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Janssen Research & Development *

Clinical Protocol

A Phase 3, randomized, active-controlled, double-blind study to evaluate efficacy and safety of darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) once daily fixed dose combination regimen versus a regimen consisting of darunavir/cobicistat fixed dose combination coadministered with emtricitabine/tenofovir disoproxil fumarate fixed dose combination in antiretroviral treatment-naïve human immunodeficiency virus type 1 infected subjects.

Protocol TMC114FD2HTX3001 Amendment 2; Phase 3

D/C/F/TAF (darunavir/cobicistat/emtricitabine/tenofovir alafenamide)

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This compound is being investigated in Phase 2 and 3 clinical studies.

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

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

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TABLE OF CONTENTS

TABLE OF CONTENTS 2

LIST OF ATTACHMENTS 5

LIST OF IN-TEXT TABLES AND FIGURES 5

PROTOCOL AMENDMENT 6

SYNOPSIS 9

TIME AND EVENT SCHEDULE 18

PERIOD 18

ABBREVIATIONS 23

DEFINITIONS OF TERMS 26

1. INTRODUCTION 27
1.1. Background 27
1.2. Darunavir (PREZISTA®) 28
1.3. Cobicistat (Tybost®) 29
1.4. Emtricitabine (Emtriva®) 30
1.5. Tenofovir Alafenamide 30
1.5.1. General Information 30
1.5.2. Preclinical Pharmacology and Toxicology 31
1.5.3. Preclinical Pharmacokinetics 32
1.5.4. Nonclinical Toxicology 33
1.5.5. Clinical Studies 34
1.6. Comparator Drug 38
1.7. Overall Rationale and Risks Assessment for the Study 38

2. OBJECTIVES AND HYPOTHESIS 40
2.1. Objectives 40
2.2. Hypothesis 41

3. STUDY DESIGN AND RATIONALE 41
3.1. Overview of Study Design 41
3.2. Study Design Rationale 45
3.3. Dose Selection Rationale 46

4. SUBJECT POPULATION 47
4.1. Inclusion Criteria 47
4.2. Exclusion Criteria 50
4.3. Prohibitions and Restrictions 52

5. TREATMENT ALLOCATION AND BLINDING 52

6. DOSAGE AND ADMINISTRATION 53

7. TREATMENT COMPLIANCE 55

8. PRESTUDY AND CONCOMITANT THERAPY 55
8.1. Disallowed and Cautioned Concomitant Therapy 56

9. STUDY EVALUATIONS 60
9.1. Study Procedures 60

9.1.1. Overview ... 60
9.1.2. Pre-treatment Phase ... 62
9.1.2.1. Screening Visit ... 62
9.1.2.2. Baseline Visit (Day 1) ... 63
9.1.3. Double-blind Treatment Phase ... 65
9.1.4. Open-label Single-arm Phase ... 67
9.1.5. Extension Phase ... 68
9.1.6. Post-treatment Phase ... 69
9.1.6.1. Early Study Treatment Discontinuation Visit ... 69
9.1.6.2. 30-Day Follow-up Visit ... 71
9.2. Efficacy Evaluations ... 71
9.2.1. Antiviral Efficacy and Immunologic Change ... 71
9.2.2. Resistance Determinations ... 72
9.2.2.1. Virologic Failure ... 72
9.2.2.2. Subjects Eligible for Resistance Testing ... 72
9.3. Pharmacokinetics Evaluations ... 77
9.3.1. Evaluations ... 77
9.3.2. Analytical Procedures ... 77
9.3.3. Pharmacokinetic Parameters ... 77
9.4. Safety Evaluations ... 78
9.4.1. Adverse Events ... 78
9.4.2. Clinical Laboratory Tests ... 79
9.4.3. Electrocardiogram ... 81
9.4.4. Vital Signs ... 81
9.4.5. Physical Examination ... 82
9.4.6. Bone Investigation Substudy ... 82
9.5. Toxicity Management ... 83
9.5.1. General Guidance for the Management of Clinical Events and Laboratory Abnormalities ... 83
9.5.2. Cutaneous Events/Rash ... 84
9.5.3. Acute Systemic Allergic Reaction ... 86
9.5.4. Potential Renal Toxicity ... 88
9.5.5. Potential Bone Toxicity ... 89
9.5.6. Potential Posterior Uveitis Cases ... 89
9.5.7. Hyperglycemia ... 89
9.5.8. Hypertriglyceridemia and Hypercholesterolemia ... 90
9.5.9. Lipodystrophy/Fat Redistribution/Body Changes ... 90
9.6. Sample Collection and Handling ... 90

