Janssen Scientific Affairs, LLC

Clinical Protocol

A Phase 3, Single-arm, Open-label Study to Evaluate the Efficacy and Safety of Darunavir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (D/C/F/TAF) Once Daily Fixed-dose Combination (FDC) Regimen in Newly Diagnosed, Antiretroviral Treatment-naïve Human Immunodeficiency Virus Type 1 (HIV-1) Infected Subjects Receiving Care in a Test and Treat Model of Care

Protocol TMC114FD2HTX3002; Phase 3
Amendment 1

D/C/F/TAF (darunavir 800 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir alafenamide 10 mg)

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

Status: Approved
Date: 16 November 2017
Prepared by: Janssen Scientific Affairs, LLC
EDMS number: EDMS-ERI-137602439, 2.0

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

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LIST OF ATTACHMENTS

LIST OF IN-TEXT TABLES

PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	03-May-2017
Amendment 1	This document

Amendments below are listed beginning with the most recent amendment.

Amendment 1 (this document)

The overall reason for the amendment: Following FDA feedback on the clinical protocol TMC114FD2HTX3002, 3-May-2017, the requested changes have been implemented. In addition, an extension period has been added to give subjects who have completed the Week 48 visit an opportunity to continue D/C/F/TAF treatment until the D/C/F/TAF FDC tablet becomes commercially available and is reimbursed, or can be accessed through another source, or until the sponsor terminates clinical development. Further changes have been made to the protocol for clarification or correction.

Applicable Section(s)	Description of Change(s)
SYNOPSIS Time and Events Schedule 2.1 Objectives and Endpoints 3.1 Overview of Study Design 3.2 Study Design Rationale 6 Dosage and Administration 9.1.1 Overview 9.1.3 Open-Label Treatment Phase 9.8 Toxicity Management 10 Subject Completion/Discontinuation of Study Treatment/ Withdrawal From the Study 11 Statistical Methods	**Rationale:** To maintain continuity of treatment, subjects who have completed 48-weeks of treatment with D/C/F/TAF will be given the opportunity to continue D/C/F/TAF treatment during an extension period until the D/C/F/TAF FDC tablet becomes commercially available and is reimbursed, or can be accessed through another source, or until the sponsor terminates clinical development.
SYNOPSIS Time and Events Schedule 3.1 Overview of Study Design Attachment 1	**Rationale:** In order to minimize the chance of resistance development, HIV-1 RNA retesting in subjects with HIV-1 RNA ≥50 copies/mL will occur 2-4 weeks after the date of confirmation of viral load ≥50 copies/mL rather than after 3-6 weeks.
SYNOPSIS 3.1 Overview of Study Design 11 Statistical Methods	**Rationale:** To ensure patient safety and allow for an early analysis of this new Test and Treat model of care paradigm, the timing of the interim analysis has been advanced from when the last subject reaches Week 24 to when the last subject has been assessed for safety at Day 3, and for resistance stopping rules at Week 4.
SYNOPSIS 4.1 Inclusion Criteria	**Rationale:** In order to make inclusion criterion #7 consistent with footnote w in the Time and Events Schedule and with the text in Section 9.7, Clinical Laboratory Tests .

Applicable Section(s)	Description of Change(s)
Rationale: In order to incorporate the footnote associated with Attachment 4 into Section 9.8.1, and to specify that the attachment footnote and the new text in Section 9.8.1 do not apply to the retesting of abnormal screening/ baseline laboratory values.	
9.7 Safety Evaluations 9.8.1 General Guidance for the Management of Clinical Events and Laboratory Abnormalities Attachment 4	

SYNOPSIS

A Phase 3, Single-arm, Open-label Study to Evaluate the Efficacy and Safety of Darunavir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (D/C/F/TAF) Once Daily Fixed-dose Combination (FDC) Regimen in Newly Diagnosed, Antiretroviral Treatment-naïve Human Immunodeficiency Virus Type 1 (HIV-1) Infected Subjects Receiving Care in a Test and Treat Model of Care

STUDY DRUGS

The darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) fixed-dose combination (FDC) tablet is a 4-agent FDC tablet in development for oral once-daily use for the treatment of human immunodeficiency virus (HIV)-1 infection. This tablet contains the protease inhibitor (PI) darunavir (DRV or D) (800 mg), the pharmacokinetic 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).

Darunavir (PREZISTA®) used with a pharmacokinetic booster is approved for treatment of HIV-1 infection in subjects aged 3 years and above, either as a 600-mg twice-daily treatment for antiretroviral therapy (ART)-experienced subjects or as an 800-mg once-daily treatment for ART-naïve subjects and ART-experienced subjects without DRV resistance-associated mutations (RAMs).

Cobicistat (Tybost®) 150 mg is approved as a pharmacokinetic enhancer of select antiretroviral (ARV) agents requiring the effects of a pharmacokinetic enhancer.

The DRV/COBI 800/150-mg FDC tablet (PREZCOBIX®) is a once-daily treatment approved for use in combination with other ARV agents for treatment of HIV-1 infected treatment-naïve and treatment-experienced adults without DRV RAMs.

Emtricitabine is approved for use in combination with other agents for the treatment of HIV-1 infection in adults and children (4 months of age or older) and is available as a single agent (Emtriva®) or as part of FDCs, including Descovy® (F/TAF).

Tenofovir alafenamide is approved as part of FDCs, including Descovy® (FTC/TAF), Genvoya® (elvitegravir [EVG]/COBI/FTC/TAF or E/C/F/TAF), and Odefsey® (rilpivirine [RPV]/FTC/TAF). Descovy® is a once-daily treatment approved for use in combination with other ARV agents (including DRV/COBI) for treatment of HIV-1 infected adults and adolescents (aged 12 years and older).

The D/C/F/TAF FDC tablet is intended as a complete regimen for the treatment of HIV-1 infection in adults and adolescents (aged 12 years and older) with no mutations known to be associated with resistance to any of the active components. The D/C/F/TAF FDC is currently being studied in 2 ongoing Phase 3 clinical studies (NCT02431247 and NCT02269917).

OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

Objectives

The primary objective of this study is to assess the efficacy of D/C/F/TAF FDC in a Test and Treat model of care in newly diagnosed HIV-1-infected, treatment-naive subjects as determined by the proportion of virologic responders defined as having HIV-1 ribonucleic acid (RNA) <50 copies/mL at Week 48 (Food and Drug Administration [FDA]-defined intent to treat [ITT] snapshot analysis).

The secondary objectives of this study are:

- To assess virologic and immunologic changes in the study population through 12, 24, and 48 weeks of treatment

- To evaluate the incidence of grade 3 and 4 adverse events, serious adverse events, and premature discontinuations due to adverse events through 24 and 48 weeks of treatment, and during the extension phase
- To evaluate the frequency of discontinuation of D/C/F/TAF FDC due to protocol-specific stopping rules (refer to the section Overview of Study Design below)
- To assess baseline viral resistance in the study population
- To assess the development of viral resistance in the study population through 24 and 48 weeks of treatment, and during the extension phase
- To assess the proportion of subjects retained in care after discontinuation of study drug before Week 48
- To evaluate the influence of various intrinsic and extrinsic factors on retention in care
- To assess the proportion of subjects lost to follow-up through 24 and 48 weeks of treatment
- To evaluate adherence by pill count to D/C/F/TAF FDC in the study population through 24 and 48 weeks of treatment
- To evaluate adherence by subject self-report, using a 4-day recall period through Weeks 24 and 48
- To describe predictors of suboptimal adherence (<95% adherence by pill count) in the study population
- To assess the HIV Treatment Satisfaction Questionnaire-status version (HIVTSQs) at Weeks 4, 24, and 48
- To evaluate healthcare resource utilization (HRU) and cost and their temporal trends in the study population through 48 weeks of treatment

Endpoints

The primary endpoint of this study is the proportion of subjects who have HIV-1 RNA <50 copies/mL at Week 48 as defined by the FDA snapshot analysis (ITT).

The secondary endpoints of this study are:

Efficacy

- Change from baseline in $\log_{10}$ HIV-1 RNA viral load at Weeks 2, 4, 8, 12, 24, 36, and 48
- Proportion of subjects who have HIV-1 RNA <50 copies/mL at Week 24
- The change from baseline in $CD4^+$ cell count at Weeks 12, 24, and 48

Safety

- Proportion of subjects that required discontinuation after enrollment based on safety stopping rules (refer to the section Overview of Study Design below)
- Proportion of subjects discontinuing therapy due to adverse events
- Proportion of subjects experiencing grade 3 and 4 adverse events
- Proportion of subjects experiencing grade 3 and 4 laboratory abnormalities

Resistance

- Proportion of subjects meeting resistance stopping rules (refer to the section Overview of Study Design below) requiring discontinuation of study drug due to baseline resistance findings

- Proportion of subjects with baseline protease (PR), reverse transcriptase (RT), and integrase (INI) RAMs
- Proportion of subjects developing RAMs and loss of phenotypic susceptibility, when available, upon meeting protocol-defined virologic failure
- Proportion of subjects with protocol-defined virologic failure at Week 24 and Week 48, and during the extension phase

Retention in Care

- Proportion of subjects lost-to-follow-up throughout the 48 weeks of treatment
- Proportion of subjects discontinuing study drug for any reason other than withdrawal of consent prior to Week 48 who have a documented clinic visit with a healthcare provider within 90 days of discontinuing study drug

Adherence

- Adherence rates by pill count at Weeks 4, 8, 12, 24, 36, and 48
- Adherence rates by subject self-report, using a 4-day recall at Weeks 4, 8, 12, 24, 36, and 48

Tolerability/Patient-reported Outcomes

- Mean total scores for the HIVTSQs at Weeks 4, 24, and 48

Healthcare Resource Utilization/Pharmacoeconomics

- The number and duration of hospitalizations, number and type of outpatient visits, number of emergency room visits, and number and type of medications used (both HIV-related and All-cause as assessed by the investigator) throughout the main study period
- Direct medical costs will be calculated in United States (USA) dollars based on HRU noted above

Hypothesis

No formal hypothesis will be tested. The findings from this study will be used to generate data on the efficacy and safety profile of D/C/F/TAF FDC in newly diagnosed HIV-1 infected, treatment-naïve subjects using a Test and Treat model of care.

OVERVIEW OF STUDY DESIGN

This is a single-arm, open-label, prospective, multicenter Phase 3 study to assess the efficacy and safety of D/C/F/TAF FDC in newly diagnosed (ie, within 2 weeks of the screening/baseline visit [Day 1]) HIV-1 infected treatment-naïve subjects at least 18 years of age as part of a Test and Treat model of care in the USA.

After obtaining informed consent, a blood sample will be collected for central laboratory testing.

Study drug will be dispensed before the results from the screening/baseline safety and resistance laboratory tests are available. Subjects must start treatment with D/C/F/TAF FDC within 24 hours of the screening/baseline visit.

Following initiation of treatment, a safety assessment will be performed by the investigator at Day 3 +1 week, or as soon as the final screening/baseline laboratory report becomes available. Subjects meeting any of the below safety stopping rules (based on the receipt of the screening/baseline laboratory findings) will be contacted to return to the study site for possible early study treatment discontinuation (ESTD) and for additional follow-up.

- Estimated glomerular filtration rate (eGFR) according to the Modification of Diet in Renal Disease (MDRD) formula <50 mL/min.
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥2.5×upper limit of normal (ULN)
- Serum lipase ≥1.5×ULN
- Positive serum human chorionic gonadotropin pregnancy test (β-hCG) for women of childbearing potential
- Laboratory results that the investigator believes should result in discontinuation of study medication (Note: It is recommended that the investigator contacts the sponsor's medical monitor to discuss the discontinuation)
- Subjects identified with active hepatitis C virus (HCV) infection that in the opinion of the investigator requires HCV treatment immediately or expected to be needed during the course of the study with agents not compatible with D/C/F/TAF FDC.

Retesting of abnormal screening/baseline safety laboratory values noted above will be allowed once. Retesting will take place during an unscheduled visit.

The investigator will review the ARV screening/baseline resistance data at Week 4 ±7 days or sooner, depending on the availability of the screening/baseline HIV genotypic drug resistance testing results from the central laboratory. Subjects who do not show full sensitivity to all drugs in the FDC study regimen according to the susceptibility assessment in the GenoSure Prime® report will be contacted to return to the study site for ESTD. Subjects with identified resistance to lamivudine/FTC, attributed to the presence of the M184I/V mutation alone will be permitted to remain in the study.

Subjects will be treated for 48 weeks in the main study period and will return to the site for visits at Weeks 2, 4, 8, 12, 24, 36, and 48. Assessment of drug accountability and reasons for non-adherence, and recording of concomitant therapies, adverse events, vital signs (including the subject's body weight), and physical examinations (complete or symptom-directed) will be performed at each visit from baseline onwards. Laboratory evaluations for efficacy and safety (HIV-1 viral load, biochemistry, hematology, and urinalysis) will be performed at all study visits. $CD4^+/CD8^+$ cell count will be assessed at Weeks 4, 8, 12, 24, 36, and 48. Patient-reported outcome (PRO) measures will be assessed at Weeks 4, 24, and 48 using the validated 10-item HIVTSQs (Version 2006). Medical resource utilization data will be collected from all subjects throughout the main study period.

Subjects who are on study drug and who experience a protocol-defined virologic failure (see below) will undergo genotypic and phenotypic resistance testing, preferably at the time of the confirmed virologic failure visit if the HIV-1 RNA is ≥ 400 copies/mL. If resistance testing is not able to be performed at the time of confirmed virologic failure, resistance testing may be performed at the point of unconfirmed virologic failure or a later time point if HIV-1 RNA is ≥400 copies/mL. Subjects who have persistent HIV-1 RNA ≥ 400 copies/mL past Week 24 but do not meet the definition of virologic failure, should have their viral load monitored closely, and if appropriate undergo genotypic and phenotypic resistance testing. In case resistance to study drugs is observed, the subject may be discontinued from the study at the investigator's discretion. If the investigator makes the decision that the subject can continue in the study, additional resistance testing may be performed as deemed necessary. Protocol-defined virologic failure is not considered a stopping rule.

Virologic failure will be defined in this study as follows:

- Virologic Nonresponse:
  - HIV-1 RNA <1 $\log_{10}$ reduction from baseline, *AND*
    HIV-1 RNA ≥400 copies/mL at the Week 12 visit, subsequently confirmed at an unscheduled visit conducted within 2 to 4 weeks after Week 12
- Virologic Rebound:
  - At any visit, after achieving confirmed consecutive HIV-1 RNA <50 copies/mL, a rebound in HIV-1 RNA to ≥50 copies/mL, which is subsequently confirmed at a scheduled or unscheduled visit conducted within 2 to 4 weeks of the HIV-1 RNA result; *OR*
  - At any visit, a >1 $\log_{10}$ increase in HIV-1 RNA from the nadir, which is subsequently confirmed at the following scheduled or unscheduled visit conducted within 2 to 4 weeks of the HIV-1 RNA result.

Subjects who prematurely discontinue study treatment during the open-label treatment period will be required to complete ESTD assessments as soon as possible but no later than 1 week of discontinuing study treatment.

In addition, a follow-up visit is required for any subject who has an ongoing adverse event or serious adverse event at the time of his/her last study visit. These subjects are required to return to the site 30 days (±7 days) after completion of the last study-related visit (unless consent is withdrawn).

Subjects who have completed the Week 48 visit will be given the opportunity to continue D/C/F/TAF treatment during an extension period until the D/C/F/TAF FDC tablet becomes commercially available and is reimbursed, or can be accessed through another source, or until the sponsor terminates clinical development. At Week 48 the investigator should dispense a sufficient supply of D/C/F/TAF to maintain continuity of care for the subject, however no more than 12 weeks of study medication should be dispensed. If a subject requires more than 12 weeks of study medication, the subject should return to the site for additional drug dispensation.

During the extension period, subjects will have a study visit at the site once every 6 months, if applicable, and complete the procedures indicated in the Time and Events Schedule, and additionally at the time of transition to commercial D/C/F/TAF, for final data collection.

At the end of the study (or at ESTD), subjects will resume routine clinical care with their care provider who will determine the future care of that subject. In anticipation of transitioning the subject to routine clinical care at the end of the study (or early discontinuation), the investigator should take steps to ensure a smooth transition (ie, secure insurance etc.) well in advance of the final study visit, so that the subjects' ART is not interrupted.

For those subjects discontinuing therapy before Week 48, the investigator will be asked to monitor the subject's retention in care defined as having one documented clinic visit within 90 days of discontinuing the study treatment (unless consent is withdrawn).

The end of the study is defined as completion of the last data collection visit for the last subject participating in the study. For the purpose of the primary analysis, a subject will be considered to have completed the study if data collection as required per protocol through the complete course of 48 weeks of ART has been completed.

An interim analysis will be conducted after the last subject enrolled has been assessed for safety at Day 3, and for resistance stopping rules at Week 4.

The primary analysis of this study will be performed once all subjects have completed the Week 48 visit and the 30-day follow-up visit (if applicable) or discontinued earlier.

SUBJECT POPULATION

Inclusion Criteria

Sign an informed consent form (ICF) indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study.

Man or woman at least 18 years of age.

Newly diagnosed with HIV-1 evidenced by any of the following within 2 weeks of the screening/baseline visit:

- HIV Rapid Antibody positive*; *OR*
- HIV Immunoassay positive; *OR*
- Positive p24 antigen and a HIV-1 RNA viral load ≥5,000 copies/mL; *OR*
- Non-reactive HIV-1 antibody/antigen assays and HIV-1 RNA viral load ≥5,000 copies/mL. HIV-1 RNA viral load must be confirmed once within 1 week of initial HIV-1 RNA viral load test.

* For those subjects testing initially positive on a 4th generation HIV Rapid Antibody Assay, results should be confirmed on a 3rd generation HIV Rapid Antibody Assay at a minimum, or an HIV Immunoassay, unless the investigator suspects acute or recent infection.

Antiretroviral treatment-naïve, except for the use of TRUVADA® for pre-exposure prophylaxis (PrEP).

Contraceptive use by men or women should be consistent with the local regulations regarding the use of contraceptive methods for subject participating in clinical studies. A woman must be either:

- Postmenopausal for at least 2 years (medical documentation of cessation of menses for at least 2 years and of hormonal ovarian failure [follicle-stimulating hormone (FSH) level ≥40 mIU/mL] is required); *OR*
- Surgically sterile (had total hysterectomy or bilateral oophorectomy, tubal ligation/bilateral tubal clips without reversal operation, or otherwise incapable of becoming pregnant); *OR*
- Not heterosexually active for the duration of the study; *OR*
- Have a vasectomized partner; *OR*
- If of childbearing potential and heterosexually active, practicing a highly effective method of birth control (as specified below) before entry, and agree to continue to use a highly effective method of contraception throughout the study, and for at least 90 days after receiving the last dose of study drug. Women with tubal ligation are required to use one additional contraceptive method.
- Estrogen-based hormonal contraception may not be reliable when taking the study drug. Therefore, to be eligible for this study, women of childbearing potential should either use:
  - a double-barrier method (male condom + either diaphragm or cervical cap); *OR*
  - non-estrogen hormonal based contraceptives in combination with a barrier contraceptive (male condom, diaphragm or cervical cap, or female condom); *OR*
  - intrauterine device in combination with a barrier contraceptive (male condom, diaphragm or cervical cap, or female condom).

Note: A male condom and female condom should not be used together due to risk of breakage or damage caused by latex friction.

A woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for 90 days after receiving the last dose of study drug.

A woman of childbearing potential must have a negative urine pregnancy test at screening.

Men with a female partner of childbearing potential must agree to use adequate reliable contraceptive methods (see above) during the study until 90 days after receiving the last dose of study drug

- Men who have had a vasectomy without reversal operation minimally 2 months prior to screening are not required to use birth control methods.
- For all male subjects, it is the responsibility of the subject to ensure that his partner(s) do(es) not become pregnant during treatment with the study drug and for up to 90 days after receiving the last dose of study drug.

Men must agree not to donate sperm during the study until 90 days after receiving the last dose of study drug (or longer, if dictated by local regulations).

Must be able to swallow whole tablets.

Exclusion Criteria
Known active cryptococcal infection, active toxoplasmic encephalitis, Mycobacterium tuberculosis infection, or another acquired immunodeficiency syndrome (AIDS)-defining condition that in the judgement of the investigator would increase the risk of morbidity or mortality.
Known history of clinically relevant hepatic disease or hepatitis that in the investigator's judgement is not compatible with D/C/F/TAF FDC.
Known history of cirrhosis as diagnosed based on local practices.
Known history of chronic (≥3 months) renal insufficiency, defined as having an eGFR <50 mL/min according to the MDRD formula.
Pregnant, or breast-feeding, or planning to become pregnant while enrolled in this study or within 90 days after the last dose of study treatment.
Plans to father a child while enrolled in this study or within 90 days after the last dose of study treatment.
Current alcohol or substance use judged by the investigator to potentially interfere with subject study adherence.
Known history of malignancy within the past 5 years or ongoing malignancy other than cutaneous Kaposi's sarcoma, basal cell carcinoma, or resected, noninvasive cutaneous squamous carcinoma.
Known active, severe infections (other than HIV-1 infection) requiring parenteral antibiotic or antifungal therapy within 30 days prior to screening.
Any other condition or prior therapy for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.
Subject unlikely to comply with the protocol requirements, based on clinical judgment.
Received an investigational drug (including investigational vaccines) or used an invasive investigational medical device within 90 days before the planned first dose of study treatment or is currently enrolled in an investigational study without prior approval from the sponsor.
Subjects receiving ongoing therapy with contraindicated, not recommended, drugs that cannot be adequately dose-adjusted, or subjects with any known allergies to the excipients of the D/C/F/TAF FDC.
Employee of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site, as well as family members of the employees or the investigator, or employees of Johnson & Johnson or Gilead.

DOSAGE AND ADMINISTRATION

All subjects will receive treatment with D/C/F/TAF FDC (DRV 800 mg + COBI 150 mg + FTC 200 mg + TAF 10 mg) in an open-label fashion.

Initiation of study treatment can only start after all screening/baseline tests and procedures have been completed and must take place within 24 hours after the baseline visit. D/C/F/TAF FDC must be taken orally with food. All subjects will be counseled to swallow D/C/F/TAF whole once daily at approximately the same time each day, according to their preference.

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

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

In order to maintain continuity of care, subjects will be given the opportunity to continue the D/C/F/TAF treatment after Week 48 during an extension period until the D/C/F/TAF FDC tablet becomes commercially available and is reimbursed, or can be accessed through another source, or until the sponsor terminates clinical development.

EFFICACY EVALUATIONS

Antiviral Efficacy and Immunologic Change

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

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

Immunologic change will be determined by changes in $CD4^+$ cell count (absolute and %).

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

Resistance Determinations

HIV-1 genotype/phenotype resistance testing will be performed at the time points specified in the Time and Events Schedule.

Resistance testing at the screening/baseline visit (Day 1) will be performed utilizing the GenoSure Prime® assay. Resistance-associated mutations present at baseline will be reported and include mutations in the domain of PR, RT, and INI.

To investigate the emergence of resistance, the following subjects will be eligible for genotypic/phenotypic resistance testing (PhenoSense GT®):

- Any subject who experiences a protocol-defined virologic failure (see above);
- Any subject who discontinues study treatment after Week 12 for any reason and has an HIV-1 RNA value ≥400 copies/mL at the last viral load measurement;
- Any subject who has persistent HIV-1 RNA ≥400 copies/mL past Week 24 but does not meet the definition of virologic failure.

Baseline phenotyping may be performed retrospectively on subjects with confirmed protocol-defined virologic failure if after virologic failure they showed evidence of reduced phenotypic susceptibility to any of the study drugs. Evaluations may be performed at other time points at the sponsor's discretion.

PHARMACOKINETIC EVALUATIONS

Plasma concentrations of DRV and COBI may be determined in subjects experiencing protocol-defined virologic failure, or subjects who have persistent HIV-1 RNA ≥400 copies/mL past Week 24 but do not meet the definition of virologic failure, using stored blood samples collected throughout the study, if deemed necessary.

MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS

Medical resource utilization data will be collected in the electronic case report form (eCRF) by the investigator and study-site personnel. The following will be evaluated throughout the study as noted in the Time and Events Schedule:

- Number and duration of hospitalizations.
- Number of outpatient visits, including type of visit (eg, general practitioner, specialist)
- Number of emergency room visits.
- Number and type of medications used (from the Concomitant Medication page of the eCRF).

Medical resource utilization will be classified as being either HIV-related or All-cause HRU as assessed by the investigator. The costs will be assigned to the type of medical resource utilization to calculate a per subject per month cost associated with the initiation and maintenance of ART. Trends will be assessed over time throughout the study.

ADHERENCE

Treatment adherence will be assessed by pill count, and by subject self-report, using a 4-day recall period.

