excluded from the PP population]
d. Using the PP population, differential semaglutide effects will be assessed for the subgroups listed in Section 4.1 by linear regression models without an intercept term. Each participant will have a single outcome measure of IHTG (%) absolute change from Pre-Entry to Week 24. Study arm and the subgroup of interest will be covariates in the model.

6.2 Secondary and Exploratory Analyses

1. IHTG (%)
    a. The IHTG (%) analyses outlined in 6.1 will be repeated using percent change in IHTG (%) from pre-entry to Week 24.

2. Safety and Tolerability
    a. No formal statistical testing will be performed for safety (Grade 3 or higher AEs related to treatment) or tolerability (premature treatment discontinuation). Data summaries are outlined in the AIP.

3. Metabolic Parameters
    a. BMI, Body Weight and Minimum Waist Circumference
        i. Absolute changes from Week 0 to 24 will use the analysis approaches outlined in 6.1 for IHTG (%). Absolute changes in these outcomes from Week 0 to 12 will only use analysis a) from 6.1.
        ii. Absolute changes in these outcomes from Week 24 to 48 will only use analysis a) from 6.1.
        iii. Using the PP population, absolute changes from Week 0 to 24 will be correlated with both absolute and percent change from Pre-Entry to Week 24 in IHTG (%).
    b. HOMA-IR, HbA1c and Glucose
        i. Absolute changes from Week 0 to 24 will use the analysis approaches outlined in 6.1 for IHTG (%). **Ab**solute changes in HbA1c and glucose from Week 0 to 12 will only use analysis a) from 6.1.
        ii. Absolute changes in these HbA1c and glucose from Week 24 to 48 will only use analysis a) from 6.1.
        iii. Using the PP population, absolute changes from Week 0 to 24 will be correlated with both absolute and percent change from Pre-Entry to Week 24 in IHTG (%).

c. Lipids (total cholesterol, LDL cholesterol, HDL cholesterol and triglyceride)
    i. Absolute changes from Week 0 to 24 will use the analysis approaches outlined in 6.1 for IHTG (%). Absolute changes in these outcomes from Week 0 to 12 will only use analysis a) from 6.1.
    ii. Using the PP population, absolute changes from Week 0 to 24 will be correlated with both absolute and percent change from Pre-Entry to Week 24 in IHTG (%).
d. Metabolic Syndrome
    i. Using the PP population, the prevalence of metabolic syndrome at Weeks 0, 12 and 24 will be estimated by a generalized estimating equation (GEE) model for binary data without an intercept term. Each participant will have up to three metabolic syndrome outcomes (Yes/No) from Weeks 0, 12 and 24. Study arm and time (study visit) will be the only covariates in the model.
    ii. The above analysis (i) will be repeated using the modified ITT population.

4. Adherence
    a. No formal statistical testing will be performed for adherence (assessed by participant treatment log information and self-reported adherence at Weeks 4, 12 and 24). Data summaries are outlined in the AIP.
5. Physical Function
    a. Chair Rise Rate (5 Rises and 10 Rises)
        i. Absolute changes from Week 0 to 24 will use the analysis approaches outlined in 6.1 for IHTG (%).
        ii. Absolute changes from Week 24 to 48 will only use analysis a) from 6.1.
    b. Gait Speed
        i. Absolute changes from Week 0 to 24 will use the analysis approaches outlined in 6.1 for IHTG (%).
        ii. Absolute changes from Week 24 to 48 will only use analysis a) from 6.1.
    c. Presence of Slow Gait Speed
        i. The prevalence of slow gait speed at Weeks 0 and 24 will use the analysis approaches outline for Metabolic Syndrome above.
        ii. Using the PP population, the prevalence of slow gait speed at Weeks 0 and 24 will be estimated by a GEE model for binary data without an intercept term. Each participant will have up to two slow gait speed outcomes (Yes/No) from Weeks 0 and 24. Study arm and time (study visit) will be the only covariates in the model.
            1. This analysis will be repeated with Week 0, 24 and 48 data.
        iii. The above analysis (i) will be repeated using the modified ITT population.
            1. This analysis will be repeated with Week 0, 24 and 48 data.
6. Muscle and Fat
    a. Total Psoas Muscle Fat Percent

i. Absolute changes from Pre-Entry to Week 24 will use the analysis approaches outlined in 6.1 for IHTG (%).
ii. Percent changes from Pre-Entry to Week 24 will use the analysis approaches outlined in 6.1 for IHTG (%).
iii. Using the PP population, absolute changes from Pre-Entry to Week 24 will be correlated with both absolute and percent change from Pre-Entry to Week 24 in IHTG (%) as well as absolute change from Week 0 to 24 in BMI, body weight, minimum WC, HOMA-IR, HbA1c, glucose and lipids.

b. Total Psoas Muscle Volume
i. Absolute changes from Pre-Entry to Week 24 will use the analysis approaches outlined in 6.1 for IHTG (%).
ii. Percent changes from Pre-Entry to Week 24 will use the analysis approaches outlined in 6.1 for IHTG (%).

c. VAT Volume and SAT Volume
i. Absolute changes from Pre-Entry to Week 24 will use the analysis approaches outlined in 6.1 for IHTG (%).
ii. Using the PP population, absolute changes from Pre-Entry to Week 24 will be correlated with both absolute and percent change from Pre-Entry to Week 24 in IHTG (%) as well as absolute change from Week 0 to 24 in BMI, body weight, minimum WC, HOMA-IR, HbA1c, glucose and lipids.