10. SUBJECT COMPLETION/WITHDRAWAL ... 91
10.1. Completion ... 91
10.2. Withdrawal From the Study ... 91

11. STATISTICAL METHODS ... 93
11.1. Analysis Objectives and Endpoints ... 93
11.2. Subject Information ... 94
11.3. Sample Size Determination ... 95
11.4. Efficacy Analyses ... 95
11.4.1. Primary Analysis ... 95
11.4.2. Secondary Analyses ... 96
11.5. Pharmacokinetic Analyses ... 96
11.6. Safety Analyses ... 97
11.7. Treatment Adherence ... 98
11.8. Data Monitoring Committee ... 99

12. ADVERSE EVENT REPORTING ... 99
12.1. Definitions ... 99
12.1.1. Adverse Event Definitions and Classifications ... 99
12.1.2. Attribution Definitions ... 102

12.1.3. Severity Criteria ... 102
12.2. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events ... 102
12.3. Special Reporting Situations ... 103
12.4. Procedures ... 103
12.4.1. All Adverse Events ... 103
12.4.2. Serious Adverse Events ... 104
12.4.3. Pregnancy ... 105
12.5. Contacting Sponsor Regarding Safety ... 106

13. PRODUCT QUALITY COMPLAINT HANDLING ... 106
13.1. Procedures ... 106
13.2. Contacting Sponsor Regarding Product Quality ... 106

14. STUDY DRUG INFORMATION ... 106
14.1. Physical Description of Study Drug(s) ... 106
14.2. Packaging ... 107
14.3. Labeling ... 108
14.4. Preparation, Handling, and Storage ... 108
14.5. Drug Accountability ... 108

15. STUDY-SPECIFIC MATERIALS ... 109

16. ETHICAL ASPECTS ... 109
16.1. Study-specific Design Considerations ... 109
16.2. Regulatory Ethics Compliance ... 109
16.2.1. Investigator Responsibilities ... 109
16.2.2. Independent Ethics Committee or Institutional Review Board ... 110
16.2.3. Informed Consent ... 111
16.2.4. Privacy of Personal Data ... 112
16.2.5. Long-term Retention of Samples for Additional Future ... 113
16.2.6. Country Selection ... 113

17. ADMINISTRATIVE REQUIREMENTS ... 113
17.1. Protocol Amendments ... 113
17.2. Regulatory Documentation ... 114
17.2.1. Regulatory Approval/Notification ... 114
17.2.2. Required Prestudy Documentation ... 114
17.3. Subject Identification, Enrollment, and Screening Logs ... 115
17.4. Source Documentation ... 115
17.5. Case Report Form Completion ... 115
17.6. Data Quality Assurance/Quality Control ... 116
17.7. Record Retention ... 116
17.8. Monitoring ... 117
17.9. Study Completion/Termination ... 118
17.9.1. Study Completion ... 118
17.9.2. Study Termination ... 118
17.10. On-site Audits ... 118
17.11. Use of Information and Publication ... 118

REFERENCES ... 121

ATTACHMENTS ... 124

INVESTIGATOR AGREEMENT ... 157

LAST PAGE ... 157

LIST OF ATTACHMENTS

Attachment 1: Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events ... 125
Attachment 2: WHO Clinical Staging of HIV/AIDS ... 147
Attachment 3: Management of Clinically Significant Laboratory Toxicities ... 149
Attachment 4: Management of Dyslipidemia ... 150
Attachment 5: Cardiovascular Safety: Definitions of Abnormalities ... 154
Attachment 6: Anticipated Events ... 155

LIST OF IN-TEXT TABLES AND FIGURES

TABLES

Table 1: Exclusionary Concomitant Medications ... 51
Table 2: Concomitant Therapy: Disallowed and Cautioned Use ... 56
Table 3: Summary of Cutaneous Reaction/Rash Follow-up ... 86
Table 4: Summary of Allergic Reaction Follow-up ... 87
Table 5: BMD at the Lumbar Spine, Power Calculations ... 95
Table 6: LDL and non-HDL Cholesterol Goals and Thresholds for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories ... 152
Table 7: Choice of Drug Therapy for Dyslipidemia in HIV-infected Individuals Receiving HAART ... 153