Subjects should be counseled regarding the importance of adherence, and be instructed to bring unused medication and empty packaging to the unit at each visit.

RETENTION IN CARE

Retention in care will be described as the proportion of subjects who discontinue study treatment prior to Week 48 and remain in care after discontinuation (defined as having a documented office visit within 90 days of discontinuing the study drug). Subjects who withdraw consent will not be followed to assess retention in care.

SAFETY EVALUATIONS

Safety and tolerability will be evaluated throughout the study from the time a signed and dated ICF is obtained until completion of the subject's last study-related activity.

The study will include the following evaluations of safety and tolerability as indicated in the Time and Events Schedule:

- Adverse events;
- Clinical laboratory tests (including biochemistry, hematology, urinalysis, urine chemistry);
- Vital signs;
- Physical examination (complete or symptom-directed);
- Follow-up on specific toxicities.

PATIENT-REPORTED OUTCOMES

Patient-reported outcomes will be assessed at the time points indicated in the Time and Events Schedule utilizing the HIVTSQs.

STATISTICAL METHODS

The following analyses will be performed:

- The interim analysis: once all subjects have been assessed for safety at Day 3, and for resistance stopping rules at Week 4.
- The primary analysis: once all subjects have completed the Week 48 assessments and the 30-day follow-up visit (if applicable), or discontinued earlier.

Sample Size Determination

The primary efficacy endpoint is the proportion of subjects who have HIV-1 RNA<50 copies/mL at Week 48 as defined by the FDA snapshot analysis (ITT). As this is an exploratory study with no formal hypothesis testing on the primary endpoint, no formal sample size calculation was performed. With a sample size of 100 subjects and an expected virologic response rate ranging from 60-80%, the exact corresponding 95% confidence intervals (CIs) are: 60% (49.7%, 69.7%), 70% (60.0%, 78.8%), and 80% (70.8%, 87.3%). The half-width of the exact corresponding 2-sided 95% CI is 10.0%, 9.4%, and 8.3%,

respectively, and is therefore less than 10% across the range of expected outcomes which is the desired precision. Additionally, with a sample size of 100 subjects, the probability to observe an adverse event with a true incidence of 1% or 4% is 63% and 98% respectively.

Efficacy Analyses

Antiviral Efficacy and Immunologic Change

The primary efficacy endpoint is the proportion of subjects who have HIV-1 RNA<50 copies/mL at Week 48 as defined by the FDA snapshot analysis (ITT).

Virologic suppression (HIV-1 RNA<50 copies/mL) will also be analyzed as secondary endpoints at Week 24 and Week 48 according to the below analyses:

- FDA Snapshot algorithm in the ITT and Per-Protocol population
- Time to loss of virological response (TLOVR) algorithm in the ITT population

Virologic decay will be reported as the mean $\log_{10}$ change in HIV-1 viral load from baseline to Weeks 2, 4, 8, 12, and 24 as part of the interim analysis as a secondary endpoint.

The proportion of subjects experiencing protocol defined virologic failure at Week 24 and Week 48 will be tabulated using descriptive statistics along with the 95% CIs. The Wilson (Score) method for the CI will be used.

The changes from baseline in $CD4^+$ cell count at Weeks 12, 24, and 48 will be summarized using descriptive statistics.

Resistance Determinations

The number of PR mutations (including International AIDS Society-United States of America [IAS-USA] primary and secondary PI RAMs), RT mutations (including IAS-USA nucleoside/nucleotide RT inhibitor [N(t)RTI] RAMs and IAS-USA non-nucleoside RT inhibitor [NN(t)RTI] RAMs), and INI mutations (including IAS-USA primary and secondary INI-RAMs) present will be tabulated based on resistance tests performed at the screening/baseline visit.

The proportion of subjects meeting resistance stopping rules, requiring discontinuation of study drug, based on the findings of screening/baseline resistance testing will be tabulated as part of the interim analysis.

HIV-1 genotype/phenotype will be analyzed from samples of subjects with protocol-defined virologic failure and with HIV-1 RNA ≥400 copies/mL.

The number of treatment-emergent PR mutations (including IAS-USA primary and secondary PI RAMs) and RT mutations (including IAS-USA N(t)RTI RAMs and IAS-USA NNRTI RAMs), as well as specific mutations associated with resistance to DRV, FTC, and TAF will be tabulated based on the observed protocol-defined virologic failures through the study period.

Fold change (FC) in 50% effective concentration (EC_{50}) of ARVs will be tabulated. Loss of phenotypic susceptibility may be analyzed dependent on the number of virologic failures and phenotypes available through the study period.

Medical Resource Utilization Analyses

All-cause and HIV-specific HRU during the study period will be summarized overall and by category as the counts per patient per month (PPPM). Monthly average counts per subject will also be calculated to show the temporal trend for each category.

Costs of care will be calculated by assigning costs based on Centers for Medicare & Medicaid Services (CMS) fee schedule to assessed HRU on a per subject per month basis. Descriptive statistics will be calculated to compare the costs of care from baseline to Weeks 12, 24, and 48.

Adherence Analyses

Treatment adherence based on pill count and on subject self-report will be summarized by means of descriptive statistics and frequency tabulations.

Adherence rates will be reported according to the proportion of subjects taking >95%, 80-95% and <80% of study drug as assessed by pill count at study visits at Weeks 4, 12, 24, and 48.

Retention in Care Analyses

Number of subject with retention of care by age, gender, race, sexual orientation, time from diagnosis to baseline visit, baseline CD4+ cell count, baseline HIV-1 RNA, patient satisfaction as assessed by HIVTSQs, and socioeconomic factors will be tabulated.

Safety Analyses

The verbatim terms used by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All reported adverse events with onset during the study will be included in the analysis. For each adverse event, the percentage of subjects who experience ≥1 occurrence of the given event will be summarized.

Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue treatment due to an adverse event, or who experience a severe or life-threatening (grade 3 or 4) or a serious adverse event.

Additionally, a summary and listing of those subjects meeting predefined stopping rules due to safety or resistance findings will be tabulated.

Laboratory data will be summarized by type of test. Descriptive statistics will be calculated for each laboratory analyte for observed values and changes from baseline at each scheduled time point. Graphical presentation of changes in laboratory parameters can be made as applicable.

Abnormalities will be determined according to the Division of AIDS (DAIDS) grading table and in accordance with the normal ranges of the clinical laboratory. Maximum toxicity grade after baseline will be tabulated and special attention will be given to the subjects who developed grade 3 or 4 toxicities.

Descriptive statistics of vital signs (pulse rate, systolic and diastolic blood pressure, and body weight) values and changes from baseline will be summarized at each scheduled time point. The percentage of subjects with values beyond clinically important limits will be tabulated.

Physical examination findings and changes from baseline at each scheduled time point will be listed.

Patient-reported Outcomes

Descriptive statistics for absolutes values and changes in HIVTSQs scores will be calculated at each time point, where applicable.

Extension Period

For the extension period, descriptive statistics or patient data listings will be provided for adverse events, virologic failure, or resistance.

TIME AND EVENTS SCHEDULE

Phase		Open-label Treatment Phase									ESTD (Early Study Treatment Discont-inuation) Visit[e]	30-day Follow-up[f]	90-day Follow-up
			Main Study Period							Extension Period[d]			
			Week[a]										
	Day 1 Screening/ Baseline[b]	Day 3 Safety Assessment[c]	2	4	8	12	24	36	48				
Study Procedures													
Screening/Administrative													
Informed consent process[g]	X												
Demographic information	X												
Medical history[h]	X												
HIV history	X												
Inclusion/exclusion criteria	X												
Determine Continued Eligibility (by Investigator)													
Formal review of central screening/baseline safety laboratory tests by investigator (no scheduled clinic visit)		X											
Formal review of screening/baseline HIV genotypic drug resistance testing by investigator				X[i]									
Study Drug Administration													
Dispense study drug[l]	X			X	X	X	X	X	X[k]	X[k]			
Drug accountability (pill count)[l]				X	X	X	X	X	X	X	X		
Adherence (subject self-report)[m]				X	X	X	X	X	X	X	X		
Efficacy Assessments													
HIV-1 RNA[n]	X		X	X	X	X	X	X	X	X	X	X	
$CD4^+/CD8^+$	X			X	X	X	X	X	X	X	X		
Combined Genotype/Phenotype[o]	X[p]		X	X	X	X	X	X	X	X	X		
Safety Assessments													
Vital signs, body weight and height[q]	X		X	X	X	X	X	X	X	X	X	X	
Full physical examination[r]	X								X	X	X		
Symptom-directed physical examination[r]			X	X	X	X	X	X		X		X	
Review concomitant medications	X		X	X	X	X	X	X	X	X	X	X	
Adverse events assessment[s]	X		X	X	X	X	X	X	X	X	X	X	

Phase		Open-label Treatment Phase									ESTD (Early Study Treatment Discont-inuation) Visit[e]	30-day Follow-up[f]	90-day Follow-up
			Main Study Period							Extension Period[d]			
			Week[a]										
	Day 1 Screening/ Baseline[b]	Day 3 Safety Assessment[c]	2	4	8	12	24	36	48				
Study Procedures													
Health Outcome Assessments													
Medical resource utilization			X	X	X	X	X	X	X		X[u]	X	
HIV Treatment Satisfaction Questionnaire (HIVTSQs)[t]				X			X		X		X[u]		
Clinical Laboratory Assessments													
Hepatitis B/C serology	X												
Estimated glomerular filtration rate (eGFR)	X		X	X	X	X	X	X	X	X	X	X	
Genotype[v]	X												
Pregnancy test[w]	X		X	X	X	X	X	X	X	X	X	X	
Hematology	X[x]		X[x]	X[x]	X	X[x]	X	X	X[x]	X	X	X	
Chemistry	X		X	X	X	X	X	X	X	X	X	X	
Serum amylase/lipase[y]	X												
Urinalysis[z]	X		X	X	X	X	X	X	X	X	X	X	
Other													
Retention in care assessment													X[bb]
Blood samples stored[aa]													

Note: Retesting of abnormal screening/baseline safety laboratory values that may lead to exclusion will be allowed once.
Unscheduled visit(s) may be required for safety reasons, for technical issues with the samples, or for confirmation of virologic failure in case of unconfirmed virologic failure (virologic nonresponse or virologic rebound [see Attachment 1]). When human immunodeficiency virus (HIV)-1 ribonucleic acid (RNA) repeat testing is required at an unscheduled visit, an HIV-1 genotype/phenotype plasma sample and a plasma storage sample should also be drawn at the same unscheduled visit.

a. All study visits are to be scheduled relative to the screening/baseline visit date and are to occur at the end of Weeks 2, 4, 8, 12, 24, 36, and 48. A window of ±2 days is allowed for Visit 2. All other study visits through Week 48 are to be completed within ±7 days of the protocol-specified visit date.
b. Screening/baseline visit should be within 2 weeks of diagnosis. The screening and baseline assessments should preferably be completed the same day (Day 1), but if necessary, can be performed on different days, but must be completed within 2 business days of signing the ICF. Study drug should not be dispensed until all screening procedures have been completed and the investigator has determined that the subject meets the inclusion/exclusion criteria.
c. A safety assessment will be performed by the investigator at Day 3 +1 week, or as soon as the final screening/baseline laboratory report becomes available. Subjects meeting any of the safety stopping rules will be contacted to return to the study site for possible ESTD and additional follow-up.
d. Subjects will have a study visit at the site once every 6 months, if applicable, and additionally at the time of transition to commercial D/C/F/TAF.
e. Subjects who prematurely discontinue study treatment during the open-label treatment period (ie, including the extension period) will be required to complete ESTD assessments as soon as possible but no later than 1 week of discontinuing study treatment.

f. Required for any subject who has an ongoing adverse event or serious adverse event at the time of his/her last study visit (unless consent is withdrawn); a ±7 days window may be used.
g. Signing of the informed consent form (ICF) needs to be done before the first study-related activity.
h. Including family history of premature cardiovascular disease, diabetes, hypertension, low high-density lipoprotein (HDL) cholesterol, and prior history of cardiovascular disease.
i. The investigator will review the antiretroviral (ARV) screening/baseline resistance data at Week 4 ±7 days or sooner, depending on the availability of the screening/baseline HIV genotypic drug resistance testing results from the central laboratory.
j. Subjects must start treatment within 24 hours of the screening/baseline visit (Day 1).
k. At Week 48 the investigator should dispense a sufficient supply of D/C/F/TAF to maintain continuity of care for the subject, however no more than 12 weeks of study medication should be dispensed. If a subject requires more than 12 weeks of study medication, the subject should return to the site for additional drug dispensation.
l. Monitoring of treatment adherence will utilize pill counts.
m. Monitoring of treatment adherence by subject self-report, using a 4-day recall.
n. Leftover blood samples from the HIV-1 RNA determinations could be used for protocol-related testing (virology, safety, pharmacokinetic analysis) at additional time points.
o. Combined genotype/phenotype (PhenoSense GT®) will be assessed at the central laboratory for subjects who experience a protocol-defined virologic failure, for subjects who discontinue study treatment after Week 12 and have HIV-1 RNA ≥400 copies/mL, or for subjects who have persistent HIV-1 RNA ≥400 copies/mL past Week 24 but do not meet the definition of virologic failure. Additional samples may be analyzed upon request of the sponsor's virologist.
p. Baseline phenotyping may be performed retrospectively on subjects with confirmed protocol-defined virologic failure if after virologic failure they showed evidence of reduced phenotypic susceptibility to any of the study drugs. Evaluations may be performed at other time points at the sponsor's discretion.
q. Vital signs include systolic and diastolic blood pressure, pulse rate (supine after at least 5 minutes rest), and weight. Height will be measured at screening.
r. A complete physical examination will be conducted at screening, Week 48, at the time of transition to commercial D/C/F/TAF, or at the ESTD visit. Symptom directed physical examinations may be conducted at all other scheduled and unscheduled study visits based on reported safety or tolerability issues.
s. In the setting of a suspected renal adverse event, urine chemistry (quantitative measurement) will be assessed: creatinine, sodium, phosphate, glucose, protein, albumin.
t. The HIVTSQs assessment should be completed before all other study-related procedures planned during these visits to prevent influencing subject perceptions.
u. MRU and the HIVTSQ will not be collected as part of ESTD during the extension period.
v. Genotype (GenoSure Prime®) will be assessed at the time of screening.
w. At screening, pregnancy will be determined by urine pregnancy test for all female subjects of childbearing potential. A serum human chorionic gonadotropin (β-hCG) pregnancy test will be assessed at a central laboratory, but the results are not required for enrollment. Subsequently pregnancy will be assessed by urine pregnancy tests.
x. Peripheral blood mononuclear cells (PBMCs) will be isolated from whole blood at the central laboratory, and stored for future analysis if needed.
y. Serum amylase and serum lipase will be assessed at screening. If a subject is suspected of having pancreatitis during the study period serum amylase and serum lipase may be reassessed at scheduled or unscheduled visits.
z. Urinalysis (dipstick). If dipstick results are abnormal, the sediment will be examined microscopically.
aa. Plasma concentrations of darunavir (DRV) and cobicistat (COBI) may be assessed from stored blood samples in those subjects who experience protocol-defined virologic failure, or subjects who have persistent HIV-1 RNA ≥400 copies/mL past Week 24 but do not meet the definition of virologic failure.
bb. Subjects who discontinue study drug for any reason before Week 48 will be assessed for completion of a documented clinic visit within 90 days of discontinuing study drug (providing consent is not withdrawn).

ABBREVIATIONS

3TC	lamivudine
ABC	abacavir
ADRs	adverse drug reactions
AGEP	acute generalized exanthematous pustulosis
AIDS	acquired immunodeficiency syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ARC	Anticipated Event Review Committee
ART	antiretroviral therapy
ARV	antiretroviral
ASMP	Anticipated Events Safety Monitoring Plan
AST	aspartate aminotransferase
ATV	atazanavir
AV	atrioventricular
β-hCG	human chorionic gonadotropin pregnancy test
BCRP	breast cancer resistance protein
BMD	bone mineral density
BMI	body mass index
BPAP	bilevel positive airway pressure
bpm	beats per minute
BUN	blood urea nitrogen
C	cobicistat
CAD	coronary artery disease
CFR	Code of Federal Regulations
CHD	coronary heart disease
CI	confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CMS	Centers for Medicare & Medicaid services
CNS	central nervous system
COBI	cobicistat
CPAP	continuous positive airway pressure
CYP	cytochrome P450
D	darunavir
D/C/F/TAF	darunavir/cobicistat/emtricitabine/tenofovir alafenamide
DAIDS	Division of AIDS
DBP	diastolic blood pressure
DHHS	Department of Health and Human Services
DRESS	drug rash with eosinophilia and systemic symptoms
DRV	darunavir (formerly known as TMC114)
DTG	dolutegravir (formerly known as S/GSK1349572)
E	elvitegravir
E/C/F/TAF	elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide
E/C/F/TDF	elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate
EC_{50}	50% effective concentration
ECG	electrocardiogram
eCRF	electronic case report form
eDC	electronic data capture
eGFR	estimated glomerular filtration rate
eGFRcreatinine	eGFR for creatinine clearance
ESTD	early study treatment discontinuation
EU	European Union
EVG	elvitegravir
F	emtricitabine
FC	fold change
FDA	Food and Drug Administration

FDC	fixed-dose combination
FTC	emtricitabine
GCP	Good Clinical Practice
GSI	Gilead Sciences, Inc
HAART	highly-active antiretroviral therapy
HBc	hepatitis B core
HBs	hepatitis B surface
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCO_3	bicarbonate
HCV	hepatitis C virus
HDL	high-density lipoprotein
HDPE	high-density polyethylene
HIV	human immunodeficiency virus
HIV-1	human immunodeficiency virus type 1
HIVTSQs	HIV Treatment Satisfaction Questionnaire-status version
HRU	healthcare resource utilization
IAS-USA	International AIDS Society-United States of America
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
ID	identification
IEC	Independent Ethics Committee
IND	Investigational New Drug
INI	integrase
INR	international normalized ratio
IRB	Institutional Review Board
ITT	intent to treat
IV	intravenous
LDL	low-density lipoprotein
LLN	lower limit of normal range
MATE	multi-antimicrobial extrusion protein
MDR1	multidrug resistance protein 1
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
N(t)RTI	nucleoside/nucleotide reverse transcriptase inhibitor
N[t]RTI	nucleoside/nucleotide reverse transcriptase inhibitor
NA	not applicable
NCEP	National Cholesterol Education Program
NN(t)RTI	non-nucleoside/nucleotide reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
OATP	organic anion-transporting polypeptide
PBMCs	peripheral blood mononucleated cells
P-gp	P-glycoprotein
PI	protease inhibitor
PPPM	patient per month
PQC	Product Quality Complaint
PR	protease
PrEP	pre-exposure prophylaxis
PRO	patient-reported outcome(s) (paper or electronic as appropriate for this study)
PT	prothrombin time
PTT	partial thromboplastin time
RAM	resistance-associated mutation
RAPID	Rapid ART Program for Individuals with an HIV Diagnosis
RBC	red blood cell
RNA	ribonucleic acid
RPV	rilpivirine
RT	reverse transcriptase

rtv	ritonavir when used as pharmacokinetic booster
RTV	ritonavir
SBP	systolic blood pressure
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SJS	Stevens-Johnson syndrome
START	Strategic Timing of Antiretroviral Therapy
SUSAR	suspected unexpected serious adverse reaction
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate
TEN	toxic epidermal necrolysis
TFV	tenofovir
TLOVR	time to loss of virologic response
TMC114	Tibotec Medicinal Compound 114 (darunavir)
UGT1A1	uridine diphosphate glucuronosyltransferase 1A1
ULN	upper limit of normal range
USA	United States of America
WBC	white blood cell
WHO	World Health Organization

1. INTRODUCTION

1.1. Study Drug

The darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) fixed-dose combination (FDC) tablet is a 4-agent FDC tablet in development for oral once-daily use for the treatment of human immunodeficiency virus (HIV)-1 infection. This tablet contains the protease inhibitor (PI) darunavir (DRV or D) (800 mg), the pharmacokinetic 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).

Darunavir (PREZISTA®) used with a pharmacokinetic booster is approved for treatment of HIV-1 infection in subjects aged 3 years and above, either as a 600-mg twice-daily treatment for antiretroviral therapy (ART)-experienced subjects or as an 800-mg once-daily treatment for ART-naïve subjects and ART-experienced subjects without DRV resistance-associated mutations (RAMs).[28]

Cobicistat (Tybost®) 150 mg is approved as a pharmacokinetic enhancer of select antiretroviral (ARV) agents requiring the effects of a pharmacokinetic enhancer.[39]

The DRV/COBI 800/150-mg FDC tablet (PREZCOBIX®) is a once-daily treatment approved for use in combination with other ARV agents for treatment of HIV-1 infected treatment-naïve and treatment-experienced adults without DRV RAMs.[27]

Emtricitabine is approved for use in combination with other agents for the treatment of HIV-1 infection in adults and children (4 months of age or older) and is available as a single agent (Emtriva®) or as part of FDCs, including Descovy® (F/TAF).[8,10]

Tenofovir alafenamide is approved as part of FDCs, including Descovy® (FTC/TAF), Genvoya® (elvitegravir [EVG]/COBI/FTC/TAF or E/C/F/TAF), and Odefsey® (rilpivirine [RPV]/FTC/TAF). Descovy® is a once-daily treatment approved for use in combination with other ARV agents (including DRV/COBI) for treatment of HIV-1 infected adults and adolescents (aged 12 years and older).[8,11,23]

The D/C/F/TAF FDC tablet is intended as a complete regimen for the treatment of HIV-1 infection in adults and adolescents (aged 12 years and older) with no mutations known to be associated with resistance to any of the active components. The D/C/F/TAF FDC is currently being studied in 2 ongoing Phase 3 clinical studies (NCT02431247 and NCT02269917).[2]

For the most comprehensive nonclinical and clinical information regarding the study drug, refer to the Investigator's Brochure (IB) for D/C/F/TAF and its addendum.[14,15]

1.2. Background

Human immunodeficiency virus infection is a life-threatening and serious disease that is of major public health interest around the world. In 2015, approximately 36.7 million people were living with HIV-1 worldwide, an estimated 2.1 million people became newly infected with

HIV-1 and 1.1 million died from acquired immunodeficiency syndrome (AIDS)-related causes.[40] The infection, if left untreated or suboptimally treated, is characterized by deterioration in immune function, the subsequent occurrence of opportunistic infections and malignancies, ultimately resulting in death.

Therapeutic strategies for the treatment of HIV-1 disease have been significantly advanced by the availability of highly-active antiretroviral therapy (HAART); the introduction of HAART was associated with a dramatic decrease in AIDS-related morbidity and mortality.[9,21,25]

The primary goal of ART is to prevent HIV-associated morbidity and mortality. This goal is best accomplished by using effective ART to maximally inhibit HIV replication to sustain plasma HIV-1 ribonucleic acid (RNA) (viral load) below limits of quantification. Durable viral suppression improves immune function and overall quality of life, lowers the risk of both AIDS-defining and non-AIDS-defining complications, and prolongs life.[9] Furthermore, high plasma HIV-1 RNA is a major risk factor for HIV transmission, and effective ART can reduce viremia and transmission of HIV to sexual partners by more than 96%.[7,29] Thus, a secondary goal of ART is to reduce the risk of HIV transmission.

Since 2012, the United States (USA) Department of Health and Human Services (DHHS) Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) has recommended initiating ART in all HIV-infected subjects, regardless of $CD4^+$ cell count.[9] More recently, based on findings from 2 large, randomized controlled studies that addressed the optimal time to initiate ART (ie, START [Strategic Timing of Antiretroviral Therapy][13] and TEMPRANO[37]), the Panel increased the strength and evidence rating of this recommendation.

While increased HIV screening efforts have helped identify nearly 85% of 1.2 million people living with HIV in the USA, a significant gap exists in the percentage of subjects who are actively engaged in care (40%), prescribed ART (37%), and those who achieve virologic suppression (30%).[3] Many factors may influence a subject's ability or desire to be engaged in care, and efforts to improve engagement in care are currently being explored as part of the National HIV/AIDS Strategy. One potential intervention to improve engagement in care and potentially the receipt of suppressive ART is the initiation of ART through a Test and Treat model of care.