7. Quality of Life
a. General Health
i. Responses will be scored (Excellent=5, Very Good=4, Good=3, Fair=2, Poor=1) at Weeks 0 and 24. Using the mITT population, the distribution of self-reported general health will be compared between Week 0 and Week 24 by calculating the absolute change and applying the Wilcoxon Signed Rank test.

b. Poor Physical Health, Poor Mental Health and Impairment
i. Using the mITT population, the average absolute change in self-reported days with each condition from Week 0 to 24 will be estimated by a linear regression model without an intercept term. Each participant will have a single outcome measure of absolute change from Week 0 to 24. Study arm will be the only covariate in the model.

8. Inflammatory Biomarkers
a. sCD14, IL-6, sCD163, CRP, IP-10, MCP-1 and CD40L
i. Absolute changes from Week 0 to 24 will use the analysis approaches outlined in 6.1 for IHTG (%). Absolute changes in these outcomes from Week 0 to 12 will only use analysis a) from 6.1.
ii. Absolute changes in these outcomes from Week 24 to 48 will only use analysis a) from 6.1.

9. Adipocytokine Levels
a. Adiponectin and GLP-1

i. Absolute changes from Week 0 to 24 will use the analysis approaches outlined in 6.1 for IHTG (%). Absolute changes in these outcomes from Week 0 to 12 will only use analysis a) from 6.1.
ii. Absolute changes in these outcomes from Week 24 to 48 will only use analysis a) from 6.1.

10. Immune Cell Profiles
    a. Activated (HLA-DR+/CD38+) CD4+ and CD8+ T lymphocytes; Monocyte (CD14/CD16/CCR2/CX3CR1/CD36/CD11c) subsets; Invariant natural killer (6B11/CD69) and mucosal associated invariant (Vα7.2/CD161) T lymphocytes
        i. Absolute changes from Week 0 to 24 will use the analysis approaches outlined in 6.1 for IHTG (%).

7 Report Contents

The following elements will be included in the primary analysis report or secondary analysis report, as noted. Detailed descriptions of these elements are provided in the AIP.

1. Study History (primary and secondary analysis reports)
2. Screen Failures (primary analysis report)
3. Accrual (primary analysis report)
4. Eligibility Violations (primary and secondary analysis reports)
5. Study Status (primary and secondary analysis reports; reported to ClinicalTrials.gov)
6. Treatment Status (primary analysis report; reported to ClinicalTrials.gov)
7. ART Adherence (primary and secondary analysis reports)
8. Treatment Adherence (primary analysis report)
9. Concomitant Medication Use (primary and secondary analysis reports)
10. Prohibited Medication Use (primary and secondary analysis reports)
11. Deaths (primary and secondary analysis reports)
12. Pregnancies (primary and secondary analysis reports)
13. Baseline Characteristics (primary analysis report; reported to ClinicalTrials.gov)
14. Adverse Events (primary [through Week 24] and secondary [all follow-up] analysis reports; reported to ClinicalTrials.gov)
15. Targeted Clinical Events (primary [through Week 24] and secondary [all follow-up] analysis reports)
16. IHTG (%) Summaries and Analyses (primary analysis report; reported to ClinicalTrials.gov)
17. BMI, Body Weight and Minimum Weight Circumference Summaries and Analyses (primary [through Week 24; reported to ClinicalTrials.gov] and secondary [Week 24 to 48] analysis reports)
18. HOMA-IR, HbA1c and Glucose Summaries and Analyses (primary analysis report; reported to ClinicalTrials.gov)
19. Lipid Summaries and Analyses (primary analysis report; reported to ClinicalTrials.gov)

20. Metabolic Syndrome Summaries and Analyses (secondary analysis report)
21. Physical Function Summaries and Analyses (primary [through Week 24] and secondary [Week 24 to 48] analysis reports)
22. Muscle and Fat Summaries and Analyses (primary analysis report [psoas muscle fat and volume] and secondary analysis report [VAT and SAT])
23. Quality of Life Summaries and Analyses (secondary analysis report)
24. Inflammatory Biomarker Summaries and Analyses (secondary analysis report)
25. Adipocytokine Summaries and Analyses (secondary analysis report)
26. Immune Cell Profile Summaries and Analyses (secondary analysis report)