In traditional care models, before starting ART, it is recommended that healthcare providers assess various patient specific factors, including but not limited to pretreatment HIV RNA level, $CD4^+$ cell count, results of baseline HIV genotypic drug resistance testing, baseline renal and hepatic function, pre-existing medical conditions that could affect or be affected by ART, and regimen-specific considerations such as potential adverse effect profile, a regimen's genetic barrier to resistance, and dosing requirements. While some of these assessments can be made relatively quickly, several require advanced laboratory testing, which can take 2 to 3 weeks for results to become available (particularly HIV genotypic drug resistance testing). Traditional care models often require multiple clinic visits to identify a feasible regimen for subjects, potentially increasing the percentage of subjects who do not return to initiate ART after diagnosis.[9]

Ongoing studies are examining a Test and Treat model of care involving the immediate provision of ART in those subjects newly diagnosed and willing to commit to treatment, typically at the same clinic visit as diagnosis. A recent study randomizing nearly 750 newly diagnosed subjects in Haiti to immediate ART or delayed ART for up to 3 weeks was halted early after a data safety monitoring board detected a 76% increase in rates of virologic suppression and a 65% decrease in the risk of mortality in the group who started ART immediately compared those who delayed ART initation.[17] A similar study (RapIT) is currently ongoing in South Africa.[30] Test and Treat models have also been explored in the developed world, but in smaller patient populations. Pilcher et al, recently compared outcomes of subjects who initiated ART between 2013 and 2014 as parted of a Test and Treat model (n=39), or a traditional model of care (n=47). In this cohort, the median time to suppression was reduced from 4.2 months in the traditional ART group to 56 days, or 1.9 months in subjects managed according to the "Rapid ART Program for Individuals with an HIV Diagnosis (RAPID)" care initiation protocol.[26]

As healthcare providers have less clinical information available to them in a Test and Treat model of care, it is important to consider a regimen's ability to work in the setting of possible resistance, the safety of that regimen, and the subject's ability to adhere to such a regimen.

Currently, the DHHS treatment guidelines recommend baseline genotypic resistance testing for all newly diagnosed subjects before starting ART as 10% to 17% of ART-naïve subjects may have evidence of transmitted drug-resistant HIV strains.[9,46] However, recognizing a potential benefit in initiating treatment sooner in certain populations such as those with acute HIV infection, pregnancy, and opportunistic infections, the DHHS treatment guidelines have provided guidance on ART initiation while awaiting the results of HIV genotypic drug resistance testing, or when resistance testing is not available. In those individuals in whom treatment needs to begin before resistance testing results are available, boosted-DRV may have an important role given the low rate of transmitted PI resistance, its high genetic barrier to resistance, and low rate of treatment-emergent resistance during many years of clinical experience.[9] While genotypic resistance testing is recommended for all newly diagnosed subjects before starting ART, once-daily boosted-DRV may be used in treatment-naïve subjects without conducting baseline genotypic and or phenotypic resistance testing due to its unique resistance profile and due to the very low prevalence of DRV RAMs in treatment-naïve subjects.[27,28] Eleven HIV-1 protease (PR) mutations associated with DRV resistance were previously identified, based on analysis of a pooled dataset of studies in highly treatment-experienced subjects (ie, V11I, V32I, L33F, I47V, I50V, I54L/M, T74P, L76V, I84V, and L89V); the virologic efficacy of DRV (with ritonavir used as pharmacokinetic booster [rtv]) is compromised in the presence of ≥3 DRV RAMs and each of the 11 DRV RAMs is found in association with a median number of 13 to 15 International AIDS Society-United States of America (IAS-USA) PI RAMs.[28] In a recent analysis of nearly 78,000 isolates obtained and submitted in the USA for routine genotypic resistance testing, the prevalence of isolates without DRV RAMs increased consistently from 77.7% in 2006 to 92.8% in 2012, indicating a low prevalence of DRV RAMs.[18] In the same analysis a very low proportion of isolates (2.6%) were identified as having ≥3 DRV RAMs. Additionally, once-daily boosted-darunavir has been extensively studied in treatment-naïve and treatment-experienced subjects with no DRV RAMs.[4,24,36] In treatment-naïve subjects

experiencing virologic failure, boosted-darunavir (either with rtv or COBI) demonstrated a high genetic barrier to resistance, with almost no treatment-emergent primary or DRV RAMs and no loss of DRV susceptibility detected.[24,36]

Another major challenge to effective treatment of subjects with HIV is medication adherence.[5] Despite the successful reduction in the morbidity and mortality associated with human HIV disease since the advent of HAART, a significant proportion of subjects eventually experience loss of virologic, immunologic, or clinical benefit from their current regimens.[25] Incomplete adherence to ARV regimens is a critical factor contributing to treatment failure and the development of viral resistance, and thus a primary barrier to successful long-term treatment. In the HIV-1 infected population receiving ART, total pill burden, dosing frequency, and safety concerns are among the greatest obstacles to achieving adherence.[5,34,35] This is supported by studies in which simple, once-daily HAART regimens demonstrate high levels of adherence and treatment satisfaction resulting in persistent suppression of HIV viral load.[16,20,41]

Co-formulated products help to decrease tablet burden and may increase a subject's ability to adhere to a regimen. Currently, there are only 3 highly effective, once-daily single-tablet regimens approved for the treatment of HIV-1 infection and recommended by the DHHS for treatment-naïve subjects: Genvoya® (or E/C/F/TAF); Stribild® (EVG/COBI/FTC/tenofovir disoproxil fumarate (TDF) or E/C/F/TDF); and Triumeq® (abacavir [ABC]/lamivudine [3TC]/dolutegravir [DTG]).[9] These single-tablet regimens have characteristics that limit their ability to be used in a Test and Treat model of care. Elvitegravir has been noted to have a low genetic barrier to resistance, evidenced by treatment-emergent primary integrase (INI) mutations developing in treatment-naïve subjects who experience virologic failure.[11] Triumeq® contains ABC, which requires human leukocyte antigen (HLA)-B*5701 testing before initiation.[38] Given these limitations, there are no currently available single-tablet regimens that provide a high genetic barrier to resistance and a clinical profile compatible with starting ART in a Test and Treat model of care.

Finally, the safety and tolerability of ARV regimens are critical factors that affect adherence levels. Once-daily boosted-darunavir has been extensively studied in Phase 3 clinical studies. ARTEMIS (AntiRetroviral Therapy with Tibotec Medicinal Compound 114 (TMC114) Examined In naïve Subjects; NCT00258557), a randomized, open-label, Phase 3, 192-week study evaluating the safety and efficacy of once daily DRV/ritonavir (RTV), showed a discontinuation rate due to adverse drug reactions (ADRs) of only 2.3% at 192 weeks. The most common clinical ADRs to DRV/RTV greater than or equal to grade 2 were diarrhea, nausea, rash, headache, abdominal pain, and vomiting.[24] Additionally, in Study 0130, a Phase 3b open-label, single-arm study designed to evaluate the safety, tolerability, efficacy, and pharmacokinetics of COBI-boosted DRV in HIV-1 infected adults (as single agents) in combination with 2 fully active, investigator-selected nucleoside/nucleotide reverse transcriptase inhibitors (N[t]RTIs), ADRs associated with DRV + COBI evaluated through Week 24 or 48 did not differ substantially from those reported in clinical studies with DRV/RTV.[36] Ongoing Phase 3 studies are evaluating the efficacy and safety profile of D/C/F/TAF.[2] The combination of D/C/F/TAF is not anticipated to exacerbate known toxicities or lead to new toxicities compared

with DRV/COBI FDC coadministered with FTC/TDF FDC. TAF and FTC have established clinical safety profiles with no significant toxicities observed.

Given these factors, the single-tablet regimen of D/C/F/TAF may serve as an ideal regimen for a Test and Treat model of care, combining potency, sustained efficacy, a high genetic barrier to resistance, with a well described safety profile of the individual components, and practical, convenient dosing.

1.2.1. Darunavir (PREZISTA®)

Darunavir (formerly known as TMC114) is an inhibitor of the catalytic activity of HIV-1 protease with potent in vitro antiviral activity against both wild-type and PI-resistant HIV-1 strains. Darunavir has a high genetic barrier to the development of resistance, resulting in continued antiviral activity against a large panel of viruses resistant to currently licensed PIs.

Darunavir has been developed by the sponsor as tablets at different strengths and as an oral suspension. In combination with low-dose rtv as a pharmacokinetic booster and other ARVs, it has shown significant efficacy in treatment-naïve and treatment-experienced patients. Darunavir, in combination with other ARVs, is currently indicated for the treatment of HIV-1 infection in adults and pediatric patients aged 3 years and older, in either a twice daily regimen with rtv or a once daily dosing regimen, with either rtv or COBI. The once daily regimens are approved only for use in treatment-naïve patients and treatment-experienced patients who have no DRV RAMs. COBI-boosted DRV is only approved for use in adults.

Darunavir was first registered in the USA (June 2006) and has obtained marketing authorization in the European Union (EU) in February 2007. As of 23 December 2014, DRV was registered in more than 99 countries around the world. Adverse drug reactions identified during postmarking experience were: drug hypersensitivity, angioedema, urticaria, osteonecrosis, toxic epidermal necrolysis (TEN), acute generalized exanthematous pustulosis (AGEP), and drug rash with eosinophilia and systemic symptoms (DRESS).

In treatment-naïve and treatment-experienced patients with no DRV RAMs, the recommended dose of DRV is 800 mg taken with a booster once daily and with food. This dose recommendation is generally safe and well tolerated. The majority of the DRV ADRs reported in the Phase 3 studies during treatment with DRV/rtv and NRTIs were mild in severity. In ART-naïve HIV-1 infected adult subjects (343 subjects, total exposure of 1,072 patient years), the most frequent (≥5%) ADRs of moderate to severe (grade 2 to 4) intensity with DRV/rtv 800/100 mg once daily were diarrhea, headache and abdominal pain. Only 2.3% of the subjects discontinued DRV treatment due to ADRs. Frequency, type and severity of ADRs in pediatric patients were comparable to those observed in adults.

1.2.2. Cobicistat (Tybost®)

Cobicistat (formerly known as GS-9350) is a structural analog of rtv that has been shown to be a potent inhibitor of cytochrome P450 (CYP) 3A enzymes. Cobicistat has been shown to be a more specific, mechanism-based CYP3A inhibitor than rtv. Cobicistat displays weak to minimal inhibition of other CYP enzymes; it is a less potent inducer of other metabolizing enzymes in

vitro, and has been shown to have less potential for clinically significant drug interactions via non-CYP3A pathways. In addition, COBI is devoid of anti-HIV activity and may have fewer adverse biochemical effects (eg, effect on adipocyte functions such as lipid accumulation) than rtv.

Cobicistat, as a single 150-mg tablet, has been developed by Gilead Sciences, Inc (GSI) and is approved for once daily use in adults as a pharmacokinetic enhancer to increase systemic exposure levels of coadministered drugs metabolized by CYP3A, including PIs such as DRV and atazanavir (ATV) for the treatment of HIV-1 infection. Cobicistat has also been coformulated with other HIV-1 ARV drugs in several FDCs such as DRV/COBI (codeveloped by GSI and the sponsor), ATV/COBI (codeveloped by GSI and Bristol-Myers Squibb), a combination tablet containing EVG boosted with COBI, and FTC + TDF (or E/C/F/TDF, by GSI) for use in HIV-1-infected, ART-naïve patients. As part of these FDCs, COBI has shown to inhibit CYP3A-mediated metabolism of EVG, ATV, and DRV similar to rtv. The FDC DRV/COBI (PREZCOBIX™/REZOLSTA®) has recently been approved in Canada, Europe and the United States, and is indicated in combination with other ARV medicinal products for the treatment of HIV-1 infection in adults aged 18 years or older.

The efficacy and safety of COBI have been established in the pivotal Phase 3 Study GS-US-216-0114 and the supportive Phase 2 Study GS-US-216-0105. Both of these studies were double-blind and active-controlled studies with combination ARV regimens in ART-naïve subjects with HIV-1 infection, and both studies were designed to compare COBI-boosted ATV with rtv-boosted ATV in combination with FTC and TDF. In addition, study GS-US-216-0130 demonstrated the safety and efficacy of COBI with DRV dosed in a once daily regimen combined with a backbone therapy of 2 NRTIs in HIV-1 infected, ART-naïve and treatment-experienced adults with no DRV RAMs.

In the clinical studies to date, COBI 150-mg tablets, dosed daily for up to 60 weeks, were generally well tolerated, did not cause clinically significant toxicities in humans that were identified in nonclinical testing (heart, liver, thyroid abnormalities, and decreased immunoglobulin G levels), and did not potentiate the side effects of the coadministered ARV medications. In Phase 2 clinical studies (GS-US-216-0105 and GS-US-236-0104), small (approximately 12% to 15%) decreases in estimated glomerular filtration rate (eGFR) calculated using the Cockcroft-Gault calculation occurred within the first few weeks of COBI initiation (in GS-US-216-0105, the decreases were comparable to those associated with rtv in the comparator group).

A Phase 1 study of the effect of COBI on eGFR was performed by measuring iohexol clearance in healthy subjects. Results indicated that COBI produces small increases in serum creatinine translating into decreases in eGFR, but not affecting actual GFR, as measured by iohexol clearance. The data suggest that COBI blocks secretion of serum creatinine, resulting in a difference between eGFR and actual GFR, as seen with several other drugs that are currently approved, including trimethoprim and cimetidine. The increase in serum creatinine with COBI occurs within days of drug initiation and is reversible with values returning to baseline within days of cessation of COBI.

1.2.3. Emtricitabine (Emtriva®)

Emtricitabine is an NRTI for the treatment of HIV-1 infection, in combination with other ARVs, in adults and pediatrics patients aged 3 months and older. Emtricitabine has been developed by GSI and is marketed as a once-daily capsule (200 mg) and as an oral solution (10 mg/mL). It is a synthetic analogue of the naturally occurring pyrimidine 2′-deoxycytidine. Intracellularly, FTC is phosphorylated by cellular enzymes to form the active metabolite, emtricitabine triphosphate.

Since first marketing authorization in the United States (July 2003), FTC obtained marketing authorization in the EU, and also Argentina, Israel, Switzerland, Mexico, Australia, Japan, New Zealand, and Canada. The registration of FTC for the treatment of HIV-1 infection in adults and pediatric patients less than 18 years of age was supported by an extensive program of clinical studies in healthy subjects and HIV-infected subjects, which provided detailed assessments of its pharmacokinetics, pharmacodynamics, potential drug-drug interactions, and clinical efficacy and safety. Emtricitabine has also been coformulated with other HIV-1 ARV drugs in several FDCs such as EVG/FTC/TDF, E/C/F/TDF, and FTC/TDF (see below).

1.2.4. Tenofovir Alafenamide

Tenofovir alafenamide (also known as GS-7340) is a second generation oral prodrug of TFV, a nucleotide analog that inhibits HIV-1 reverse transcription, developed by GSI. TAF has been coformulated with other ARVs, such as E/C/F/TAF and F/TAF (developed by GSI) and D/C/F/TAF (codeveloped by GSI and the sponsor), for the treatment of HIV-1 infection because of its potential for enhanced distribution of TFV into peripheral blood mononucleated cells (PBMCs) and to lymphatic organs following oral administration. This provides the possibility for using a low dose and to reduce systemic TFV concentrations, resulting in lower potential for adverse effects (including renal and bone toxicity) without compromising antiviral activity. Based on nonclinical data, the clinical safety and resistance profile for TAF is expected to be similar to that characterized for TDF.

Following its release from the TAF prodrug, TFV is metabolized intracellularly to the active metabolite, TFV-diphosphate, a competitive inhibitor of HIV-1 reverse transcriptase (RT), thereby effectively blocking the replication and spread of infectious HIV-1. The in vitro activity of TAF against HIV-1 in various human immune cell types is 100- to 600-fold greater than that of TFV and 4- to 6-fold greater than that of TDF.

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

1.3. Overall Rationale for the Study

The goals of this study are to assess the efficacy and safety of D/C/F/TAF in newly diagnosed HIV-1 infected subjects starting ART in a Test and Treat model.

Thus far, only a few studies have examined Test and Treat models of HIV care. Most studies that have been completed or are ongoing are limited to the developing world, and conducted with regimens that are not recommended by the DHHS Treatment Guidelines.[9] Differences in screening, healthcare system administration, treatment guidelines, and treatment regimens may

affect the applicability of these studies to newly diagnosed HIV-1 infected subjects in the United States and other developed nations. As the D/C/F/TAF FDC is still being examined in Phase 3 clinical studies, no evidence currently exists using D/C/F/TAF FDC in a Test and Treat model. Given these factors, findings from this study will be used to generate data on the efficacy and safety profile of D/C/F/TAF FDC in newly diagnosed HIV-1 infected, treatment-naïve subjects using a Test and Treat model of care.

2. OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

2.1. Objectives and Endpoints

2.1.1. Objectives

Primary Objective

The primary objective of this study is to assess the efficacy of D/C/F/TAF FDC in a Test and Treat model of care in newly diagnosed HIV-1-infected, treatment-naive subjects as determined by the proportion of virologic responders defined as having HIV-1 RNA <50 copies/mL at Week 48 (Food and Drug Administration [FDA]-defined intent to treat [ITT] snapshot analysis).

Secondary Objectives

The secondary objectives of this study are:

- To assess virologic and immunologic changes in the study population through 12, 24, and 48 weeks of treatment
- To evaluate the incidence of grade 3 and 4 adverse events, serious adverse events, and premature discontinuations due to adverse events through 24 and 48 weeks of treatment, and during the extension phase
- To evaluate the frequency of discontinuation of D/C/F/TAF FDC due to protocol-specific stopping rules (refer to Section 3.1)
- To assess baseline viral resistance in the study population
- To assess the development of viral resistance in the study population through 24 and 48 weeks of treatment, and during the extension phase
- To assess the proportion of subjects retained in care after discontinuation of study drug before Week 48
- To evaluate the influence of various intrinsic and extrinsic factors on retention in care
- To assess the proportion of subjects lost to follow-up through 24 and 48 weeks of treatment
- To evaluate adherence by pill count to D/C/F/TAF FDC in the study population through 24 and 48 weeks of treatment
- To evaluate adherence by subject self-report, using a 4-day recall period through Weeks 24 and 48
- To describe predictors of suboptimal adherence (<95% adherence by pill count) in the study population

- To assess the HIV Treatment Satisfaction Questionnaire-status version (HIVTSQs) at Weeks 4, 24, and 48
- To evaluate healthcare resource utilization (HRU) and cost and their temporal trends in the study population through 48 weeks of treatment

2.1.2. Endpoints

Primary Endpoint

The primary endpoint of this study is the proportion of subjects who have HIV-1 RNA <50 copies/mL at Week 48 as defined by the FDA snapshot analysis (ITT).

Secondary Endpoints

The secondary endpoints of this study are:

Efficacy

- Change from baseline in $\log_{10}$ HIV-1 RNA viral load at Weeks 2, 4, 8, 12, 24, 36, and 48
- Proportion of subjects who have HIV-1 RNA <50 copies/mL at Week 24
- The change from baseline in $CD4^+$ cell count at Weeks 12, 24, and 48

Safety

- Proportion of subjects that required discontinuation after enrollment based on safety stopping rules (refer to Section 3.1)
- Proportion of subjects discontinuing therapy due to adverse events
- Proportion of subjects experiencing grade 3 and 4 adverse events
- Proportion of subjects experiencing grade 3 and 4 laboratory abnormalities

Resistance

- Proportion of subjects meeting resistance stopping rules (refer to Section 3.1), requiring discontinuation of study drug due to baseline resistance findings
- Proportion of subjects with baseline PR, RT, and INI RAMs
- Proportion of subjects developing RAMs and loss of phenotypic susceptibility, when available, upon meeting protocol-defined virologic failure
- Proportion of subjects with protocol-defined virologic failure at Week 24 and Week 48, and during the extension phase

Retention in Care

- Proportion of subjects lost-to-follow-up throughout the 48 weeks of treatment
- Proportion of subjects discontinuing study drug for any reason other than withdrawal of consent prior to Week 48 who have a documented clinic visit with a healthcare provider within 90 days of discontinuing study drug

Adherence

- Adherence rates by pill count at Weeks 4, 8, 12, 24, 36, and 48
- Adherence rates by subject self-report, using a 4-day recall at Weeks 4, 8, 12, 24, 36, and 48

Tolerability/Patient-reported Outcomes

- Mean total scores for the HIVTSQs at Weeks 4, 24, and 48[12]

Healthcare Resource Utilization/Pharmacoeconomics

- The number and duration of hospitalizations, number and type of outpatient visits, number of emergency room visits, and number and type of medications used (both HIV-related and All-cause as assessed by the investigator) throughout the main study period
- Direct medical costs will be calculated in USA dollars based on HRU noted above

Refer to Section 9, Study Evaluation, for evaluations related to endpoints.

2.2. Hypothesis

No formal hypothesis will be tested. The findings from this study will be used to generate data on the efficacy and safety profile of D/C/F/TAF FDC in newly diagnosed HIV-1 infected, treatment-naïve subjects using a Test and Treat model of care.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a single-arm, open-label, prospective, multicenter Phase 3 study to assess the efficacy and safety of D/C/F/TAF FDC in newly diagnosed (ie, within 2 weeks of the screening/baseline visit [Day 1]) HIV-1 infected treatment-naïve subjects at least 18 years of age as part of a Test and Treat model of care in the USA.

A target of approximately 100 subjects will participate in this study.

After obtaining informed consent, a blood sample will be collected for central laboratory testing. The in- and exclusion criteria will be reviewed to confirm the subject's eligibility. The screening/baseline visit (Day 1) should take place no later than 2 weeks following evidence of newly documented HIV-1 infection.

Study drug will be dispensed before the results from the screening/baseline safety and resistance laboratory tests are available. Subjects will receive treatment in a single-arm open-label fashion as follows:

- **D/C/F/TAF: DRV 800 mg + COBI 150 mg + FTC 200 mg + TAF 10 mg FDC**

Subjects must start treatment within 24 hours of the screening/baseline visit.

Following initiation of treatment, a safety assessment will be performed by the investigator at Day 3 +1 week, or as soon as the final screening/baseline laboratory report becomes available.

Subjects meeting any of the below safety stopping rules (based on the receipt of the screening/baseline laboratory findings) will be contacted to return to the study site for possible early study treatment discontinuation (ESTD) and for additional follow-up.

- Estimated glomerular filtration rate (eGFR) according to the Modification of Diet in Renal Disease (MDRD[19,22,33]) formula <50 mL/min.
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥2.5×upper limit of normal (ULN)
- Serum lipase ≥1.5×ULN
- Positive serum human chorionic gonadotropin pregnancy test (β-hCG) for women of childbearing potential
- Laboratory results that the investigator believes should result in discontinuation of study medication (Note: It is recommended that the investigator contacts the sponsor's medical monitor to discuss the discontinuation)
- Subjects identified with active hepatitis C virus (HCV) infection that in the opinion of the investigator requires HCV treatment immediately or expected to be needed during the course of the study with agents not compatible with D/C/F/TAF FDC.

Retesting of abnormal screening/baseline safety laboratory values noted above will be allowed once. Retesting will take place during an unscheduled visit.

The investigator will review the ARV screening/baseline resistance data at Week 4 ±7 days or sooner, depending on the availability of the screening/baseline HIV genotypic drug resistance testing results from the central laboratory. Subjects who do not show full sensitivity to all drugs in the FDC study regimen according to the susceptibility assessment in the GenoSure Prime® report will be contacted to return to the study site for ESTD. Subjects with identified resistance to lamivudine/FTC, attributed to the presence of the M184I/V mutation alone will be permitted to remain in the study.

Subjects will be treated for 48 weeks in the main study period and will return to the site for visits at Weeks 2, 4, 8, 12, 24, 36, and 48. Assessment of drug accountability and reasons for non-adherence, and recording of concomitant therapies, adverse events, vital signs (including the subject's body weight), and physical examinations (complete or symptom-directed) will be performed at each visit from baseline onwards. Laboratory evaluations for efficacy and safety (HIV-1 viral load, biochemistry, hematology, and urinalysis) will be performed at all study visits. $CD4^+/CD8^+$ cell count will be assessed at Weeks 4, 8, 12, 24, 36, and 48. Patient-reported outcome (PRO) measures will be assessed at Weeks 4, 24, and 48 using the validated 10-item HIVTSQs (Version 2006)[12] (Attachment 7). Medical resource utilization data will be collected from all subjects throughout the main study period.

Subjects who are on study drug and who experience a protocol-defined virologic failure (see below) will undergo genotypic and phenotypic resistance testing, preferably at the time of the confirmed virologic failure visit if the HIV-1 RNA is ≥400 copies/mL. If resistance testing is not able to be performed at the time of confirmed virologic failure, resistance testing may be

performed at the point of unconfirmed virologic failure or a later time point if HIV-1 RNA is ≥400 copies/mL. Subjects who have persistent HIV-1 RNA ≥400 copies/mL past Week 24 but do not meet the definition of virologic failure, should have their viral load monitored closely, and if appropriate undergo genotypic and phenotypic resistance testing. In case resistance to study drugs is observed, the subject may be discontinued from the study at the investigator's discretion. If the investigator makes the decision that the subject can continue in the study, additional resistance testing may be performed as deemed necessary. Protocol defined virologic failure is not considered a stopping rule.

Virologic failure will be defined in this study as follows:

- Virologic Nonresponse:
  - HIV-1 RNA <1 $\log_{10}$ reduction from baseline, *AND*
    HIV-1 RNA ≥400 copies/mL at the Week 12 visit, subsequently confirmed at an unscheduled visit conducted within 2 to 4 weeks after Week 12
- Virologic Rebound:
  - At any visit, after achieving confirmed consecutive HIV-1 RNA <50 copies/mL, a rebound in HIV-1 RNA to ≥50 copies/mL, which is subsequently confirmed at a scheduled or unscheduled visit conducted within 2 to 4 weeks of the HIV-1 RNA result; *OR*
  - At any visit, a >1 $\log_{10}$ increase in HIV-1 RNA from the nadir, which is subsequently confirmed at the following scheduled or unscheduled visit conducted within 2 to 4 weeks of the HIV-1 RNA result.

Subjects who meet the criteria for protocol-defined virologic failure will be managed according to the schema provided in Attachment 1.

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

Subjects who prematurely discontinue study treatment during the open-label treatment period will be required to complete ESTD assessments as soon as possible but no later than 1 week of discontinuing study treatment.

In addition, a follow-up visit is required for any subject who has an ongoing adverse event or serious adverse event at the time of his/her last study visit. These subjects are required to return to the site 30 days (±7 days) after completion of the last study-related visit (unless consent is withdrawn).

Subjects who have completed the Week 48 visit will be given the opportunity to continue D/C/F/TAF treatment during an extension period until the D/C/F/TAF FDC tablet becomes commercially available and is reimbursed, or can be accessed through another source, or until the sponsor terminates clinical development. At Week 48 the investigator should dispense a sufficient supply of D/C/F/TAF to maintain continuity of care for the subject, however no more

than 12 weeks of study medication should be dispensed. If a subject requires more than 12 weeks of study medication, the subject should return to the site for additional drug dispensation.

During the extension period, subjects will have a study visit at the site once every 6 months, if applicable, and complete the procedures indicated in the Time and Events Schedule, and additionally at the time of transition to commercial D/C/F/TAF, for final data collection.

At the end of the study (or at ESTD), subjects will resume routine clinical care with their care provider who will determine the future care of that subject. In anticipation of transitioning the subject to routine clinical care at the end of the study (or early discontinuation), the investigator should take steps to ensure a smooth transition (ie, secure insurance etc.) well in advance of the final study visit, so that the subjects' ART is not interrupted.

For those subjects discontinuing therapy before Week 48, the investigator will be asked to monitor the subject's retention in care defined as having one documented clinic visit within 90 days of discontinuing the study treatment (unless consent is withdrawn).

The end of the study is defined as completion of the last data collection visit for the last subject participating in the study. For the purpose of the primary analysis, a subject will be considered to have completed the study if data collection as required per protocol through the complete course of 48 weeks of ART has been completed.

An interim analysis will be conducted after the last subject enrolled has been assessed for safety at Day 3, and for resistance stopping rules at Week 4.

The primary analysis of this study will be performed once all subjects have completed the Week 48 visit and the 30-day follow-up visit (if applicable), or discontinued earlier.

3.2. Study Design Rationale

Study Period

A treatment duration of 48 weeks is chosen to align with the traditional efficacy endpoint of previous clinical studies in treatment-naïve subjects. This is the minimal duration of time required to provide clinically relevant results regarding the efficacy and safety of this regimen in this patient population. To assure continued follow-up of the study participants and gain further safety information, subjects who prematurely discontinue study treatment will be asked to attend the ESTD (and an additional follow-up visit, if applicable). In order to maintain continuity of care, subjects will be given the opportunity to continue D/C/F/TAF treatment after Week 48 during an extension period, until the D/C/F/TAF FDC tablet becomes commercially available and is reimbursed, or can be accessed through another source, or until the sponsor terminates clinical development.

Dose Selection

Darunavir 800 mg boosted by COBI 150 mg, and FTC 200 mg in the D/C/F/TAF FDC tablet represent the marketed doses. The dose of TAF 10 mg in the D/C/F/TAF FDC tablet is the study

selected dose expected to attain TAF plasma concentrations in range of those demonstrated to show potent antiviral activity with TAF as a stand-alone agent, and TFV plasma concentrations that are considerably lower than those obtained with TDF. A TAF 10 mg dose is also being used for other TAF regimens including a pharmacoenhancer (rtv or COBI), currently in development. The proof-of-concept study GS-US-120-0104 evaluated 3 doses of TAF monotherapy (8, 25, and 40 mg once daily) and demonstrated potent antiviral activity in HIV-1 patients, with mean (±SD) change from baseline in HIV-1 RNA of -0.95±0.45, -1.53±0.40, -1.7±0.22 $\log_{10}$ copies/mL at TAF 8, 25, 40 mg once daily, respectively (data unblinded only at dose level; TAF dosed for 10 days).[15] Administration of TAF 25 mg in the presence of DRV/COBI resulted in approximately 3-fold higher than historical TFV exposures following administration of TAF 25 mg alone (GS-US-120-0104, GS-US-292-0101, and GS-US-292-0103).[15] GS-US-299-0101 was a Phase 1, healthy-volunteer, adaptive-design, multiple-dose study that evaluated the bioavailability of 3 formulations of a D/C/F/TAF FDC tablet. The results indicated that the D/C/F/TAF 25 mg tablet formulations provided TAF exposures in a range associated with antiviral activity (GS-US-120-0104) and consistent with the findings from study GS-US-311-0101 (Cohorts 2 and 3), where DRV/COBI was coadministered with FTC/TAF 25 mg. The pharmacokinetic data also demonstrated achievement of TAF exposures that were associated with potent antiviral activity with the D/C/F/TAF 10 mg (monolayer formulation) tablet, and moreover TFV exposures with this formulation were in the range of historical data with TAF 25 mg dosed alone or with the E/C/F/TAF 10 mg tablet. In addition, administration of the D/C/F/TAF 10 mg tablet resulted in ~90% lower steady-state TFV exposure versus COBI-boosted DRV plus FTC/TDF. Exposures of COBI-boosted DRV and FTC were comparable when administered as a single D/C/F/TAF tablet or as individual components. Study GS-US-299-0101 also evaluated the relative bioavailability of DRV, COBI, FTC, and TFV when administered as COBI-boosted DRV plus FTC/TDF relative to the administration of the individual components. Results showed that the exposures of all analytes were similar between both treatments. Thus, cumulative results from studies GS-US-120-0104, GS-US-311-0101 and GS-US-299-0101 were used in selecting a 10 mg TAF dose for subsequent clinical development of the D/C/F/TAF FDC tablet.

Toxicity Management

The combination of D/C/F/TAF is not anticipated to exacerbate known toxicities or lead to new toxicities. Measures and guidelines for the monitoring and management of specific toxicities with DRV, COBI, FTC, or TAF are included in Section 9.8 of this protocol. The presented toxicity management guidelines are applicable throughout the entire study starting from baseline through the 48-week main study period and through the extension period (or ESTD and an additional follow-up visit, if applicable).

Medical Resource Utilization and Health Economics Data Collection

Treatment of HIV-1 infection with D/C/F/TAF may result in a change in medical resource utilization from baseline over the duration of the study.

Medical resource utilization data as defined in Section 9.4 will be collected throughout the main study period. Additionally, costs will be assigned to type of HRU to calculate a per subject per

month cost associated with the initiation and maintenance of ART. These outcome measures are being examined as part of this study to ensure they are captured as accurately as possible, in a prospective fashion. Previous retrospective data have demonstrated a decrease in overall medical resource utilization with the initiation of a boosted-darunavir based regimen.[45] While there is no comparator arm in this study, the inclusion of these endpoints as part of this study will help describe if similar observations are seen in a prospective cohort starting treatment on D/C/F/TAF. The data can also provide input for future economic modeling analysis.

Similarly, this study aims to describe changes in PRO assessed by the 10-item HIVTSQs throughout the main study period (ie, Weeks 4, 24, and 48). Satisfaction with HIV therapy is being evaluated more frequently in HIV clinical studies. The HIVTSQ was designed specifically to measure satisfaction with medication for people infected with HIV.[43,44] In FLAMINGO, an open-label comparative study of DRV and DTG in combination with NRTIs, improvements in HIVTSQ score from baseline was observed over a 48-week period.[6] While this study itself is non-comparative, the aim is to describe changes in patient satisfaction as a result of starting treatment with D/C/F/TAF.

4. SUBJECT POPULATION

Screening for eligible subjects will be performed within 2 weeks following evidence of newly documented HIV-1 infection. The screening and baseline assessments should preferably be completed the same day (Day 1), but if necessary, can be performed on different days, but must be completed within 2 business days of signing the ICF. Study drug should not be dispensed until all screening procedures have been completed and the investigator has determined that the subject meets the inclusion/exclusion criteria.

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following 2 subsections. If there is a question about the inclusion or exclusion criteria below, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a subject in the study. Waivers are not allowed.

4.1. Inclusion Criteria

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

1. Sign an informed consent form (ICF) indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study.
2. Man or woman at least 18 years of age.
3. Newly diagnosed with HIV-1 evidenced by any of the following within 2 weeks of the screening/baseline visit:
    - HIV Rapid Antibody positive*; *OR*
    - HIV Immunoassay positive; *OR*
    - Positive p24 antigen and a HIV-1 RNA viral load ≥5,000 copies/mL; *OR*
    - Non-reactive HIV-1 antibody/antigen assays and HIV-1 RNA viral load ≥5,000 copies/mL. HIV-1 RNA viral load must be confirmed once within 1 week

of initial HIV-1 RNA viral load test.

* For those subjects testing initially positive on a 4th generation HIV Rapid Antibody Assay, results should be confirmed on a 3rd generation HIV Rapid Antibody Assay at a minimum, or an HIV Immunoassay, unless the investigator suspects acute or recent infection.

4. Antiretroviral treatment-naïve, except for the use of TRUVADA® for pre-exposure prophylaxis (PrEP).

5. Contraceptive use by men or women should be consistent with the local regulations regarding the use of contraceptive methods for subject participating in clinical studies.

   A woman must be either:

   - Postmenopausal for at least 2 years (medical documentation of cessation of menses for at least 2 years and of hormonal ovarian failure [follicle-stimulating hormone (FSH) level ≥40 mIU/mL] is required); *OR*
   - Surgically sterile (had total hysterectomy or bilateral oophorectomy, tubal ligation/bilateral tubal clips without reversal operation, or otherwise incapable of becoming pregnant); *OR*
   - Not heterosexually active for the duration of the study; *OR*
   - Have a vasectomized partner; *OR*
   - If of childbearing potential and heterosexually active, practicing a highly effective method of birth control (as specified below) before entry, and agree to continue to use a highly effective method of contraception throughout the study, and for at least 90 days after receiving the last dose of study drug. Women with tubal ligation are required to use one additional contraceptive method.
   - Estrogen-based hormonal contraception may not be reliable when taking the study drug. Therefore, to be eligible for this study, women of childbearing potential should either use:
     - a double-barrier method (male condom + either diaphragm or cervical cap); *OR*
     - non-estrogen hormonal based contraceptives in combination with a barrier contraceptive (male condom, diaphragm or cervical cap, or female condom); *OR*
     - intrauterine device in combination with a barrier contraceptive (male condom, diaphragm or cervical cap, or female condom).

   Note: A male condom and female condom should not be used together due to risk of breakage or damage caused by latex friction.

6. A woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for 90 days after receiving the last dose of study drug.

7. A woman of childbearing potential must have a negative urine pregnancy test at screening.

8. Men with a female partner of childbearing potential must agree to use adequate reliable contraceptive methods (see also Inclusion Criterion 5) during the study until 90 days

after receiving the last dose of study drug

- Men who have had a vasectomy without reversal operation minimally 2 months prior to screening are not required to use birth control methods.
- For all male subjects, it is the responsibility of the subject to ensure that his partner(s) do(es) not become pregnant during treatment with the study drug and for up to 90 days after receiving the last dose of study drug.

9. Men must agree not to donate sperm during the study until 90 days after receiving the last dose of study drug (or longer, if dictated by local regulations).
10. Must be able to swallow whole tablets.

4.2. Exclusion Criteria

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

1. Known active cryptococcal infection, active toxoplasmic encephalitis, *Mycobacterium tuberculosis* infection, or another AIDS-defining condition that in the judgement of the investigator would increase the risk of morbidity or mortality.
2. Known history of clinically relevant hepatic disease or hepatitis that in the investigator's judgement is not compatible with D/C/F/TAF FDC.
3. Known history of cirrhosis as diagnosed based on local practices.
4. Known history of chronic (≥3 months) renal insufficiency, defined as having an eGFR <50 mL/min according to the MDRD formula.
5. Pregnant, or breast-feeding, or planning to become pregnant while enrolled in this study or within 90 days after the last dose of study treatment.
6. Plans to father a child while enrolled in this study or within 90 days after the last dose of study treatment.
7. Current alcohol or substance use judged by the investigator to potentially interfere with subject study adherence.
8. Known history of malignancy within the past 5 years or ongoing malignancy other than cutaneous Kaposi's sarcoma, basal cell carcinoma, or resected, noninvasive cutaneous squamous carcinoma.
9. Known active, severe infections (other than HIV-1 infection) requiring parenteral antibiotic or antifungal therapy within 30 days prior to screening.
10. Any other condition or prior therapy for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.
11. Subject unlikely to comply with the protocol requirements, based on clinical judgment.
12. Received an investigational drug (including investigational vaccines) or used an invasive investigational medical device within 90 days before the planned first dose of study treatment or is currently enrolled in an investigational study without prior approval from the sponsor.

13. Subjects receiving ongoing therapy with contraindicated, not recommended, drugs that cannot be adequately dose-adjusted, or subjects with any known allergies to the excipients of the D/C/F/TAF FDC.[14,15]

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

4.3. Prohibitions and Restrictions

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

1. Refer to Section 8, Prestudy and Concomitant Therapy, for details regarding prohibited and restricted therapy during the study.
2. Agree to follow all requirements that must be met during the study as noted in the Inclusion and Exclusion Criteria (eg, contraceptive requirements) in Sections 4.1 and 4.2.
3. All HIV-infected subjects should be advised to take the necessary precautions to reduce the risk of transmitting HIV.

5. TREATMENT ALLOCATION AND BLINDING

Treatment Allocation

As this is single-arm study, randomization is not applicable. All subjects will receive the same treatment.

Blinding

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

6. DOSAGE AND ADMINISTRATION

At the screening/baseline visit (Day 1), eligible subjects will start treatment with D/C/F/TAF FDC in a single-arm open-label fashion. All subjects will receive treatment as follows:

- **D/C/F/TAF FDC: DRV 800 mg + COBI 150 mg + FTC 200 mg + TAF 10 mg FDC**

Initiation of study treatment can only start after all screening/baseline tests and procedures have been completed and must take place within 24 hours after the baseline visit. D/C/F/TAF FDC must be taken orally with food. All subjects will be counseled to swallow D/C/F/TAF whole once daily at approximately the same time each day, according to their preference.

Study-site personnel will instruct subjects on how to store study drug for at-home use as indicated for this protocol.

If subjects notice that they have missed a medication intake and it is still within 12 hours of their regular dosing time, they should take the medication immediately with food. Subjects can then

continue their usual dosing schedule. If subjects notice that they have missed a dose more than 12 hours after the time it is usually taken, they should be instructed not to take it and simply resume the usual dosing schedule. Subjects should not take a double dose to make up for a missed dose.

Instructions regarding how to take the study drug, what to do if a dose is missed and how to store the medication will be provided on the wallet (study) card (refer to Section 12.3.1).

The last time of study drug administration will be recorded at each visit.

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

In order to maintain continuity of care, subjects will be given the opportunity to continue the D/C/F/TAF treatment after Week 48 during an extension period until the D/C/F/TAF FDC tablet becomes commercially available and is reimbursed, or can be accessed through another source, or until the sponsor terminates clinical development.

7. TREATMENT COMPLIANCE

Adherence to study treatment will be assessed by pill counts and by subject self-report, using a 4-day recall period. Subjects will be requested to bring unused medication and empty packaging to the study site at each visit, and the amount of study drug dispensed will be compared with the amount returned, and taking into account the period elapsed since the previous visit.

The investigator/designated study-site personnel will maintain a log of all study drug dispensed and returned. Drug supplies for each subject will be inventoried and accounted for throughout the study (see also Section 14.5, Drug Accountability). If a subject's medication intake is not according to the study protocol, it will be the investigator's responsibility to take the necessary measures to ensure future compliance to the protocol.

If non-adherence is identified during drug accountability the reasons for non-adherence will be captured in the electronic case report form (eCRF).

8. PRESTUDY AND CONCOMITANT THERAPY

Prestudy therapies administered up to 30 days before the first dose of study drug must be recorded at screening.

All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; non-pharmacologic therapies such as electrical stimulation, acupuncture, special diets, exercise regimens) different from study drug must be recorded in the eCRF. Recorded information will include a description of the type of drug, treatment period, dosing regimen, route of administration, and its indication. Modification of an effective pre-existing therapy should not be made for the explicit purpose of entering a subject into the study if such

modification of treatment is not clinically acceptable. Any change in dosage of the medication must be reported in the eCRF.

For any concomitant therapy given as a treatment for a new condition or for a worsening of an existing condition occurring after signing of the ICF, the condition must be documented in the Adverse Event/HIV-related event section of the eCRF.

Data on concomitant therapies will be collected up to the last study visit. Concomitant therapies should be recorded beyond the last study visit only in conjunction with the treatment of serious adverse events that meet the criteria outlined in this protocol.

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

Contraindicated and Disallowed Concomitant Agents

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

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

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

Tenofovir alafenamide is a substrate of the efflux transporter P-gp. Drugs that induce P-gp activity are expected to decrease the absorption of TAF, resulting in decreased plasma concentrations of TAF, which may lead to loss of therapeutic effect of D/C/F/TAF FDC and development of resistance. These medicinal products include antimycobacterials (rifabutin,

rifampin, rifapentine) and anticonvulsants (carbamazepine, oxcarbazepine, phenobarbital, phenytoin). Coadministration of D/C/F/TAF FDC with drugs that inhibit P-gp may increase the absorption and plasma concentration of TAF.

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

Administration of any of the contraindicated or disallowed concomitant medication must have been discontinued at least 30 days before the screening/baseline visit (Day 1) and for the duration of the study. If such discontinuation of treatment is not clinically acceptable, the subject should not be allowed to participate in the study.

ART beyond study drug is also prohibited during the study.

Should a subject have a need to initiate treatment with any excluded concomitant medication, the sponsor's medical monitor must be consulted beforehand. If an excluded medication is initiated before discussion with the medical monitor, the investigator must notify the sponsor as soon as becoming aware.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The Time and Events Schedule summarizes the frequency and timing of efficacy, medical resource utilization, health economic, safety, and other measurements applicable to this study. The protocol procedures are described in detail in Sections 9.2 through 9.8.

Additional visits may be required if, in the investigator's opinion, further clinical or laboratory evaluation is needed. Repeat or unscheduled samples may be required for safety reasons, for technical issues with the samples, or for confirmation of protocol-defined virologic failure.

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

Some flexibility in the planning of the visits is allowed, however, the total treatment duration at the end of the main study period should be 48 weeks. A window of ±2 days is allowed for Visit 2. All other study visits through Week 48 are to be completed within ±7 days of the protocol-specified visit date.

Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time

during the subject's participation in the study. If a serum or urine pregnancy test is positive, the subject will be withdrawn from the study.

The HIVTSQs assessment should be completed at scheduled visits (see the Time and Events Schedule) before all other study-related procedures planned during these visits to prevent influencing subject perceptions.

9.1.2. Screening Phase

The screening assessments indicated in the Time and Events Schedule will occur within 2 weeks following evidence of newly documented HIV-1 infection.

The ICF must be signed before any study-specific procedures at the start of the screening period.

Only subjects complying with the selection criteria as specified in Section 4, Subject Population, will be included in the study. The investigator will provide detailed information about the study to the subject and will obtain written informed consent before each subject's study participation. Procedures indicated in the Time and Events Schedule will only be performed after the subject's written informed consent has been obtained. Relevant historical data obtained from the subject's medical records and/or subject interview will be captured.

Subjects meeting all of the inclusion criteria and none of the exclusion criteria will enter the open-label treatment phase.

9.1.3. Open-Label Treatment Phase

9.1.3.1. Main Study Period

All subjects must start dosing within 24 hours of the screening/baseline visit (Day 1).

Following initiation of treatment, a safety assessment will be made by the investigator at Day 3 +1 week (or as soon as the final screening/baseline laboratory report becomes available), and the ARV screening/baseline resistance data will be reviewed by the investigator at Week 4±7 days or sooner, depending on the availability of screening/baseline HIV genotypic drug resistance testing results from the central laboratory. The investigator will determine as to whether treatment should be discontinued, based on the stopping rules provided in Section 3.1.

Subjects will be treated for 48 weeks in the main study period and will return to the site for visits at Weeks 2, 4, 8, 12, 24, 36, and 48 (scheduled relative to the date of the baseline visit) and complete the procedures indicated in the Time and Events Schedule. Subjects should be counseled regarding the importance of adherence, and be instructed to bring unused medication and empty packaging to the unit at each visit.

Subjects experiencing protocol-defined virologic failure (as defined in Section 3.1) will undergo genotypic and phenotypic resistance testing. In case resistance to study drugs is observed, the subject may be discontinued from the study at the investigator's discretion. Protocol-defined virologic failure is not considered a stopping rule.

9.1.3.2. Extension Period

Subjects who have completed the Week 48 visit will be given the opportunity to continue D/C/F/TAF treatment during an extension period until the D/C/F/TAF FDC tablet becomes commercially available and is reimbursed, or can be accessed through another source, or until the sponsor terminates clinical development. At Week 48 the investigator should dispense a sufficient supply of D/C/F/TAF to maintain continuity of care for the subject, however no more than 12 weeks of study medication should be dispensed. If a subject requires more than 12 weeks of study medication, the subject should return to the site for additional drug dispensation. During the extension period, subjects will have a study visit at the site once every 6 months, if applicable, and complete the procedures indicated in the Time and Events Schedule, and additionally at the time of transition to commercial D/C/F/TAF, for final data collection.

Early Study Treatment Discontinuation (ESTD)

Subjects who prematurely discontinue study treatment during the open-label treatment period (ie, including the extension period) will be required to complete ESTD assessments as soon as possible but no later than 1 week of discontinuing study treatment.

For subjects who discontinue study treatment after Week 12 for any reason and have HIV-1 RNA ≥400 copies/mL at the last viral load measurement, the ESTD assessments will also include genotypic and phenotypic resistance testing. In case of early discontinuation, an HIV-1 resistance report will be forwarded to the subject's primary care provider to assist in the selection of a new ARV regimen.

30-Day Follow-up

In addition, a follow-up visit is required for any subject who has an ongoing adverse event or serious adverse event at the time of his/her last study visit. These subjects 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 Time and Events Schedule.

End of Study

At the end of the study (or at ESTD), subjects will resume routine clinical care with their care provider who will transition them to an appropriate treatment regimen.

9.2. Efficacy Evaluations

9.2.1. Antiviral Efficacy and Immunologic Change

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

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

Immunologic change will be determined by changes in $CD4^+$ cell count (absolute and %).

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

9.2.2. Resistance Determinations

HIV-1 genotype/phenotype resistance testing will be performed at the time points specified in the Time and Events Schedule.

Resistance testing at the screening/baseline visit (Day 1) will be performed utilizing the GenoSure Prime® assay. Resistance-associated mutations present at baseline will be reported and include mutations in the domain of PR, RT, and INI.

To investigate the emergence of resistance, the following subjects will be eligible for genotypic/phenotypic resistance testing (PhenoSense GT®):

- Any subject who experiences a protocol-defined virologic failure;
- Any subject who discontinues study treatment after Week 12 for any reason and has an HIV-1 RNA value ≥400 copies/mL at the last viral load measurement;
- Any subject who has persistent HIV-1 RNA ≥400 copies/mL past Week 24 but does not meet the definition of virologic failure.

Baseline phenotyping may be performed retrospectively on subjects with confirmed protocol-defined virologic failure if after virologic failure they showed evidence of reduced phenotypic susceptibility to any of the study drugs. Evaluations may be performed at other time points at the sponsor's discretion.

9.3. Pharmacokinetics

Plasma concentrations of DRV and COBI may be determined in subjects experiencing protocol-defined virologic failure, or subjects who have persistent HIV-1 RNA ≥400 copies/mL past Week 24 but do not meet the definition of virologic failure, using stored blood samples collected throughout the study, if deemed necessary.

9.4. Medical Resource Utilization and Health Economics

Medical resource utilization data will be collected in the eCRF by the investigator and study-site personnel. The following will be evaluated throughout the study as noted in the Time and Events Schedule:

- Number and duration of hospitalizations.
- Number of outpatient visits, including type of visit (eg, general practitioner, specialist)
- Number of emergency room visits.
- Number and type of medications used (from the Concomitant Medication page of the eCRF).

Medical resource utilization will be classified as being either HIV-related or All-cause HRU as assessed by the investigator. The costs will be assigned to the type of medical resource utilization to calculate a per subject per month cost associated with the initiation and maintenance of ART.

Trends will be assessed over time throughout the study.

9.5. Adherence

Treatment adherence will be assessed by pill count and by subject self-report at the time points specified in the Time and Events Schedule.

Subjects should be counseled regarding the importance of adherence, and be instructed to bring unused medication and empty packaging to the unit at each visit.

If non-adherence is identified during drug accountability the reasons for non-adherence will be captured in the eCRF.

9.6. Retention in Care

Retention in care will be described as the proportion of subjects who discontinue study treatment prior to Week 48 and remain in care after discontinuation (defined as having a documented office visit within 90 days of discontinuing the study drug). Subjects who withdraw consent will not be followed to assess retention in care.

9.7. Safety Evaluations

The study will include the following evaluations of safety and tolerability according to the time points provided in the Time and Events Schedule: adverse event reporting, clinical laboratory tests (including biochemistry, hematology, urinalysis, and urine chemistry), vital signs, and physical examinations (complete or symptom-directed). These protocol procedures are described below. In addition to these measurements, guidelines for the management of toxicities are described in Section 9.8.

Any clinically relevant changes occurring during the study must be recorded on the Adverse Event section of the eCRF.

Clinical events and clinically significant laboratory abnormalities will be graded according to the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events located in Attachment 2.

Any evaluations showing abnormal results at any time during the study will be followed until satisfactory clinical resolution or stabilization. All grade 3 and grade 4 laboratory abnormalities and all laboratory abnormalities resulting in an increase of 2 DAIDS grades from baseline will be followed until return to baseline or within 1 grade from baseline (ie, ≤grade 2) (see Section 9.8.1, General Guidance for the Management of Clinical Events and Laboratory Abnormalities).

Evaluations at the ESTD visit showing abnormal results indicating a possible causal relationship with the study treatment must be followed by the investigator (as often as deemed prudent) until

satisfactory clinical resolution or stabilization. Certain long-term adverse events of ART cannot be followed to resolution within the setting of this protocol; in these cases, follow-up will be the responsibility of the treating physician, which will be agreed upon with the sponsor's medical monitor.

Adverse Events

Adverse events will be reported by the subject (or, when appropriate, by a caregiver or surrogate) for the duration of the study. Adverse events will be followed by the investigator as specified in Section 12, Adverse Event Reporting.

Special attention will be paid to those subjects who discontinue the study for an adverse event, or who experience severe (grade 3) or potentially life-threatening (grade 4) adverse events, or a serious adverse events. For reported HIV events, further details will be recorded if these events are AIDS-defining illnesses (World Health Organization Clinical Staging of HIV/AIDS, located in Attachment 3). For subjects with specific adverse events, toxicity management should be done as described in Section 9.8, Toxicity Management.

Clinical Laboratory Tests

Blood samples for serum chemistry and hematology and a urine sample for urinalysis will be collected at predefined time points (see Time and Events Schedule).

All clinical laboratory testing will be performed by the central laboratory and results will be sent to the investigator. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the eCRF. The laboratory reports must be filed with the source documents.

The central laboratory will send the investigator and sponsor an alert form whenever a grade 3 or grade 4 laboratory abnormality (see Attachment 2) is observed. In case a grade 3 or grade 4 laboratory abnormality occurs, a confirmatory test should be performed preferably within 72 hours after the results have become available, before study treatment interruption or discontinuation, unless such delay is not consistent with good medical practice.

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

- Asymptomatic grade 3 or grade 4 glucose elevations in subjects with pre-existing diabetes.
- Asymptomatic grade 3 or grade 4 triglyceride or cholesterol elevations.

For more details on the management of grade 3 and 4 laboratory toxicities that occur during the open-label treatment phase, see Section 9.8.1, General Guidance for the Management of Clinical Events and Laboratory Abnormalities, and Attachment 4. Please note that this attachment does not apply to screening/baseline eGFR, AST, ALT, and lipase, and does also not apply to the allowed retesting of abnormal screening/baseline eGFR, AST, ALT, and lipase values (see Section 3.1).

The following tests will be performed by the central laboratory:

- Hematology Panel*

-hemoglobin	-platelet count
-hematocrit	-$CD4^+$ cell count
-absolute neutrophil count	-$CD8^+$ cell count
-white blood cell count (WBC) with differential	-$CD4^+CD8^+$ ratio
-red blood cell count (RBC)	

  * Peripheral blood mononuclear cells (PBMCs) will be isolated from whole blood at the central laboratory at predefined time points (see Time and Events Schedule), and stored for future analysis if needed.

- Serum Chemistry Panel

-glucose	-chloride
-calcium	-phosphate
-calcium corrected for albumin	-blood urea nitrogen (BUN)
-albumin	-serum creatinine, including calculated eGFR
-total protein	-alkaline phosphatase (ALP)
-sodium	-AST
-potassium	-ALT
-bicarbonate (HCO_3)	-bilirubin (total, direct, indirect)

- Urinalysis (dipstick)

-specific gravity	-ketones
-pH	-bilirubin
-glucose	-urobilinogen
-protein	-nitrite
-blood	-leukocyte esterase

If dipstick results are abnormal, the sediment will be examined microscopically.

In the microscopic examination, observations other than the presence of WBCs, RBCs, and casts may also be reported by the laboratory.

- Urine chemistry panel (only in the setting of a suspected renal adverse event; quantitative)

-creatinine	-glucose
-sodium	-protein
-phosphate	-albumin

Additional clinical laboratory assessments to be performed are as follows:

- 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.

- A urine pregnancy test will be performed at screening for all female subjects of childbearing potential. A serum human chorionic gonadotropin pregnancy test will be assessed at a central laboratory, but the results are not required for enrollment. A urine pregnancy test will be performed at subsequent study visits as outlined in the Time and Events Schedule. Positive urine pregnancy tests will be confirmed with a serum pregnancy test. The results of the serum and urine pregnancy tests should be recorded in the eCRF and in the subject's medical records.
- Amylase (pancreatic) (only at screening and in case of suspected pancreatitis during the study period)
- Lipase (only at screening and reflex if amylase elevated)
- 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 9.8.2, Cutaneous Events/Rash.

Vital Signs (Including Height and Weight)

Blood pressure (systolic and diastolic) and pulse/heart rate measurements (supine after at least 5 minutes rest) should be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones). Blood pressure and pulse/heart rate measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

To obtain the actual body weight, subjects should be weighed lightly clothed.

Height should be measured barefooted at the screening visit.

Any clinically relevant findings at screening and changes occurring during the study must be recorded in the Adverse Event section of the eCRF.

Physical Examination

Complete physical examinations, or symptom-directed examinations (physical examinations for which symptoms have been reported by the subject) as needed, will take place at the time points in the Time and Events Schedule.

Complete physical examinations include skin, eyes, ears, nose, and throat, head, neck, and thyroid, heart, lung, chest (incl. breasts), abdomen, genitalia, anorectal, lymph nodes, musculoskeletal, and neurological. Urogenital/anorectal examination will be performed at the discretion of the investigator if clinically relevant. Subjects should be undressed during the complete physical examinations, which should be performed by a licensed medical doctor, physician's assistant or nurse practitioner in accordance with local guidelines.

Any clinically relevant findings at screening and changes occurring during the study must be recorded in the Adverse Event section of the eCRF.

Patient-reported Outcomes

Patient-reported outcomes will be assessed at the time points indicated in the Time and Events Schedule utilizing the HIVTSQs. The HIVTSQs should be completed before all other study-related procedures planned during these visits to prevent influencing subject perceptions.

9.8. Toxicity Management

The toxicity management guidelines in this section are applicable throughout the entire study starting from when the subject starts study medication through the 48-week main study period and the extension period.

General guidance for the management of toxicities is provided in Section 9.8.1. Guidance for specific toxicities is provided in Sections 9.8.2 through 9.8.8. In addition, see Section 9.7, Safety Evaluations, and Section 12, Adverse Event Reporting, for details on procedures concerning the measurement and reporting of clinically relevant abnormalities and toxicities.

Questions regarding toxicity management should be directed to the sponsor's medical monitor.

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

Grade 1 and 2

Continue study treatment at the discretion of the investigator.

Grade 3

- For a grade 3 clinical event or clinically relevant laboratory abnormality, study treatment may be continued if the event is considered to be unrelated to study treatment.
- For a grade 3 clinical event, or clinically relevant laboratory abnormality confirmed by repeat testing (see Section 9.7), that is considered related to study treatment, study treatment should be withheld until the toxicity returns to baseline or within 1 grade from baseline, ie, ≤grade 2.
- Mandatory confirmation is not warranted for asymptomatic grade 3 glucose elevations in subjects with pre-existing diabetes, and for asymptomatic grade 3 triglyceride or cholesterol elevations.
- If a laboratory abnormality recurs to ≥grade 3 following rechallenge with study treatment and is considered to be related to study treatment, study treatment should be permanently discontinued and the subject managed according to local practice. Recurrence of laboratory abnormalities considered unrelated may not require permanent discontinuation.

Grade 4

- For a grade 4 clinical event or clinically relevant laboratory abnormality confirmed by repeat testing (see Section 9.7), that is considered related to study treatment, study treatment should be permanently discontinued and the subject managed according to local practice. The subject should be followed as clinically indicated until the laboratory abnormality returns to baseline or is otherwise explained, whichever occurs first. A clinically relevant grade 4 laboratory

abnormality that is not confirmed upon repeat testing should be managed according to the algorithm for the new toxicity grade.

- Mandatory confirmation is not warranted for asymptomatic grade 4 glucose elevations in subjects with pre-existing diabetes, and for asymptomatic grade 4 triglyceride or cholesterol elevations.
- Study treatment may be continued without dose interruption for a clinically nonrelevant grade 4 laboratory abnormalities (eg, grade 4 creatine phosphokinase after strenuous exercise, or triglyceride elevation that is nonfasting or that can be medically managed), or a clinical event considered unrelated to study treatment.

A schematic overview of these guidelines is provided in Attachment 4 for clinically relevant laboratory toxicities that occur while on treatment. Please note that this attachment does not apply to screening/baseline eGFR, AST, ALT, and lipase, and does also not apply to the allowed retesting of abnormal screening/baseline eGFR, AST, ALT, and lipase values (see Section 3.1).

9.8.2. Cutaneous Events/Rash

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

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

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

Grade 1 and 2 Cutaneous Reaction/Rash

A grade 1 cutaneous reaction/rash is defined as localized rash.

A grade 2 cutaneous reaction/rash is defined as diffuse rash or target lesions.

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

Grade 3 and 4 Cutaneous Reaction/Rash

A grade 3 cutaneous reaction/rash is defined as:

- Diffuse rash with vesicles or limited number of bullae or superficial ulceration of mucous membrane limited to 1 site.

For the purpose of this study, the sponsor considers qualifying as a grade 3 rash:

- Cutaneous reaction/rash with at least 1 of the following:
  - elevations of ALT/AST >2× baseline but ≥5×ULN
  - fever ≥38°C or 100°F
  - serum sickness-like reaction
  - eosinophil count >1,000/mm^3
- The syndromes of DRESS and AGEP

A grade 4 cutaneous reaction/rash is defined as:

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

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

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

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

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

9.8.3. Acute Systemic Allergic Reaction

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

Grade 1

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

Subjects may continue study treatment or have their study treatment interrupted at the investigator's discretion. The subject should be advised to contact the investigator immediately if there is any worsening of the pruritus, or if any systemic signs or symptoms develop. Antihistamines or topical corticosteroids or antipruritic agents may be prescribed as long as these are in line with the (dis)allowed medications as indicated in Section 8, Prestudy and Concomitant Therapy, or in the local Prescribing Information of the ARV agents.

Grade 2

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

Subjects may continue study treatment or have their study treatment interrupted at the investigator's discretion. If there is any worsening of the allergic reaction, the subject should be advised to contact the investigator immediately and to discontinue study treatment. Antihistamines or topical corticosteroids or antipruritic agents may be prescribed as supportive care as long as these are in line with the (dis)allowed medications as indicated in Section 8, Prestudy and Concomitant Therapy, or in the local Prescribing Information of the ARV agents.

Grade 3

A grade 3 acute systemic allergic reaction is defined as generalized urticaria, or angioedema with intervention indicated or symptoms of mild bronchospasm.

Subjects will permanently discontinue study treatment. Subjects will be treated as clinically appropriate. Standard management should be undertaken.

Grade 4

A grade 4 acute systemic allergic reaction is defined as acute anaphylaxis, or life-threatening bronchospasm, or laryngeal edema.

Subjects will permanently discontinue study treatment. Subjects will be treated as clinically appropriate. Standard management should be undertaken.

Table 2: Summary of Allergic Reaction Follow-up

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

9.8.4. Potential Renal Toxicity

Estimated glomerular filtration rate for creatinine clearance ($eGFR_{creatinine}$ calculated according to the MDRD formula will be followed postbaseline during the treatment phase.

Any subjects who have an $eGFR_{creatinine}$ of <50 and a decrease of 20% in $eGFR_{creatinine}$ from baseline, or who have other clinical and/or laboratory evidence of acute renal failure will be discussed with the sponsor's medical monitor and may permanently discontinue study treatment.

The eGFR calculations will be performed and provided to the investigator by the central laboratory.

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

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

9.8.5. Potential Posterior Uveitis Cases

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

9.8.6. Hyperglycemia

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

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

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

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

9.8.7. Hypertriglyceridemia and Hypercholesterolemia

Hypertriglyceridemia: Grade 3: 5.7 to 11.4 mmol/L (>500-1,000 mg/dL)
Grade 4: >11.4 mmol/L (>1,000 mg/dL)

Hypercholesterolemia: Grade 3: ≥7.77 mmol/L (>300 mg/L)
Grade 4: Not applicable

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

Subjects who experienced asymptomatic triglyceride or cholesterol elevations of grade 3 or 4 may continue study treatment unless clinical assessment foresees an immediate health risk to the subject.

Hypertriglyceridemia and hypercholesterolemia should be treated according to the specific guidelines for treating HIV-positive subjects (see Attachment 5). Current treatment guidelines specify different lipid thresholds for intervention for different degrees of cardiovascular risk. The presence or absence of other significant cardiovascular risk factors, which include smoking, age, family history of premature cardiovascular disease, diabetes, hypertension, low high-density lipoprotein (HDL), and prior history of cardiovascular disease should be taken into account. Appropriate clinical management of hyperlipidemia in the setting of HIV should be started in a timely fashion if applicable, and taking into account the disallowed medications (refer to Section 8, Prestudy and Concomitant Therapy).

9.8.8. Lipodystrophy/Fat Redistribution/Body Changes

Investigators are requested to avoid using the term 'lipodystrophy acquired' or 'fat redistribution' to describe and report body fat abnormalities, as these terms are not descriptive nor fully accurate. The different symptoms and gradings are listed in the DAIDS grading table (Attachment 2) under Endocrine/Metabolic. The following terms are included: lipohypertrophy, lipoatrophy, and gynecomastia.

Although metabolic abnormalities such as hyperlipidemia or hyperglycemia are often associated with body changes, these events should be recorded separately at adverse event reporting.

9.9. Sample Collection and Handling

Blood samples drawn will be frozen and stored. These stored samples may be used by the sponsor or its research partners for HIV-1 genotype/phenotype assays, for retesting the amount of HIV-1 RNA in the blood, for additional measurement of antiviral drug levels in the blood, clinical laboratory testing to provide additional safety data, or future testing to learn more about how the investigational drug has worked against HIV-1. Additionally, pharmacokinetic analyses for DRV and COBI may be performed for those subjects experiencing virologic failure at the request of the sponsor. No human genetic testing will be performed on these samples. See also Section 16.2.5.

In addition, PBMCs will be isolated from whole blood at the central laboratory and stored for future analysis if needed.

The actual dates and times of sample collection must be recorded in the eCRF or laboratory requisition form. See the Time and Events Schedule for the timing and frequency of all sample collections.

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

10. SUBJECT COMPLETION/DISCONTINUATION OF STUDY TREATMENT/ WITHDRAWAL FROM THE STUDY

10.1. Completion

In the period up to Week 48, a subject will be considered to have completed the main study period if he or she has continued study medication intake up to Week 48 and has completed assessments at Week 48. Subjects who prematurely discontinue study treatment for any reason before completion of the 48-week treatment period will not be considered to have completed the main study period.

In the period after Week 48, subjects will be considered to have completed the extension period if he or she continued study medication intake until D/C/F/TAF becomes commercially available and is reimbursed, or can be accessed through another source, or until the sponsor terminates clinical development and has completed assessments until that point. Subjects who prematurely discontinue study treatment for any reason before that point, will not be considered to have completed the extension period.

10.2. Withdrawal From the Study

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

- Lost to follow-up
- Withdrawal of consent
- Discontinuation of study treatment for any reason
- Subject request to stop study treatment for any reason.

A subject's study treatment **must** be discontinued if:

  - The investigator or sponsor believes (eg, that for safety or tolerability reasons (eg, adverse event) it is in the best interest of the subject to discontinue treatment
  - The subject becomes pregnant
  - The subject meets any of the safety stopping rules (see Section 3.1, Overview of Study Design)

- The subject meets any of the resistance stopping rules (see Section 3.1, Overview of Study Design)
- The subject experiences unacceptable toxicity (as defined in Section 9.8, Toxicity Management)
- The subject develops clinical hepatitis
- Prolonged temporary study treatment discontinuation >4 consecutive weeks
- The study is discontinued at the request of the sponsor, concerned regulatory agency, or Independent Ethics Committee/Institutional Review Board (IEC/IRB)

A subject's study treatment **may** be discontinued if:

- A serious adverse event occurs
- The subject fails to comply with the protocol or study staff requirements
- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree
- The subject starts disallowed treatment, or requires new onset treatment with one of the disallowed medications (please refer to Section 8, Prestudy and Concomitant Therapy)
- The subject experiences protocol-defined virologic failure, shows resistance to study drug(s) upon genotypic and phenotypic resistance testing, and the investigator makes the decision to discontinue study treatment
- The subject experiences persistent HIV-1 RNA ≥400 copies/mL after Week 24, that does not meet the protocol-defined virologic failure criteria, but shows resistance to study drug(s) upon genotypic and phenotypic resistance testing, and the investigator makes the decision to discontinue study treatment

Protocol-defined virologic failure is not considered a stopping rule.

If the investigator considers withdrawing a subject from study treatment for one of the above reasons, he/she should contact the sponsor for further discussion and final decision, unless the medical condition requires immediate action that cannot wait contact with the sponsor.

Subjects who prematurely discontinue study treatment during the open-label treatment period will be required to complete ESTD assessments as soon as possible but no later than 1 week of discontinuing study treatment.

In addition, a follow-up visit is required for any subject who has an ongoing adverse event or serious adverse event at the time of his/her last study visit. These subjects are required to return to the site 30 days (±7 days) after completion of the last study-related visit (unless consent is withdrawn).

Investigators will refer subjects discontinuing therapy for any reason before Week 48 for follow-up care, either at a clinic associated with the investigator or an external care facility according to subject preference. To assess whether subjects have been retained in care, investigators will be

asked to monitor subject's engagement with the referral site. Retention in care will be defined as having a documented office visit within 90 days of discontinuing the study drug before Week 48. Subjects who complete the study through Week 48 will not be monitored for retention in care.

If a subject is lost to follow-up, every reasonable effort must be made by the study site personnel to contact the subject and determine the reason for discontinuation/withdrawal. The measures taken to follow up must be documented.

When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the eCRF and the source document. Study drug dispensed to the withdrawn subject may not be dispensed to another subject (unless the bottles are unopened). Subjects who withdraw will not be replaced.

10.3. Withdrawal From the Use of Research Samples

Withdrawal From the Use of Samples in Future Research

The subject may withdraw consent for use of samples for research (refer to Section 16.2.5, Long-Term Retention of Samples for Additional Future Research). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF.

11. STATISTICAL METHODS

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

The following analyses will be performed:

- The interim analysis: once all subjects have been assessed for safety at Day 3, and for resistance stopping rules at Week 4.
- The primary analysis: once all subjects have completed the Week 48 assessments and the 30-day follow-up visit (if applicable), or discontinued earlier.

11.1. Analysis Sets

The following analysis sets will be used and are defined:

- Intent-to-treat (ITT) population: all subjects who have received at least one dose of study drug.
- Per-protocol population: ITT population without major protocol deviation that is considered to have an impact on the safety or efficacy assessments.

11.2. Subject Information

Subject information will be analyzed based on the ITT population, unless otherwise specified.

For all subjects who receive at least 1 dose of study drug descriptive statistics will be provided.

11.3. Sample Size Determination

The primary efficacy endpoint is the proportion of subjects who have HIV-1 RNA <50 copies/mL at Week 48 as defined by the FDA snapshot analysis (ITT). As this is an exploratory study with no formal hypothesis testing on the primary endpoint, no formal sample size calculation was performed. With a sample size of 100 subjects and an expected virologic response rate ranging from 60-80%, the exact corresponding 95% confidence intervals (CIs) are: 60% (49.7%, 69.7%), 70% (60.0%, 78.8%), and 80% (70.8%, 87.3%). The half-width of the exact corresponding 2-sided 95% CI is 10.0%, 9.4%, and 8.3%, respectively, and is therefore less than 10% across the range of expected outcomes which is the desired precision. Additionally, with a sample size of 100 subjects, the probability to observe an adverse event with a true incidence of 1% or 4% is 63% and 98% respectively.

11.4. Efficacy Analyses

11.4.1. Antiviral Efficacy and Immunologic Change

The primary efficacy endpoint is the proportion of subjects who have HIV-1 RNA<50 copies/mL at Week 48 as defined by the FDA snapshot analysis (ITT).

Virologic suppression (HIV-1 RNA<50 copies/mL) will also be analyzed as secondary endpoints at Week 24 and Week 48 according to the below analyses:

- FDA Snapshot algorithm in the ITT and Per-Protocol population
- Time to loss of virological response (TLOVR) algorithm in the ITT population

Virologic decay will be reported as the mean $\log_{10}$ change in HIV-1 viral load from baseline to Weeks 2, 4, 8, 12, and 24 as part of the interim analysis as a secondary endpoint.

The proportion of subjects experiencing protocol defined virologic failure at Week 24 and Week 48 will be tabulated using descriptive statistics along with the 95% CIs. The Wilson (Score) method for the CI will be used.

The changes from baseline in $CD4^+$ cell count at Weeks 12, 24, and 48 will be summarized using descriptive statistics.

11.4.2. Resistance Determinations

The number of PR mutations (including IAS-USA primary and secondary PI RAMs), RT mutations (including IAS-USA N[t]RTI RAMs and IAS-USA non-nucleoside RT inhibitor [NN(t)RTI] RAMs), and INI mutations (including IAS-USA primary and secondary INI-RAMS) present will be tabulated based on resistance tests performed at the screening/baseline visit.

The proportion of subjects meeting resistance stopping rules, requiring discontinuation of study drug, based on the findings of screening/baseline resistance testing will be tabulated as part of the interim analysis.

HIV-1 genotype/phenotype will be analyzed from samples of subjects with protocol-defined virologic failure and with HIV-1 RNA ≥400 copies/mL.

The number of treatment-emergent PR mutations (including IAS-USA primary and secondary PI RAMs) and RT mutations (including IAS-USA N(t)RTI RAMs and IAS-USA NNRTI RAMs), as well as specific mutations associated with resistance to DRV, FTC, and TAF will be tabulated based on the observed virologic failures through the study period.

Fold change (FC) in 50% effective concentration (EC_{50}) of ARVs will be tabulated. Loss of phenotypic susceptibility may be analyzed dependent on the number of virologic failures and phenotypes available through the study period.

11.5. Medical Resource Utilization and Health Economics Analyses

All-cause and HIV-specific HRU during the study period will be summarized overall and by category as the counts per patient per month (PPPM). Monthly average counts per subject will also be calculated to show the temporal trend for each category.

Costs of care will be calculated by assigning costs based on Centers for Medicare & Medicaid Services (CMS) fee schedule to assessed HRU on a per subject per month basis. Descriptive statistics will be calculated to compare the costs of care from baseline to Weeks 12, 24, and 48.

11.6. Adherence Analyses

Treatment adherence based on pill count and on subject self-report will be summarized by means of descriptive statistics and frequency tabulations.

Adherence rates will be reported according to the proportion of subjects taking >95%, 80-95% and <80% of study drug as assessed by pill count at study visits at Weeks 4, 8, 12, 24, 36, and 48.

11.7. Retention in Care Analyses

Number of subject with retention of care by age, gender, race, sexual orientation, time from diagnosis to baseline visit, baseline CD4+ cell count, baseline HIV-1 RNA, patient satisfaction as assessed by HIVTSQs, and socioeconomic factors will be tabulated.

11.8. Safety Analyses

For all safety endpoints listed in Section 2.1.2, descriptive statistics will be used to summarize the endpoints.

Adverse Events

The verbatim terms used in the eCRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events are adverse events with onset during the treatment phase or that are a consequence of a pre-existing condition that has worsened since baseline. All reported adverse events will be

included in the analysis. For each adverse event, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized.

Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue treatment due to an adverse event, or who experience a severe or life-threatening (grade 3 or 4) or a serious adverse event.

Additionally, a summary and listing of those subjects meeting predefined stopping rules due to safety or resistance findings will be tabulated.

Clinical Laboratory Tests

Abnormalities will be analyzed according to the DAIDS grading table (see Attachment 2) and in accordance with the normal ranges of the clinical laboratory. Maximum toxicity grades after baseline will be tabulated, and special attention will be given to subjects who develop grade 3 or grade 4 toxicities.

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results (specified in the Statistical Analysis Plan) will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled time point. Changes from baseline results will be presented in pre- versus posttreatment cross-tabulations (with classes for below, within, and above normal ranges).

Vital Signs

Descriptive statistics of blood pressure (systolic and diastolic), pulse/heart rate, and body weight and changes from baseline will be summarized at each scheduled time point. The percentage of subjects with values beyond clinically important limits will be summarized. See Attachment 6 for the definitions of vital signs abnormalities.

Physical Examination

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

Patient-reported Outcomes

Descriptive statistics for absolutes values and changes in HIVTSQs scores will be calculated at each timepoint, where applicable.

11.9. Extension Period

For the extension period, descriptive statistics or patient data listings will be provided for adverse events, virologic failure, or resistance.

11.10. Interim Analysis

An interim analysis is planned once all subjects have been assessed for safety at Day 3, and for resistance stopping rules at Week 4.

12. ADVERSE EVENT REPORTING

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

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

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

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

Note: The sponsor collects adverse events starting with the signing of the ICF (refer to Section 12.3.1, All Adverse Events, for time of last adverse event recording).

An adverse event does not include the following:

- Medical or surgical procedures if the condition that leads to the procedure is an adverse event.
- Pre-existing diseases or conditions or laboratory abnormalities present or detected before the screening visit that do not worsen; any medical condition or clinically significant laboratory abnormality with an onset date before the ICF is signed, is not an adverse event. It is considered to be pre-existing and should be documented in the medical history eCRF.
- Situations where no untoward medical occurrence has occurred (eg, hospitalization for elective surgery, social and/or convenience admissions).
- Overdose without clinical sequelae.
- Uncomplicated pregnancy.

See also Section 12.2, Special Reporting Situations and Section 12.3.3, Pregnancy.

Serious Adverse Event

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

- Results in death
- Is life-threatening
  (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

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

- Intensive treatment in an emergency room or at home for allergic bronchospasm.
- Blood dyscrasias or convulsions that do not result in hospitalization.
- Development of drug dependency or drug abuse.

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

Additional clarification on adverse events/serious adverse events:

- Complications occurring during hospitalizations are adverse events. If a complication prolongs the hospitalization, it is a serious adverse event.
- In-patient hospitalization means that the subject has been formally admitted to a hospital for medical reasons, for any length of time; this may or may not be overnight. It does not include presentation or care within an emergency department.
- The investigator should attempt to establish the diagnosis of an event on the basis of signs, symptoms, and/or other clinical information; in such cases, the diagnosis must be documented as the adverse event and/or serious adverse event and not the individual signs or symptoms.
- A distinction should be made between seriousness and severity of adverse events. An adverse event that is assessed as grade 4 (potentially life-threatening) should not be confused with a serious adverse event. Severity is a category utilized for rating the intensity of an event, and

both adverse events and serious adverse events can be assessed as grade 4. An adverse event is defined as 'severe' when it meets the predefined criteria as described the DAIDS toxicity grading table in Attachment 2 (see also Section 12.1.3, Severity Criteria).

Unlisted (Unexpected) Adverse Event/Reference Safety Information

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

Adverse Event Associated With the Use of the Drug

An adverse event is considered associated with the use of the drug if the attribution is possible, probable, or very likely by the definitions listed in Section 12.1.2, Attribution Definitions.

12.1.2. Attribution Definitions

Not Related

An adverse event that is not related to the use of the drug.

Doubtful

An adverse event for which an alternative explanation is more likely, eg, concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible

An adverse event that might be due to the use of the drug. An alternative explanation, eg, concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable

An adverse event that might be due to the use of the drug. The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation is less likely, eg, concomitant drug(s), concomitant disease(s).

Very Likely

An adverse event that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (eg, it is confirmed by dechallenge and rechallenge).

12.1.3. Severity Criteria

An assessment of severity grade will be made using the general categorical descriptors outlined in the DAIDS toxicity grading table in Attachment 2.

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the subject (eg, laboratory abnormalities).

A distinction should be made between seriousness and severity of adverse events. An adverse event assessed as grade 4 (potentially life-threatening) should not be confused with a serious adverse event. Severity is a category utilized for rating the intensity of an event, and both adverse events and serious adverse events can be assessed as grade 4. An event is defined as 'serious' when it meets one of the predefined outcomes listed in Section 12.1.1, Adverse Event Definitions and Classifications.

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

Laboratory abnormalities are usually not recorded as adverse events or serious adverse events. However, laboratory abnormalities independent of the underlying medical condition that require medical or surgical intervention or lead to study drug interruption or discontinuation must be recorded as an adverse event as well as a serious adverse event, if applicable. Laboratory or other abnormal assessments (eg, vital signs) that are associated with signs and/or symptoms must be recorded as an adverse event or serious adverse event if they meet the definitions as described in Section 12.1.1, Adverse Event Definitions and Classifications. If the laboratory abnormality is part of a syndrome, the syndrome/diagnosis (ie, anemia) must be recorded and not the laboratory result (ie, decreased hemoglobin).

12.2. Special Reporting Situations

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

- Overdose of a sponsor study drug
- Suspected abuse/misuse of a sponsor study drug
- Accidental or occupational exposure to a sponsor study drug
- Any failure of expected pharmacologic action (ie, lack of effect) of a sponsor study drug
- Unexpected therapeutic or clinical benefit from use of a sponsor study drug
- Medication error involving a sponsor product (with or without subject/patient exposure to the sponsor study drug, eg, name confusion)
- Exposure to a sponsor study drug from breastfeeding
- Lack of effect reports
- Pregnancy reports, whether or not maternal exposure to the product occurred (see also Section 12.3.3, Pregnancy)
- Reports of adverse reactions in infants following exposure from breastfeeding.

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

12.3. Procedures

12.3.1. All Adverse Events

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

All events that meet the definition of a serious adverse event will be reported as serious adverse events, regardless of whether they are protocol-specific assessments. Anticipated events will be recorded and reported as described in Attachment 8.

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

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). For anticipated events reported as individual serious adverse events the sponsor will make a determination of relatedness in addition to and independent of the investigator's assessment. The sponsor will periodically evaluate the accumulating data and, when there is sufficient evidence and the sponsor has determined there is a reasonable possibility that the drug caused a serious anticipated event, they will submit a safety report in narrative format to the investigators (and the head of the investigational institute where required). The investigator (or sponsor where required) must report SUSARs to the appropriate IEC/IRB that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

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

- Study number
- Statement, in the local language(s), that the subject is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical staff only)
- Site number
- Subject number

12.3.2. Serious Adverse Events

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

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

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

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

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

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

Disease progression should not be recorded as an adverse event or serious adverse event term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the serious adverse event definition (refer to Section 12.1.1, Adverse Event Definitions and Classifications).

12.3.3. Pregnancy

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

Because the effect of the study drug on sperm is unknown, pregnancies in partners of male subjects included in the study will be reported as noted above.

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

12.4. Contacting Sponsor Regarding Safety

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

13. PRODUCT QUALITY COMPLAINT HANDLING

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

13.1. Procedures

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

If the defect is combined with a serious adverse event, the study-site personnel must report the PQC to the sponsor according to the serious adverse event reporting timelines (refer to Section 12.3.2, Serious Adverse Events). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

13.2. Contacting Sponsor Regarding Product Quality

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

14. STUDY DRUG INFORMATION

14.1. Physical Description of Study Drug(s)

D/C/F/TAF FDC tablets will be manufactured and provided under the responsibility of the sponsor.

The D/C/F/TAF FDC tablets supplied for this study are yellow capsule-shaped, plain-faced, film-coated tablets containing 800 mg of DRV (as 867 mg of DRV ethanolate), 150 mg of COBI (288 mg total weight of COBI on silicon dioxide carrier), 200 mg of FTC, and 10 mg of TAF (as 11.2 mg TAF fumarate). The D/C/F/TAF tablet cores contain silicon dioxide, croscarmellose sodium, microcrystalline cellulose, magnesium stearate polyvinyl alcohol, iron oxide yellow, polyethylene glycol, talc, and titanium dioxide.

14.2. Packaging

D/C/F/TAF FDC tablets will be packaged under responsibility of the sponsor

The D/C/F/TAF FDC tablets are packaged in white, high-density polyethylene (HDPE) bottles with a silica gel desiccant and polyester coil fiber in each bottle. Each bottle is capped with a white, continuous thread, child-resistant polypropylene screw cap fitted with an induction-sealed, aluminum-faced liner.

No study drug can be repacked without prior approval from the sponsor.

14.3. Labeling

Study drug labels will contain information to meet the applicable regulatory requirements.

No study drug can be relabeled without prior approval from the sponsor.

14.4. Preparation, Handling, and Storage

All study drug must be stored according to the storage conditions printed on the label.

To ensure the stability of D/C/F/TAF FDC tablets, the study drug should not be dispensed into a container other than the container in which it is supplied.

Refer to the pharmacy manual/study site investigational product and procedures manual for additional guidance on study drug preparation, handling, and storage.

14.5. Drug Accountability

The investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. The dispensing of study drug to the subject, and the

return of study drug from the subject (if applicable), must be documented on the drug accountability form. Subjects must be instructed to return all original containers, whether empty or containing study drug. All study drug will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study drug containers.

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

Potentially hazardous materials such as used ampules, needles, syringes and vials containing hazardous liquids, should be disposed of immediately in a safe manner and therefore will not be retained for drug accountability purposes.

Study drug should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study drug will be supplied only to subjects participating in the study. Returned study drug must not be dispensed again, even to the same subject, unless the bottles are unopened. Whenever a subject brings his or her study drug to the study site for pill count, this is not seen as a return of supplies. Study drug may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the sponsor.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Investigator's Brochure and Addendum[14,15]
- Pharmacy manual/study site investigational product and procedures manual
- Laboratory manual
- HIVTSQs questionnaire
- electronic Data Capture (eDC) Manual
- Sample ICF
- Interactive Web Response System manual

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which

they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential adverse events of the study, and provide their consent voluntarily will be enrolled.

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

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

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

16.2.2. Independent Ethics Committee or Institutional Review Board

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

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the subjects)
- Investigator's Brochure (or equivalent information) and amendments/addenda
- Sponsor-approved subject recruiting materials
- Information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects
- Any other documents that the IEC/IRB requests to fulfill its obligation

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

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to subjects
- If applicable, new or revised subject recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- New edition(s) of the IB and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of adverse events that are serious, unlisted/unexpected, and associated with the study drug
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required.

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion (if applicable, the notification will be submitted through the head of investigational institution).

16.2.3. Informed Consent

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

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential subjects the aims, methods, reasonably anticipated benefits,

and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive for the treatment of his or her disease. Subjects will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a subject identification register for the purposes of long-term follow up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the subject is authorizing such access, which includes permission to obtain information about his or her survival status. It also denotes that the subject agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, and subsequent disease-related treatments, if needed. The physician may also recontact the subject for the purpose of obtaining consent to collect information about his or her survival status.

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

If the subject is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent of the subject is obtained.

16.2.4. Privacy of Personal Data

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

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

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

The subject has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps

will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

16.2.5. Long-Term Retention of Samples for Additional Future Research

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

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Subjects may withdraw their consent for their samples to be stored for research (refer to Section 10.3, Withdrawal From the Use of Samples in Future Research.

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

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

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

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

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

17.2.2. Required Prestudy Documentation

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

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

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

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

17.3. Subject Identification, Enrollment, and Screening Logs

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

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All

reports and communications relating to the study will identify subjects by subject identification and date of birth. In cases where the subject is not enrolled into the study, the date seen and date of birth will be used.

The investigator must also complete a subject screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the study.

17.4. Source Documentation

At a minimum, source documentation must be available for the following to confirm data collected in the eCRF: subject identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all AEs and follow-up of AEs; concomitant medication; drug receipt/dispensing/return records; study drug administration information; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

In addition, the author of an entry in the source documents should be identifiable.

At a minimum, the type and level of detail of source data available for a subject should be consistent with that commonly recorded at the study site as a basis for standard medical care. Specific details required as source data for the study will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

Data that will be recorded directly into the eCRF are specified in the Source Document Identification Form.

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

17.5. Case Report Form Completion

Case report forms are prepared and provided by the sponsor for each subject in electronic format.

Electronic Data Capture will be used for this study. The study data will be transcribed by study-site personnel from the source documents onto an electronic eCRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor within the timeframe agreed upon between the sponsor and the study site. The electronic file will be considered to be the eCRF.

Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the subject's source documentation. All data relating to the study must be recorded in eCRFs prepared by the sponsor. Data must be entered into the eCRF in English. The eCRF must be completed as soon as possible after a subject visit and the forms should be available for review at the next scheduled monitoring visit.

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

All eCRF entries, corrections, and alterations must be made by the investigator or authorized study-site personnel. The investigator must verify that all data entries in the eCRF are accurate and correct.

If necessary, queries will be generated in the eDC tool. The investigator or study-site personnel must adjust the eCRF (if applicable) and complete the query.

If corrections to a eCRF are needed after the initial entry into the eCRF, this can be done in either of the following ways:

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

17.6. Data Quality Assurance/Quality Control

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

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

17.7. Record Retention

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

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an

agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

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

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

17.8. Monitoring

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

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

17.9. Study Completion/Termination

17.9.1. Study Completion/End of Study

The study is considered completed with the last visit for the last subject participating in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final subject visit at that study site, in the time frame specified in the Clinical Trial Agreement.

17.9.2. Study Termination

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A

study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

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

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

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

17.10. On-Site Audits

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

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

17.11. Use of Information and Publication

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

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

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator. Results of analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report. Study subject identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 12 months of the availability of the final data (tables, listings, graphs), or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the existence of and the results of clinical studies as required by law.

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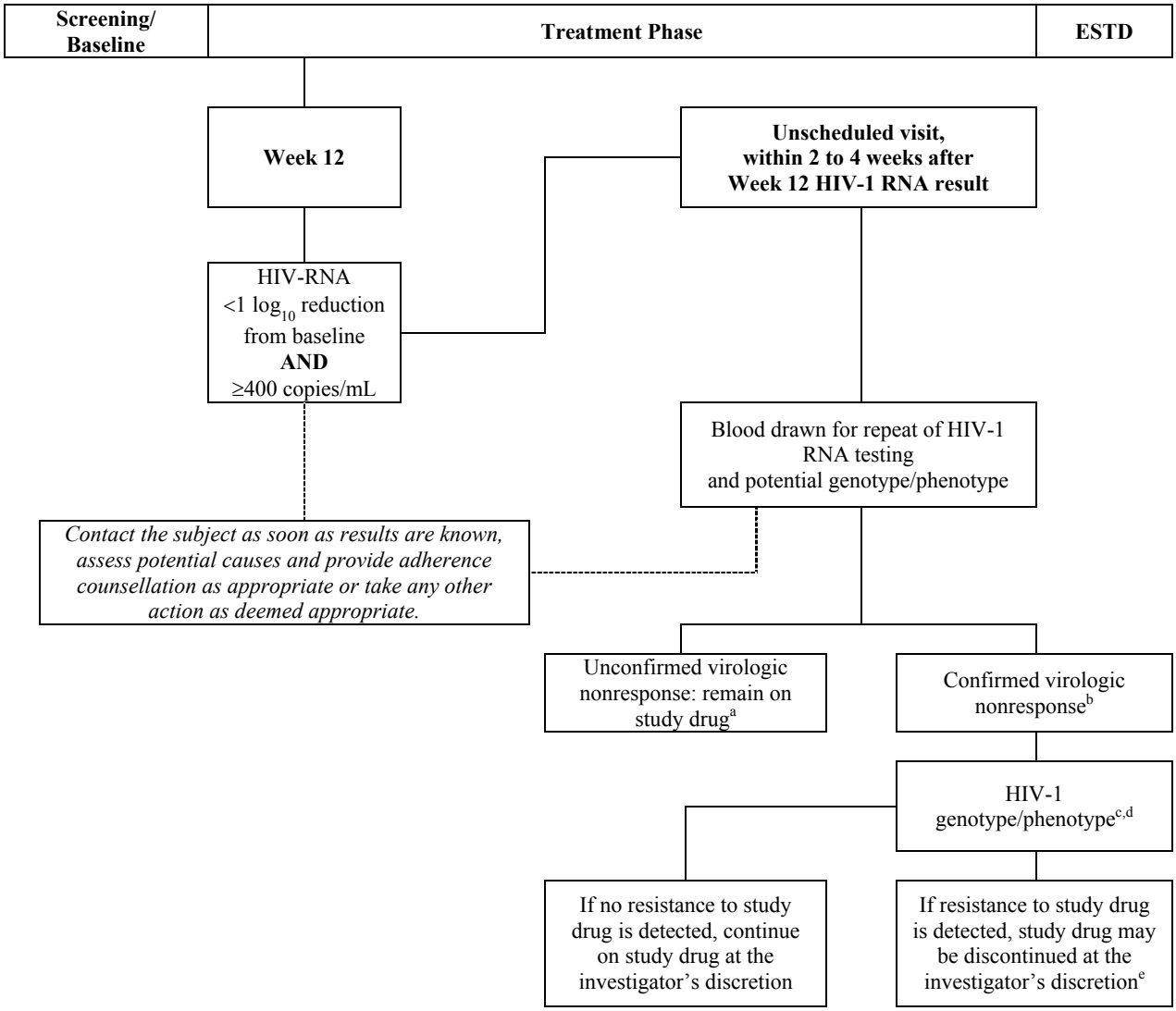
ATTACHMENTS

Attachment 1: Schema for Follow-up of Subjects who Meet the Criteria for Protocol-Defined Virologic Failure

Virologic Nonresponse Schema



[a] If virologic nonresponse is not confirmed, the subject will continue study drug and the subject's viral load will be further monitored.

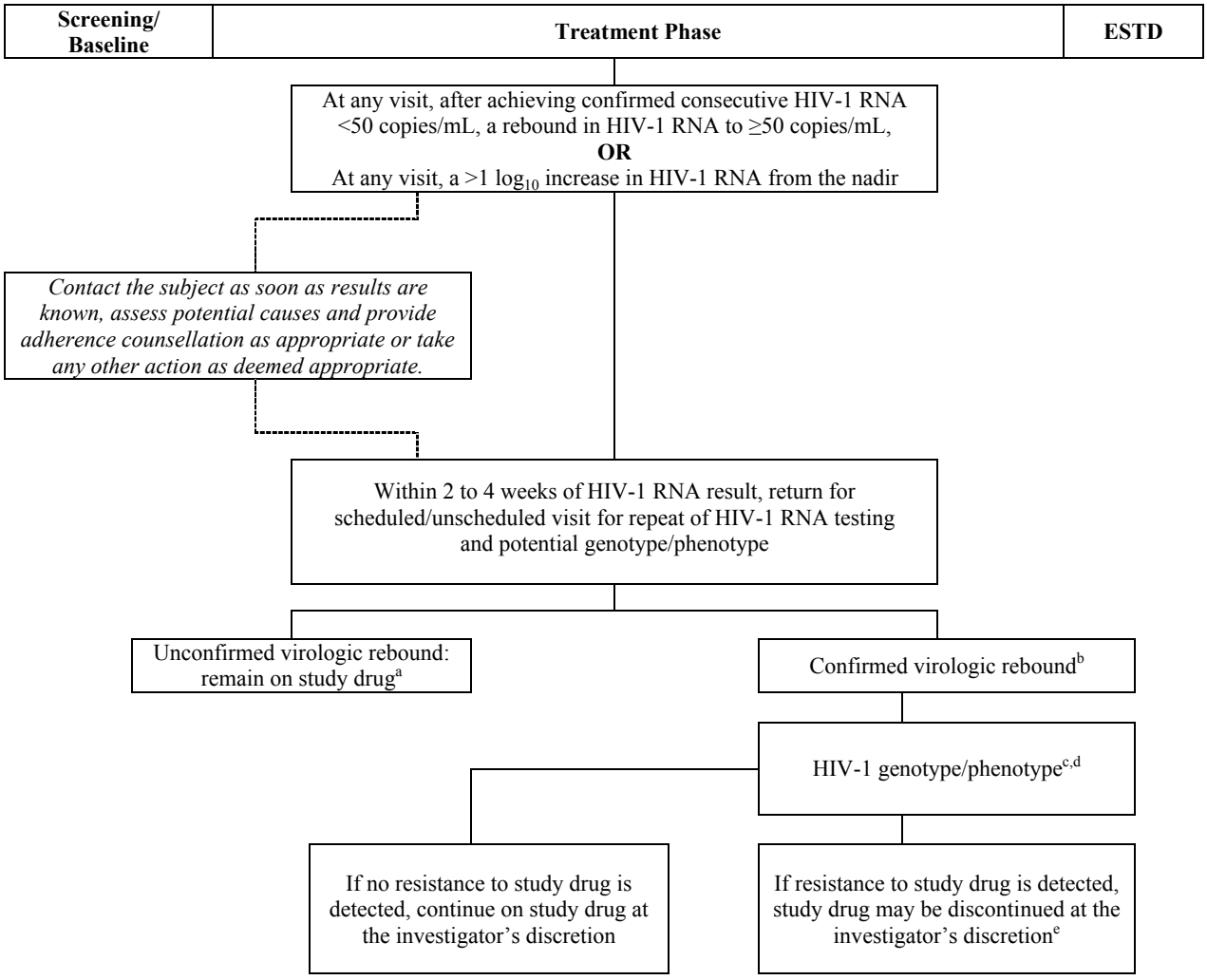
[b] Upon confirmation of virologic nonresponse potential causes should be documented. Assessment should include lack of adherence, concomitant medication, and comorbidities (eg, active substance abuse, depression, or other intercurrent illnesses).

[c] If virologic nonresponse is confirmed, the HIV-1 genotype/phenotype (PhenoSense GT®) will be analyzed.

[d] In case of early discontinuation, an HIV-1 resistance report, if available, will be forwarded to the treating physician to assist in the selection of a new ARV regimen.

[e] Investigators should carefully evaluate the benefits and risks of remaining on study drug for each individual subject and document this assessment in the on-site medical record. Investigators who opt to discontinue study drug for an individual subject must inform the sponsor's medical monitor before study drug discontinuation.

Virologic Rebound Schema



[a] If virologic rebound is not confirmed, the subject will continue study drug and the subject's viral load will be further monitored.

[b] Upon confirmation of virologic rebound, potential causes should be documented. Assessment should include lack of adherence, concomitant medication, and comorbidities (eg, active substance abuse, depression, or other intercurrent illnesses).

[c] If virologic rebound is confirmed, the HIV-1 genotype/phenotype (PhenoSense GT®) will be analyzed.

[d] In case of early discontinuation, an HIV-1 resistance report, if available, will be forwarded to the treating physician to assist in the selection of a new ARV regimen.

[e] Investigators should carefully evaluate the benefits and risks of remaining on study drug for each individual subject and document this assessment in the on-site medical record. Investigators who opt to discontinue study drug for an individual subject must inform the sponsor's medical monitor before study drug discontinuation.

Attachment 2: DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (v 2.0, November 2014), or 'DAIDS grading table', is a descriptive terminology to be utilized for adverse event reporting in this study. A grading (severity) scale is provided for each adverse event term.

General Instructions

Estimating Severity Grade for Parameters Not Identified in the Grading Table

If the need arises to grade a clinical adverse event that is not identified in the DAIDS grading table, use the category 'Estimating Severity Grade' located at the top of the table on the following page. In addition, all deaths related to an adverse event are to be classified as grade 5.

Grading Adult and Pediatric Adverse Events

The DAIDS grading table includes parameters for grading both adult and pediatric adverse events. When a single set of parameters is not appropriate for grading specific types of adverse events for both adult and pediatric populations, separate sets of parameters for adult and/or pediatric populations (with specified respective age ranges) are provided. If there is no distinction in the table between adult and pediatric values for a type of adverse event, then the single set of parameters listed is to be used for grading the severity of both adult and pediatric events of that type.

Determining Severity Grade

If the severity of an adverse event could fall under either 1 of 2 grades (eg, the severity of an adverse event could be either grade 2 or grade 3), select the higher of the 2 grades for the adverse event.

Laboratory normal ranges should be taken into consideration to assign gradings to a laboratory value.

Definitions

Basic Self-care Functions	Adult Activities such as bathing, dressing, toileting, transfer or movement, continence, and feeding. Young Children Activities that are age and culturally appropriate, such as feeding one's self with culturally appropriate eating implements.
Usual Social & Functional Activities	Activities which adults and children perform on a routine basis and those which are part of regular activities of daily living, for example: Adults Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, or pursuing a hobby. Young Children Activities that are age and culturally appropriate, such as social interactions, play activities, or learning tasks.
Intervention	Medical, surgical, or other procedures recommended or provided by a healthcare professional for the treatment of an adverse event.

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

MAJOR CLINICAL CONDITIONS				
CARDIOVASCULAR				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Arrhythmia (by ECG or physical examination) *Specify type, if applicable*	No symptoms AND No intervention indicated	No symptoms AND Non-urgent intervention indicated	Non-life-threatening symptoms AND Non-urgent intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Blood Pressure Abnormalities[1]				
Hypertension *(with the lowest reading taken after repeat testing during a visit)* *≥18 years of age*	140 to <160 mmHg systolic OR 90 to <100 mmHg diastolic	≥160 to <180 mmHg systolic OR ≥100 to <110 mmHg diastolic	≥180 mmHg systolic OR ≥110 mmHg diastolic	Life-threatening consequences in a participant not previously diagnosed with hypertension (eg, malignant hypertension) OR Hospitalization indicated
<18 years of age	>120/80 mmHg	≥95th to <99th percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	≥99th percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences in a participant not previously diagnosed with hypertension (eg, malignant hypertension) OR Hospitalization indicated
Hypotension	No symptoms	Symptoms corrected with oral fluid replacement	Symptoms AND IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Cardiac Ischemia or Infarction *Report only one*	NA	NA	New symptoms with ischemia (stable angina) OR New testing consistent with ischemia	Unstable angina OR Acute myocardial infarction
Heart Failure	No symptoms AND Laboratory or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Symptoms at rest or with minimal activity or exertion (eg, hypoxemia) OR Intervention indicated (eg, oxygen)	Life-threatening consequences OR Urgent intervention indicated (eg, vasoactive medications, ventricular assist device, heart transplant)
Hemorrhage (with significant acute blood loss)	NA	Symptoms AND No transfusion indicated	Symptoms AND Transfusion of ≤2 units packed RBCs indicated	Life-threatening hypotension OR Transfusion of >2 units packed RBCs (for children, packed RBCs >10 cc/kg) indicated

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

CARDIOVASCULAR				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Prolonged PR Interval or AV Block *Report only one* *>16 years of age* *≤16 years of age*	PR interval 0.21 to <0.25 seconds 1st degree AV block (PR interval >normal for age and rate)	PR interval ≥0.25 seconds OR Type I 2nd degree AV block Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥3.0 seconds Type II 2nd degree AV block OR Ventricular pause ≥3.0 seconds	Complete AV block Complete AV block
Prolonged QTc Interval[2]	0.45 to 0.47 seconds	>0.47 to 0.50 seconds	>0.50 seconds OR ≥0.06 seconds above baseline	Life-threatening consequences (eg, Torsade de pointes, other associated serious ventricular dysrhythmia)
Thrombosis or Embolism *Report only one*	NA	Symptoms AND No intervention indicated	Symptoms AND intervention indicated	Life-threatening embolic event (eg, pulmonary embolism, thrombus)

[2] Per Bazett's formula.

DERMATOLOGIC				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Alopecia (scalp only)	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	NA	NA
Bruising	Localized to one area	Localized to more than one area	Generalized	NA
Cellulitis	NA	Non-parenteral treatment indicated (eg, oral antibiotics, antifungals, antivirals)	IV treatment indicated (eg, IV antibiotics, antifungals, antivirals)	Life-threatening consequences (eg, sepsis, tissue necrosis)
Hyperpigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Hypopigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Petechiae	Localized to one area	Localized to more than one area	Generalized	NA
Pruritus[3] (without skin lesions)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA
Rash *Specify type, if applicable* For the rash management applicable in this study, see Section 9.8.2.	Localized rash	Diffuse rash OR Target lesions	Diffuse rash AND Vesicles or limited number of bullae OR superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Stevens-Johnson syndrome OR Toxic epidermal necrolysis

[3] For pruritus associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section.

ENDOCRINE AND METABOLIC				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Diabetes Mellitus	Controlled without medication	Controlled with medication OR Modification of current medication regimen	Uncontrolled despite treatment modification OR Hospitalization for immediate glucose control indicated	Life-threatening consequences (eg, ketoacidosis, hyperosmolar non-ketotic coma, end organ failure)
Gynecomastia	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing pain with greater than minimal interference with usual social & functional activities	Disfiguring changes AND Symptoms requiring intervention or causing inability to perform usual social & functional activities	NA
Hyperthyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (eg, thyroid storm)
Hypothyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (eg, myxedema coma)
Lipoatrophy[4]	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA
Lipohypertrophy[5]	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA

[4] Definition: A disorder characterized by fat loss in the face, extremities, and buttocks.
[5] Definition: A disorder characterized by abnormal fat accumulation on the back of the neck, breasts, and abdomen.

GASTROINTESTINAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated (eg, tube feeding, total parenteral nutrition)
Ascites	No symptoms	Symptoms AND Intervention indicated (eg, diuretics, therapeutic paracentesis)	Symptoms recur or persist despite intervention	Life-threatening consequences
Bloating or Distension *Report only one*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Cholecystitis	NA	Symptoms AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (eg, sepsis, perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (eg, obstruction)
Diarrhea *≥1 year of age*	Transient or intermittent episodes of unformed stools OR Increase of ≤3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools OR Increase of 4 to 6 stools over baseline per 24-hour period	Increase of ≥7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (eg, hypotensive shock)
<1 year of age	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR Mild dehydration	Liquid stools with moderate dehydration	Life-threatening consequences (eg, liquid stools resulting in severe dehydration, hypotensive shock)
Dysphagia or Odynophagia *Report only one and specify location*	Symptoms but able to eat usual diet	Symptoms causing altered dietary intake with no intervention indicated	Symptoms causing severely altered dietary intake with intervention indicated	Life-threatening reduction in oral intake
Gastrointestinal Bleeding	Not requiring intervention other than iron supplement	Endoscopic intervention indicated	Transfusion indicated	Life-threatening consequences (eg, hypotensive shock)
Mucositis or Stomatitis *Report only one and specify location*	Mucosal erythema	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Life-threatening consequences (eg, aspiration, choking) OR Tissue necrosis OR Diffuse spontaneous mucosal bleeding
Nausea	Transient (<24 hours) or intermittent AND No or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 to 48 hours	Persistent nausea resulting in minimal oral intake for >48 hours OR Rehydration indicated (eg, IV fluids)	Life-threatening consequences (eg, hypotensive shock)

GASTROINTESTINAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Pancreatitis	NA	Symptoms with hospitalization not indicated	Symptoms with hospitalization indicated	Life-threatening consequences (eg, circulatory failure, hemorrhage, sepsis)
Perforation (colon or rectum)	NA	NA	Intervention indicated	Life-threatening consequences
Proctitis	Rectal discomfort with no intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social & functional activities OR Operative intervention indicated	Life-threatening consequences (eg, perforation)
Rectal Discharge	Visible discharge	Discharge requiring the use of pads	NA	NA
Vomiting	Transient or intermittent AND No or minimal interference with oral intake	Frequent episodes with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (eg, IV fluids)	Life-threatening consequences (eg, hypotensive shock)

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

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

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

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

PREGNANCY, PUERPERIUM, AND PERINATAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Fetal Death or Stillbirth (report using mother's participant ID) *Report only one*	NA	NA	Fetal loss occurring at ≥20 weeks gestation	NA
Preterm Delivery[7] (report using mother's participant ID)	Delivery at 34 to <37 weeks gestational age	Delivery at 28 to <34 weeks gestational age	Delivery at 24 to <28 weeks gestational age	Delivery at <24 weeks gestational age
Spontaneous Abortion or Miscarriage[8] (report using mother's participant ID) *Report only one*	Chemical pregnancy	Uncomplicated spontaneous abortion or miscarriage	Complicated spontaneous abortion or miscarriage	NA

[7] Definition: A delivery of a live-born neonate occurring at ≥20 to <37 weeks gestational age.
[8] Definition: A clinically recognized pregnancy occurring at <20 weeks gestational age.

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

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

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

SYSTEMIC				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Acute Allergic Reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with intervention indicated OR Mild angioedema with no intervention indicated	Generalized urticaria OR Angioedema with intervention indicated OR Symptoms of mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR Laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Cytokine Release Syndrome[9]	Mild signs and symptoms AND Therapy (ie, antibody infusion) interruption not indicated	Therapy (ie, antibody infusion) interruption indicated AND Responds promptly to symptomatic treatment OR Prophylactic medications indicated for ≤24 hours	Prolonged severe signs and symptoms OR Recurrence of symptoms following initial improvement	Life-threatening consequences (eg, requiring pressor or ventilator support)
Fatigue or Malaise *Report only one*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating symptoms of fatigue or malaise causing inability to perform basic self-care functions
Fever (non-axillary temperatures only)	38.0 to <38.6°C or 100.4 to <101.5°F	≥38.6 to <39.3°C or ≥101.5 to <102.7°F	≥39.3 to <40.0°C or ≥102.7 to <104.0°F	≥40.0°C or ≥104.0°F
Pain[10] (not associated with study agent injections and not specified elsewhere) *Specify location*	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization indicated
Serum Sickness[11]	Mild signs and symptoms	Moderate signs and symptoms AND Intervention indicated (eg, antihistamines)	Severe signs and symptoms AND Higher level intervention indicated (eg, steroids or IV fluids)	Life-threatening consequences (eg, requiring pressor or ventilator support)
Underweight[12] *>5 to 19 years of age*	NA	WHO BMI z-score <-2 to ≤-3	WHO BMI z-score <-3	WHO BMI z-score <-3 with life-threatening consequences
2 to 5 years of age	NA	WHO Weight-for-height z-score <-2 to ≤-3	WHO Weight-for-height z-score <-3	WHO Weight-for-height z-score <-3 with life-threatening consequences
<2 years of age	NA	WHO Weight-for-length z-score <-2 to ≤-3	WHO Weight-for-length z-score <-3	WHO Weight-for-length z-score <-3 with life-threatening consequences

[9] Definition: A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and/or shortness of breath.
[10] For pain associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section.
[11] Definition: A disorder characterized by fever, arthralgia, myalgia, skin eruptions, lymphadenopathy, marked discomfort, and/or dyspnea.
[12] WHO reference tables may be accessed by clicking the desired age range or by accessing the following URLs: http://www.who.int/growthref/who2007_bmi_for_age/en/ for participants >5 to 19 years of age and http://www.who.int/childgrowth/standards/chart_catalogue/en/ for those ≤5 years of age. BMI: Body mass index.

SYSTEMIC				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Weight Loss (excludes postpartum weight loss)	NA	5 to <9% loss in body weight from baseline	≥9 to <20% loss in body weight from baseline	≥20% loss in body weight from baseline OR Aggressive intervention indicated (eg, tube feeding, total parenteral nutrition)

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

SITE REACTIONS TO INJECTIONS AND INFUSIONS				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Injection Site Pain or Tenderness *Report only one*	Pain or tenderness causing no or minimal limitation of use of limb	Pain or tenderness causing greater than minimal limitation of use of limb	Pain or tenderness causing inability to perform usual social & functional activities	Pain or tenderness causing inability to perform basic self-care function OR Hospitalization indicated
Injection Site Erythema or Redness[13] *Report only one* *>15 years of age*	2.5 to <5 cm in diameter OR 6.25 to <25 cm^2 surface area AND Symptoms causing no or minimal interference with usual social & functional activities	≥5 to <10 cm in diameter OR ≥25 to <100 cm^2 surface area OR Symptoms causing greater than minimal interference with usual social & functional activities	≥10 cm in diameter OR ≥100 cm^2 surface area OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage OR Symptoms causing inability to perform usual social & functional activities	Potentially life-threatening consequences (eg, abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
≤15 years of age	≤2.5 cm in diameter	>2.5 cm in diameter with <50% surface area of the extremity segment involved (eg, upper arm or thigh)	≥50% surface area of the extremity segment involved (eg, upper arm or thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Potentially life-threatening consequences (eg, abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
Injection Site Induration or Swelling *Report only one* *>15 years of age*	Same as for **Injection Site Erythema or Redness,** *>15 years of age*	Same as for **Injection Site Erythema or Redness,** *>15 years of age*	Same as for **Injection Site Erythema or Redness,** *>15 years of age*	Same as for **Injection Site Erythema or Redness,** *>15 years of age*
≤15 years of age	Same as for **Injection Site Erythema or Redness,** *≤15 years of age*	Same as for **Injection Site Erythema or Redness,** *≤15 years of age*	Same as for **Injection Site Erythema or Redness,** *≤15 years of age*	Same as for **Injection Site Erythema or Redness,** *≤15 years of age*
Injection Site Pruritus	Itching localized to the injection site that is relieved spontaneously or in <48 hours of treatment	Itching beyond the injection site that is not generalized OR Itching localized to the injection site requiring ≥48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NA

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

LABORATORY VALUES				
CHEMISTRIES				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Acidosis	NA	pH ≥7.3 to <LLN[14]	pH <7.3 without life-threatening consequences	pH <7.3 with life-threatening consequences
Albumin, Low (g/dL; *g/L*)	3.0 to <LLN *30 to <LLN*	≥2.0 to <3.0 *≥20 to <30*	<2.0 *<20*	NA
Alkaline Phosphatase, High	1.25 to <2.5×ULN	2.5 to <5.0×ULN	5.0 to <10.0×ULN	≥10.0×ULN
Alkalosis	NA	pH >ULN to ≤7.5	pH >7.5 without life-threatening consequences	pH >7.5 with life-threatening consequences
ALT or SGPT, High *Report only one*	1.25 to <2.5×ULN	2.5 to <5.0×ULN	5.0 to <10.0×ULN	≥10.0×ULN
Amylase (Pancreatic) or Amylase (Total), High *Report only one*	1.1 to <1.5×ULN	1.5 to <3.0×ULN	3.0 to <5.0×ULN	≥5.0×ULN
AST or SGOT, High *Report only one*	1.25 to <2.5×ULN	2.5 to <5.0×ULN	5.0 to <10.0×ULN	≥10.0×ULN
Bicarbonate, Low (mEq/L; *mmol/L*)	16.0 to <LLN *16.0 to <LLN*	11.0 to <16.0 *11.0 to <16.0*	8.0 to <11.0 *8.0 to <11.0*	<8.0 *<8.0*
Bilirubin ***Direct Bilirubin[15], High*** *>28 days of age* *≤28 days of age* ***Total Bilirubin, High*** *>28 days of age* *≤28 days of age*	 NA ULN to ≤1 mg/dL 1.1 to <1.6×ULN See Appendix A. Total Bilirubin for Term and Preterm Neonates	 NA >1 to ≤1.5 mg/dL 1.6 to <2.6×ULN See Appendix A. Total Bilirubin for Term and Preterm Neonates	 >ULN >1.5 to ≤2 mg/dL 2.6 to <5.0×ULN See Appendix A. Total Bilirubin for Term and Preterm Neonates	 >ULN with life-threatening consequences (eg, signs and symptoms of liver failure) >2 mg/dL ≥5.0×ULN See Appendix A. Total Bilirubin for Term and Preterm Neonates
Calcium, High (mg/dL; *mmol/L*) *≥7 days of age* *<7 days of age*	10.6 to <11.5 *2.65 to <2.88* 11.5 to <12.4 *2.88 to <3.10*	11.5 to <12.5 *2.88 to <3.13* 12.4 to <12.9 *3.10 to <3.23*	12.5 to <13.5 *3.13 to <3.38* 12.9 to <13.5 *3.23 to <3.38*	≥13.5 *≥3.38* ≥13.5 *≥3.38*
Calcium (Ionized), High (mg/dL; *mmol/L*)	>ULN to <6.0 *>ULN to <1.5*	6.0 to <6.4 *1.5 to <1.6*	6.4 to <7.2 *1.6 to <1.8*	≥7.2 *≥1.8*
Calcium, Low (mg/dL; *mmol/L*) *≥7 days of age* *<7 days of age*	7.8 to <8.4 *1.95 to <2.10* 6.5 to <7.5 *1.63 to <1.88*	7.0 to <7.8 *1.75 to <1.95* 6.0 to <6.5 *1.50 to <1.63*	6.1 to <7.0 *1.53 to <1.75* 5.50 to <6.0 *1.38 to <1.50*	<6.1 *<1.53* <5.50 *<1.38*
Calcium (Ionized), Low (mg/dL; *mmol/L*)	<LLN to 4.0 *<LLN to 1.0*	3.6 to <4.0 *0.9 to <1.0*	3.2 to <3.6 *0.8 to <0.9*	<3.2 *<0.8*
Cardiac Troponin I, High	NA	NA	NA	Levels consistent with myocardial infarction or unstable angina as defined by the local laboratory

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

CHEMISTRIES				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Creatine Kinase, High	3 to <6×ULN	6 to <10×ULN	10 to <20×ULN	≥20×ULN
Creatinine, High	1.1 to 1.3×ULN	>1.3 to 1.8×ULN OR Increase of >0.3 mg/dL above baseline	>1.8 to <3.5×ULN OR Increase of 1.5 to <2.0×above baseline	≥3.5×ULN OR Increase of ≥2.0×above baseline
Creatinine Clearance[16] or eGFR, Low *Report only one*	NA	<90 to 60 ml/min or ml/min/1.73 m^2 OR 10 to <30% decrease from baseline	<60 to 30ml/min or ml/min/1.73 m^2 OR ≥30 to <50% decrease from baseline	<30 ml/min or ml/min/1.73 m^2 OR ≥50% decrease from baseline or dialysis needed
Glucose (mg/dL; *mmol/L*) ***Fasting, High*** ***Nonfasting, High***	110 to 125 *6.11 to <6.95* 116 to 160 *6.44 to <8.89*	>125 to 250 *6.95 to <13.89* >160 to 250 *8.89 to <13.89*	>250 to 500 *13.89 to <27.75* >250 to 500 *13.89 to <27.75*	>500 *≥27.75* >500 *≥27.75*
Glucose, Low (mg/dL; *mmol/L*) *≥1 month of age* *<1 month of age*	55 to 64 *3.05 to 3.55* 50 to 54 *2.78 to 3.00*	40 to <55 *2.22 to <3.05* 40 to <50 *2.22 to <2.78*	30 to <40 *1.67 to <2.22* 30 to <40 *1.67 to <2.22*	<30 *<1.67* <30 *<1.67*
Lactate, High	ULN to <2.0×ULN without acidosis	≥2.0×ULN without acidosis	Increased lactate with pH <7.3 without life-threatening consequences	Increased lactate with pH <7.3 with life-threatening consequences
Lipase, High	1.1 to <1.5×ULN	1.5 to <3.0×ULN	3.0 to <5.0×ULN	≥5.0×ULN
Lipid Disorders (mg/dL; *mmol/L*) ***Cholesterol, Fasting, High*** *≥18 years of age* *<18 years of age* ***LDL[17], Fasting, High*** *≥18 years of age* *>2 to <18 years of age* ***Triglycerides, Fasting, High***	 200 to <240 *5.18 to <6.19* 170 to <200 *4.40 to <5.15* 130 to <160 *3.37 to <4.12* 110 to <130 *2.85 to <3.34* 150 to 300 *1.71 to 3.42*	 240 to <300 *6.19 to <7.77* 200 to <300 *5.15 to <7.77* 160 to <190 *4.12 to <4.90* 130 to <190 *3.34 to <4.90* >300 to 500 *>3.42 to 5.7*	 ≥300 *≥7.77* ≥300 *≥7.77* ≥190 *≥4.90* ≥190 *≥4.90* >500 to <1,000 *>5.7 to 11.4*	 NA NA NA NA >1,000 *>11.4*
Magnesium[18], Low (mEq/L; *mmol/L*)	1.2 to <1.4 *0.60 to <0.70*	0.9 to <1.2 *0.45 to <0.60*	0.6 to <0.9 *0.30 to <0.45*	<0.6 *<0.30*
Phosphate, Low (mg/dL; *mmol/L*) *>14 years of age* *1 to 14 years of age* *<1 year of age*	2.0 to <LLN *0.81 to <LLN* 3.0 to <3.5 *0.97 to <1.13* 3.5 to <4.5 *1.13 to <1.45*	1.4 to <2.0 *0.65 to <0.81* 2.5 to <3.0 *0.81 to <0.97* 2.5 to <3.5 *0.81 to <1.13*	1.0 to <1.4 *0.32 to <0.65* 1.5 to <2.5 *0.48 to <0.81* 1.5 to <2.5 *0.48 to <0.81*	<1.0 *<0.32* <1.5 *<0.48* <1.5 *<0.48*
Potassium, High (mEq/L; *mmol/L*)	5.6 to <6.0 *5.6 to <6.0*	6.0 to <6.5 *6.0 to <6.5*	6.5 to <7.0 *6.5 to <7.0*	≥7.0 *≥7.0*
Potassium, Low (mEq/L; *mmol/L*)	3.0 to <3.4 *3.0 to <3.4*	2.5 to <3.0 *2.5 to <3.0*	2.0 to <2.5 *2.0 to <2.5*	<2.0 *<2.0*

[16] Use the applicable formula (Modification of Diet in Renal Disease [MDRD]).
[17] Low-density lipoprotein
[18] To convert a magnesium value from mg/dL to mmol/L, laboratories should multiply by 0.4114.

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

HEMATOLOGY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Absolute $CD4^+$ Count, Low (cell/mm^3; *cells/L*) *>5 years of age (not HIV infected)*	300 to <400 *300 to <400*	200 to <300 *200 to <300*	100 to <200 *100 to <200*	<100 *<100*
Absolute Lymphocyte Count, Low (cell/mm^3; *cells/L*) *>5 years of age (not HIV infected)*	600 to <650 *0.600×10^9 to <0.650×10^9*	500 to <600 *0.500×10^9 to <0.600×10^9*	350 to <500 *0.350 x10^9 to <0.500×10^9*	<350 *<0.350×10^9*
Absolute Neutrophil Count (ANC), Low (cells/mm^3; *cells/L*) *>7 days of age* *2 to 7 days of age* *≤1 day of age*	800 to 1,000 *0.800×10^9 to 1.000×10^9* 1,250 to 1,500 *1.250×10^9 to 1.500×10^9* 4,000 to 5,000 *4.000×10^9 to 5.000×10^9*	600 to 799 *0.600×10^9 to 0.799×10^9* 1,000 to 1,249 *1.000×10^9 to 1.249×10^9* 3,000 to 3,999 *3.000×10^9 to 3.999×10^9*	400 to 599 *0.400×10^9 to 0.599×10^9* 750 to 999 *0.750×10^9 to 0.999×10^9* 1,500 to 2,999 *1.500×10^9 to 2.999×10^9*	<400 *<0.400×10^9* <750 *<0.750×10^9* <1,500 *<1.500×10^9*
Fibrinogen, Decreased (mg/dL; *g/L*)	100 to <200 *1.00 to <2.00* OR 0.75 to <1.00×LLN	75 to <100 *0.75 to <1.00* OR ≥0.50 to <0.75×LLN	50 to <75 *0.50 to <0.75* OR 0.25 to <0.50×LLN	<50 *<0.50* OR <0.25×LLN OR Associated with gross bleeding
Hemoglobin[17], Low (g/dL; *mmol/L*)[18] *≥13 years of age (male only)* *≥13 years of age (female only)* *57 days of age to <13 years of age (male and female)* *36 to 56 days of age (male and female)* *22 to 35 days of age (male and female)* *8 to ≤21 days of age (male and female)* *≤7 days of age (male and female)*	10.0 to 10.9 *6.19 to 6.76* 9.5 to 10.4 *5.88 to 6.48* 9.5 to 10.4 *5.88 to 6.48* 8.5 to 9.6 *5.26 to 5.99* 9.5 to 11.0 *5.88 to 6.86* 11.0 to 13.0 *6.81 to 8.10* 13.0 to 14.0 *8.05 to 8.72*	9.0 to <10.0 *5.57 to <6.19* 8.5 to <9.5 *5.25 to <5.88* 8.5 to <9.5 *5.25 to <5.88* 7.0 to <8.5 *4.32 to <5.26* 8.0 to <9.5 *4.94 to <5.88* 9.0 to <11.0 *5.57 to <6.81* 10.0 to <13.0 *6.19 to <8.05*	7.0 to <9.0 *4.34 to <5.57* 6.5 to <8.5 *4.03 to <5.25* 6.5 to <8.5 *4.03 to <5.25* 6.0 to <7.0 *3.72 to <4.32* 6.7 to <8.0 *4.15 to <4.94* 8.0 to <9.0 *4.96 to <5.57* 9.0 to <10.0 *5.59 to <6.19*	<7.0 *<4.34* <6.5 *<4.03* <6.5 *<4.03* <6.0 *<3.72* <6.7 *<4.15* <8.0 *<4.96* <9.0 *<5.59*
INR[19], High (not on anticoagulation therapy)	1.1 to <1.5×ULN	1.5 to <2.0×ULN	2.0 to <3.0×ULN	≥3.0×ULN
Methemoglobin (% hemoglobin)	5.0 to <10.0%	10.0 to <15.0%	15.0 to <20.0%	≥20.0%

[17] Male and female sex are defined as sex at birth.
[18] The conversion factor used to convert g/dL to mmol/L is 0.6206 and is the most commonly used conversion factor. For grading hemoglobin results obtained by an analytic method with a conversion factor other than 0.6206, the result must be converted to g/dL using the appropriate conversion factor for the particular laboratory.
[19] International normalized ratio.

HEMATOLOGY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
PTT[20], High (not on anticoagulation therapy)	1.1 to <1.66×ULN	1.66 to <2.33×ULN	2.33 to <3.00×ULN	≥3.00×ULN
Platelets, Decreased (cells/mm^3; *cells/L*)	100,000 to <124,999 *100.000×10^9 to <124.999×10^9*	50,000 to <100,000 *50.000×10^9 to <100.000×10^9*	25,000 to <50,000 *25.000×10^9 to <50.000×10^9*	<25,000 *<25.000×10^9*
PT[21], High (not on anticoagulation therapy	1.1 to <1.25×ULN	1.25 to <1.50×ULN	1.50 to <3.00×ULN	≥3.00×ULN
WBC, Decreased (cells/mm^3; *cells/L*) *>7 days of age* *≤7 days of age*	 2,000 to 2,499 *2.000×10^9 to 2.499×10^9* 5,500 to 6,999 *5.500×10^9 to 6.999×10^9*	 1,500 to 1,999 *1.500×10^9 to 1.999×10^9* 4,000 to 5,499 *4.000×10^9 to 5.499×10^9*	 1,000 to 1,499 *1.000×10^9 to 1.499×10^9* 2,500 to 3,999 *2.500×10^9 to 3.999×10^9*	 <1,000 *<1.000×10^9* <2,500 *<2.500×10^9*

[20] Partial thromboplastin time.
[21] Prothrombin time

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

APPENDIX A: TOTAL BILIRUBIN TABLE FOR TERM AND PRETERM NEONATES

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Total Bilirubin[19], **High** (mg/dL; *µmol/L*)[20]				
Term Neonate[21]				
<24 hours of age	4 to <7 *68.4 to <119.7*	7 to <10 *119.7 to <171*	10 to <17 *171 to <290.7*	≥17 *≥290.7*
24 to <48 hours of age	5 to <8 *85.5 to <136.8*	8 to <12 *136.8 to <205.2*	12 to <19 *205.2 to <324.9*	≥19 *≥324.9*
48 to <72 hours of age	8.5 to <13 *145.35 to <222.3*	13 to <15 *222.3 to <256.5*	15 to <22 *256.5 to <376.2*	≥22 *≥376.2*
72 hours to <7 days of age	11 to <16 *188.1 to <273.6*	16 to <18 *273.6 to <307.8*	18 to <24 *307.8 to <410.4*	≥24 *≥410.4*
7 to 28 days of age (breast feeding)	5 to <10 *85.5 to <171*	10 to <20 *171 to <342*	20 to <25 *342 to <427.5*	≥25 *≥427.5*
7 to 28 days of age (not breast feeding)	1.1 to <1.6×ULN	1.6 to <2.6×ULN	2.6 to <5.0×ULN	≥5.0×ULN
Preterm Neonate[21]				
35 to <37 weeks gestational age	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).
32 to <35 weeks gestational age and <7 days of age	NA	NA	10 to <14 *171 to <239.4*	≥14 *≥239.4*
28 to <32 weeks gestational age and <7 days of age	NA	NA	6 to <10 *102.6 to <171*	≥10 *≥171*
<28 weeks gestational age and <7 days of age	NA	NA	5 to <8 *85.5 to <136.8*	≥8 *≥136.8*
7 to 28 days of age (breast feeding)	5 to <10 *85.5 to <171*	10 to <20 *171 to <342*	20 to <25 *342 to <427.5*	≥25 *≥427.5*
7 to 28 days of age (not breast feeding)	1.1 to <1.6×ULN	1.6 to <2.6×ULN	2.6 to <5.0×ULN	≥5.0×ULN

[19] Severity grading for total bilirubin in neonates is complex, because of rapidly changing total bilirubin normal ranges in the first week of life followed by the benign phenomenon of breast milk jaundice after the first week of life. Severity grading in this appendix corresponds approximately to cut-offs for indications for phototherapy at grade 3 and for exchange transfusion at grade 4.
[20] A laboratory value of 1 mg/dL is equivalent to 17.1 µmol/L.
[21] Definitions: Term is defined as ≥37 weeks gestational age; near-term, as ≥35 weeks gestational age; preterm, as <35 weeks gestational age; and neonate, as 0 to 28 days of age.

Attachment 3: WHO Clinical Staging of HIV/AIDS

The clinical stages of HIV infection for adults and adolescents are defined as follows. (Adapted from: 1993 Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR 1992;41(RR-17):1-19; and WHO 2007 Case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children [Table 3]).[31,42]

Clinical Stage 1

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

- Asymptomatic HIV infection
- Persistent generalized lymphadenopathy

Clinical Stage 2

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

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

Clinical Stage 3

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

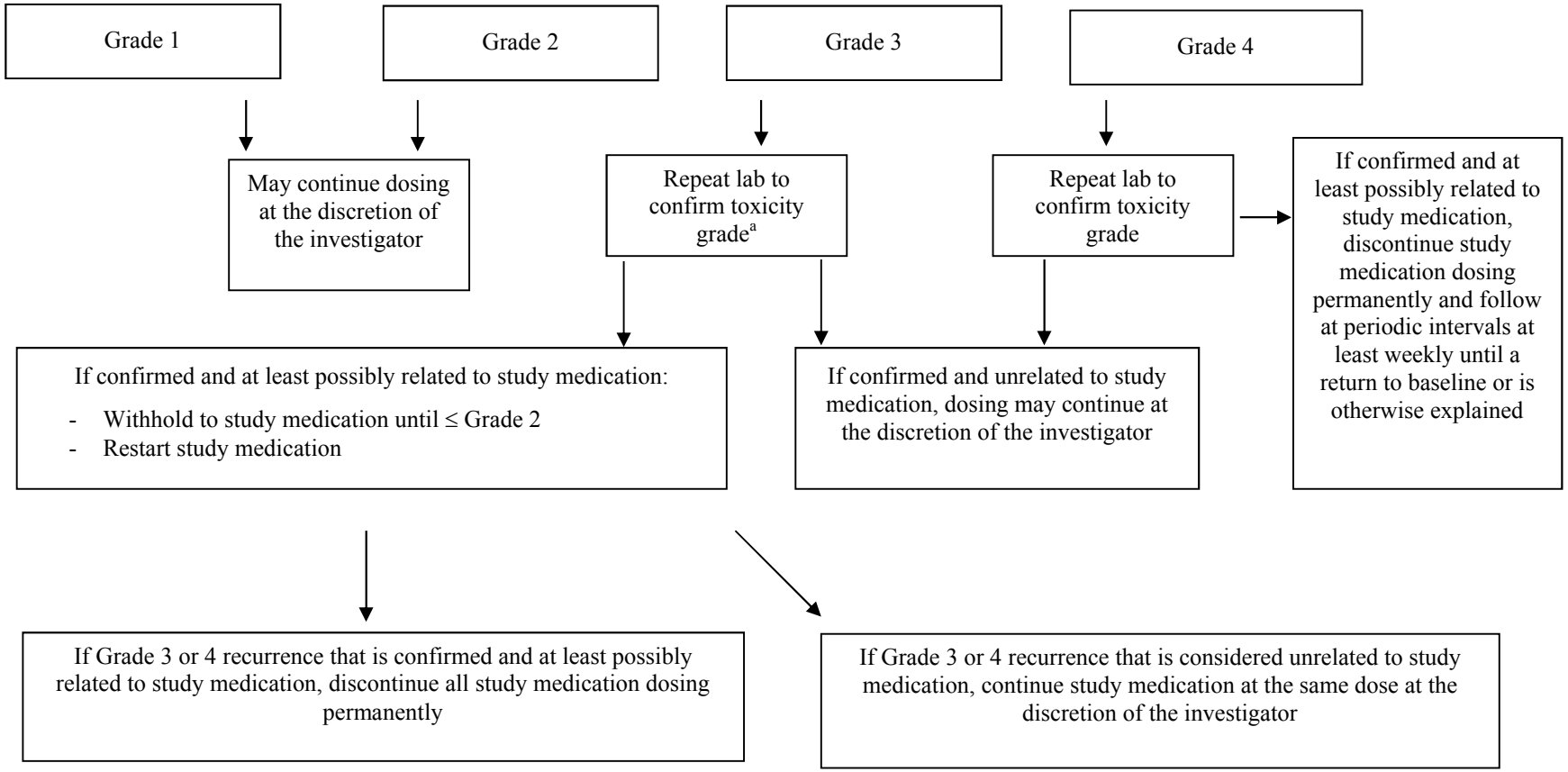
- Unexplained (not explained by other causes) severe weight loss (>10% of presumed or measured body weight)
- Unexplained chronic diarrhea for longer than 1 month
- Unexplained persistent fever (above 37.6°C intermittent or constant, for longer than 1 month)
- Persistent oral candidiasis
- Oral hairy leukoplakia
- Pulmonary tuberculosis (current)
- Severe bacterial infections (such as pneumonia, empyema, pyomyositis, bone or joint infection, meningitis or bacteremia)
- Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis
- Unexplained anemia (<8 g/dL), neutropenia (<0.5x10^9/L) or chronic thrombocytopenia (<50x10^9/L)

Clinical Stage 4

HIV wasting syndrome:

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

Attachment 4: Management of Clinically Significant Laboratory Toxicities*



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

*** Please note that this Attachment does not apply to screening/baseline eGFR, AST, ALT, and lipase, and does also not apply to the allowed retesting of abnormal screening/baseline eGFR, AST, ALT, and lipase values (see Section 3.1).**

Attachment 5: Management of Dyslipidemia

RECOMMENDATIONS

(Adapted from: Guidelines for the evaluation and management of dyslipidemia in human immunodeficiency virus [HIV]-Infected adults receiving antiretroviral therapy: Recommendations of the HIV Medicine Association of the Infectious Disease Society of America and the Adult AIDS Clinical Trials Group. Clin Infect Dis. 2003;37(5):613-627.)[1]

Clinicians should monitor patients receiving ARV therapy for dyslipidemia by obtaining a fasting lipid profile before and after starting ARV therapy. Frequent monitoring may be indicated by the presence of persistent lipid elevation, cardiovascular risk factors, or cardiovascular symptoms.

Clinicians should recommend lifestyle modifications, such as increased exercise, weight loss, nutrition therapy, smoking cessation, and drug addiction treatment.

Pharmacologic treatment of dyslipidemia should be guided by currently available clinical guidelines.

Lipid abnormalities in HIV-infected patients, specifically hypocholesterolemia and hypertriglyceridemia, were described before the advent of ARV therapy; however, the number of patients with lipid abnormalities appears to be increasing in the highly active antiretroviral therapy (HAART) era. Patients often develop lipid abnormalities within 3 months of initiation of ARV therapy. The full clinical significance of these laboratory abnormalities is not yet clear, although the abnormalities may be associated with premature coronary artery disease (CAD) in some patients, especially those with other risk factors for coronary heart disease (CHD) or the metabolic syndrome previously referred to as syndrome X.

Major risk factors (LDL cholesterol excluded) that modify LDL goals* are:

- cigarette smoking;
- hypertension (blood pressure ≥140/90 mmHg or on antihypertensive medication);
- low HDL cholesterol (<40 mg/dL)†;
- family history of premature CHD
  (CHD in male first-degree relative <55 years; CHD in female first-degree relative <65 years)
- age (men ≥45 years; women ≥55 years)

* All these risk factors are captured in the eCRF.

† HDL cholesterol ≥60 mg/dL counts as a 'negative' risk factor; its presence removes one risk factor from the total count

Hypertriglyceridemia, low HDL cholesterol levels, and elevated LDL cholesterol levels have been described in patients receiving ARV therapy, especially PIs. Non-nucleoside reverse transcriptase inhibitor (NNRTI) use has been associated with hypercholesterolemia. The mechanism by which PIs cause dyslipidemia is unclear. Hypertriglyceridemia seems to be most significant in patients with regimens that include low-dose rtv. Significant hypertriglyceridemia (>500 mg/dL) is associated with an increased risk of pancreatitis, particularly in patients with other risk factors for pancreatitis eg, alcohol or didanosine use).

Lipid abnormalities in HIV-infected patients receiving ARV therapy may occur in conjunction with body fat changes. Secondary causes of dyslipidemia, including diabetes, hypothyroidism, liver disease, chronic renal failure, and other medications, such as progestins, anabolic steroids, and corticosteroids, should be considered in patients with new onset dyslipidemia.

A fasting lipid profile (total, LDL and HDL cholesterol, triglycerides) should be obtained before starting ARV treatment (ideally at baseline visit). A fasting lipid profile should be obtained 3 to 6 months after starting or changing ARV therapy (ideally at each visit of the study protocol).

Alternatively, if collection of a fasting sample is not feasible, a nonfasted total cholesterol and HDL cholesterol may be obtained. The clinician should proceed with a fasting lipoprotein profile when the nonfasted total cholesterol is >200 mg/dL or HDL cholesterol is <40 mg/dL.

The management of lipid disorders in HIV-infected patients parallels management in non-HIV-infected patients (see Table 3 and Table 4). Individual risk assessments for an acute coronary event and management of lipid disorders can be accomplished by following current guidelines for assessment and management, such as those published by the National Cholesterol Education Program (NCEP) and the AIDS Clinical Trial Group (ACTG) Cardiovascular Disease Focus Group (see Table 3 and Table 4). Treatment of dyslipidemia should include lifestyle and risk modification with or without pharmacological therapies.

For patients without known CAD, therapeutic lifestyle changes should be the first intervention for the treatment of lipid disorders. These changes include increased physical exercise, weight reduction when indicated, smoking cessation and dietary changes. Consultation with a registered dietitian may be helpful in achieving dietary goals [restriction of total fat to 25%-30% of total caloric intake, and dietary cholesterol to <200 mg/day; use of plant sterols (2 g/d) found in commercial margarines (eg, Benecol or Basikol), and increased soluble fiber (10-25 g/d)].

Lipid-lowering agents should be considered for hyperlipidemias that do not respond to changes in ARV therapy or therapeutic lifestyle changes, or for patients in whom such modifications are not appropriate. The first-line pharmacological treatment for patients with isolated elevation of LDL cholesterol is statin therapy (see Table 4). Pravastatin is the safest drug for treating hyperlipidemia during concurrent therapy with currently FDA approved PIs. Atorvastatin can be used cautiously at lower doses (5-10 mg) with careful titration. Rosuvastatin will not likely interact with PIs and NNRTIs. Use of other statins, particularly lovastatin and simvastatin, is contraindicated.

Fibric acid derivatives, such as gemfibrozil and fenofibrate, are the first-line treatment for isolated elevation of fasting triglyceride levels. The threshold suggested for intervention is 500 mg/dL.

Gemfibrozil and fenofibrate are not metabolized via the CYP system and are generally safe to use in patients receiving ARV therapy. For patients with high triglycerides in whom LDL cholesterol cannot be measured, the non-HDL cholesterol level may be calculated to guide initiation of therapy (total – HDL cholesterol).

Patients with persistent high-grade hypertriglyceridemia (>1,000 mg/dL) may benefit from a very low-fat diet, even if they are not overweight.

Table 3: LDL and non-HDL Cholesterol Goals and Thresholds for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories

Risk Category	LDL Goal (mg/dL)	LDL Level at Which to Initiate Lifestyle Changes (mg/dL)	LDL Level at Which to Consider Drug Therapy (mg/dL)	Non-HDL Goal (mg/dL)*
CHD or CHD risk equivalents: diabetes mellitus, atherosclerotic disease (CAD or stroke), or multiple risk factors (10-year risk >20%)	<100	≥100	<130 (100-129: drug optional)†	≥130
2+ risk factors: HDL <40, strong family history, age >45 years, and smoking (10-year risk >20%)	<130	≥130	10-year risk 10%-20%: ≥130 10-year risk <10%: ≥160	<160
0-1 risk factor‡	<160	≥160	≥190 (160-189: LDL-lowering drug optional)	<190

* Non-HDL cholesterol = (total – HDL cholesterol). When LDL cholesterol cannot be measured because the triglyceride level is >200 mg/dL, non-HDL cholesterol may be used as a secondary goal. The non-HDL cholesterol goal is 30 mg/dL higher than the LDL cholesterol goal.

† Some authorities recommend use of LDL-lowering drugs in this category if an LDL cholesterol level of <100 mg/dL cannot be achieved by therapeutic lifestyle changes (dietary and exercise intervention). Others prefer use of drugs that primarily modify triglycerides and HDL cholesterol (eg, nicotine acid or fibrate). Clinical judgment also may suggest deferring drug therapy in this subcategory.

‡ Almost all people with 0 or 1 risk factors have a 10-year risk <10%; thus, 10-year risk assessment in people with 0 or 1 risk factors is not necessary.

For those with both elevated serum LDL cholesterol and triglyceride levels, combination therapy with a statin and fibrate may be needed but should be used with extreme caution because of overlapping toxicity (rhabdomyolysis) profiles. Therapy should begin first with a statin, followed by the addition of the fibric acid derivative if response to the maximal statin dose is suboptimal after 3 to 4 months of treatment. Routine monitoring for hepatic and muscle toxicity should be performed in these situations.

The use of additional drugs, such as nicotinic acid or bile sequestrants, may be necessary to manage dyslipidemia. Nicotinic acid may cause hepatotoxicity and elevated serum glucose levels. Therefore, low-dose therapy with incremental dose increases is advisable for those patients who require this drug. Bile acid sequestrants (eg, colesevelam 3 tablets twice daily or ezetimibe 10 mg once daily) may also be used but may interfere with absorption of oral medications; therefore, proper timing of the dosing of this drug is important when used in conjunction with ARV medications (ie, 1 hour before or 4 hours after).

Table 4: Choice of Drug Therapy for Dyslipidemia in HIV-infected Individuals Receiving HAART

Lipid Abnormality	First Choice	Second Choice (or if Additional Treatment is Needed)	Comments
Isolated high LDL cholesterol	Statin*	Fibrate	Start with low doses of statins and titrate upward. Patients receiving PIs may be at increased risk of statin-induced myopathy.
Combined hyperlipidemia (high cholesterol and high triglycerides)	Fibrate or statin*	If starting with fibrate, add statin* If starting with statin*, add fibrate	Combining statin and a fibrate may increase risk for myopathy
Isolated hypertriglyceridemia	Fibrate	Statin*	Combining statin and a fibrate may increase risk for myopathy.

* Statins should be dosed at bedtime. Simvastatin and lovastatin are not allowed in patients receiving DRV.

Attachment 6: Cardiovascular Safety: Definitions of Abnormalities

Vital Signs

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 (Attachment 2).

Attachment 7: HIV-Treatment Satisfaction Questionnaire (HIVTSQs)

The following questions are concerned with your medical treatment for HIV and your experience over the past few weeks. Please answer each question by circling a number on each of the scales.

1. How satisfied are you with your current treatment?

very satisfied	6	5	4	3	2	1	0	very dissatisfied

2. How well controlled do you feel your HIV has been recently?

very well controlled	6	5	4	3	2	1	0	very poorly controlled

3. How satisfied are you with any side effects of your present treatment?

very satisfied	6	5	4	3	2	1	0	very dissatisfied

4. How satisfied are you with the demands made by your current treatment?

very satisfied	6	5	4	3	2	1	0	very dissatisfied

5. How convenient have you been finding your treatment to be recently?

very convenient	6	5	4	3	2	1	0	very inconvenient

6. How flexible have you been finding your treatment to be recently?

very flexible	6	5	4	3	2	1	0	very inflexible

7. How satisfied are you with your understanding of your HIV?

very satisfied	6	5	4	3	2	1	0	very dissatisfied

8. How satisfied are you with the extent to which the treatment fits in with your lifestyle?

very satisfied	6	5	4	3	2	1	0	very dissatisfied

9. Would you recommend your present treatment to someone else with HIV?

yes, I would definitely recommend the treatment	6	5	4	3	2	1	0	no, I would definitely not recommend the treatment

10. How satisfied would you be to continue with your present form of treatment?

very satisfied	6	5	4	3	2	1	0	very dissatisfied

Please make sure that you have circled one number on each of the scales.
Thank you for taking the time to complete this questionnaire.

Attachment 8: Anticipated Events

Anticipated Event

An anticipated event is an adverse event (serious or non-serious) that commonly occurs as a consequence of the underlying disease or condition under investigation (disease related) or background regimen.

For the purposes of this study the following events will be considered anticipated events:

- AIDS dementia (PT AIDS dementia complex)
- Bacterial infections, multiple or recurrent*
- Candidiasis of bronchi, trachea, or lungs
- Candidiasis of esophagus†
- Cervical cancer, invasive§
- Chronic hepatitis secondary to hepatitis B infection
- Chronic hepatitis secondary to hepatitis C infection
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (>1 month's duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age >1 month
- Cytomegalovirus retinitis (with loss of vision)†
- Encephalopathy, HIV related
- Herpes simplex: chronic ulcers (>1 month's duration) or bronchitis, pneumonitis, or esophagitis (onset at age >1 month)
- Herpes zoster infections
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (>1 month's duration)
- Kaposi sarcoma†
- Leishmaniasis
- Lymphoid interstitial pneumonia or pulmonary lymphoid hyperplasia complex*†
- Lymphoma, Burkitt (or equivalent term)
- Lymphoma, immunoblastic (or equivalent term)
- Lymphoma, primary, of brain
- *Mycobacterium avium* complex or *Mycobacterium kansasii,* disseminated or extrapulmonary†
- *Mycobacterium tuberculosis* of any site, pulmonary,†§ disseminated,† or extrapulmonary†
- *Mycobacterium*, other species or unidentified species, disseminated† or extrapulmonary†
- Oral candidiasis
- Peripheral neuropathy
- *Pneumocystis jirovecii* pneumonia†
- Pneumonia, recurrent†§
- Progressive multifocal leukoencephalopathy
- *Salmonella* septicemia, recurrent
- Toxoplasmosis of brain, onset at age >1 month†
- Tuberculosis
- Wasting syndrome attributed to HIV

* Only among children aged <13 years[32]
† Condition that might be diagnosed presumptively
§ Only among adults and adolescents aged ≥13 years[31]

Reporting of Anticipated Events

All adverse events will be recorded in the CRF regardless of whether considered to be anticipated events and will be reported to the sponsor as described in Section 12.3.1, All Adverse Events. Any anticipated event that meets serious adverse event criteria will be reported to the sponsor as described in Section 12.3.2, Serious Adverse Events. These anticipated events are exempt from expedited reporting as individual single cases to Health Authorities. However if based on an aggregate review, it is determined that an anticipated event is possibly related to study drug, the sponsor will report these events in an expedited manner.

Anticipated Event Review Committee (ARC)

An Anticipated Event Review Committee (ARC) will be established to perform reviews of pre-specified anticipated events at an aggregate level. The ARC is a safety committee within the sponsor's organization that is independent of the sponsor's study team. The ARC will meet to aid in the recommendation to the sponsor's study team as to whether there is a reasonable possibility that an anticipated event is related to the study drug.

Statistical Analysis

Details of statistical analysis of anticipated events, including the frequency of review and threshold to trigger an aggregate analysis of anticipated events will be provided in a separate Anticipated Events Safety Monitoring Plan (ASMP).

INVESTIGATOR AGREEMENT

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

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

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): R. Nettles

Institution: Janssen Scientific Affairs, LLC.

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

(Day Month Year)

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

SIGNATURES

Signed by	Date	Justification
Richard Nettles	29Nov2017, 14:17:02 PM, UTC	Document Approval