FIGURES

Figure 1: Schematic Overview of the Study ... 44
Figure 2: Virologic Nonresponse Schema ... 74
Figure 3: Virologic Rebound Schema ... 76

PROTOCOL AMENDMENT

Protocol History TMC114FD2HTX3001_Protocol			
Document Type and *File Name*	Issued Date	Amendment Type	Comments
Initial Clinical Protocol *TMC114FD2HTX3001_Protocol*	10-Mar-2015	-	-
Protocol Amendment 1 *TMC114FD2HTX3001_Protocol_Amend_1*	*23-Jul-2015*	Substantial	For details, please refer to Section Amendment_1
Protocol Amendment 2 *TMC114IFD2HTX3001_Protocol_Amend_2*	*This document*	Non-Substantial	For details, please refer to Section Amendment_2

Amendment_2 (this document)

The overall reason for the amendment: The main reason for this amendment is to clarify that the appearance of the D/C/F/TAF FDC tablets provided in the open-label treatment phase is different from the appearance of the D/C/F/TAF FDC tablets provided in the double-blind treatment phase. Debossed D/C/F/TAF FDC tablets are only provided once patients roll over from the double-blind treatment phase, in which plain-faced D/C/F/TAF FDC tablets are used, to the open-label treatment phase. Further changes have been made to the protocol for clarification or correction.

The changes made to the clinical protocol amendment 1, TMC114FD2HTX3001_Protocol Amend_1, dd. 23-Jul-2015, are listed below, including rationale of each change and a list of all applicable sections.

Rationale: Debossed D/C/F/TAF FDC tablets were added to support the transition from plain-faced D/C/F/TAF FDC tablets in the double-blind treatment phase to debossed D/C/F/TAF FDC tablets in the open-label treatment phase.

14.1 Physical Description of Study Drug(s)

Rationale: A writing error was made: An incorrect power of 86% was provided in the text, and was therefore corrected to 90% power, consistent with what is presented in Table 5.

11.3 Sample Size Determination

Rationale: Section "ECG" in section 11.6 on safety statistical analyses was corrected as there is no data collected in the CRF for HR, RR, PR, QRS, QTcB, or QTcF but only an overall interpretation (normal or abnormal) for the ECG.

11.6 Safety Analyses

Rationale: Correction to the description of the randomization procedure.

5 TREATMENT ALLOCATION AND BLINDING

Rationale: Minor editorial changes were made for clarity and consistency.

3.3 Dose Selection Rationale
5 TREATMENT ALLOCATION AND BLINDING
14.1 Physical Description of Study Drug(s)

Amendment_1 (23-Jul-2015)

The overall reason for the amendment: Following Health Authority feedback on the clinical protocol TMC114FD2HTX3001, dd. 10-Mar-2015, the requested changes have been implemented. Further changes have been made to the protocol for clarification or correction.

The changes made to the clinical protocol TMC114FD2HTX3001, dd. 10-Mar-2015, are listed below, including rationale of each change and a list of all applicable sections.

Rationale: Due to the high rate of discontinuations observed in Gilead's study GS-US-236-0118 (3/12 subjects) among subjects with baseline CrCl <70 mL/min because of renal adverse events, the creatinine clearance threshold for eligibility has therefore been increased from 50 to 70 mL/min.

SYNOPSIS
1.7 Overall Rationale and Risks Assessment for the Study
4.1 Inclusion Criteria
9.1.2.1 Screening Visit

Rationale: Subjects treated with post-exposure prophylaxis and/or pre-exposure prophylaxis who became HIV-1 infected are not considered treatment-naïve and may have resistance to emtricitabine and/or tenofovir disoproxil fumarate that may be undetectable 30 days following treatment. Following Health Authority feedback, subjects previously treated with post-exposure prophylaxis and/or pre-exposure prophylaxis will therefore no longer be allowed in the study.

4.1 Inclusion Criteria

Rationale: For completeness, it has been added in inclusion criterion 13 that the use of birth control methods does not apply for women who are surgically sterile (have had a total hysterectomy or bilateral oophorectomy, tubal ligation/bilateral tubal clips without reversal operation, or otherwise are incapable of becoming pregnant).

4.1 Inclusion Criteria

Rationale: For completeness, penile intra-epithelial neoplasia has been added to the exceptions in exclusion criterion 6.

4.2 Exclusion Criteria

Rationale: To ensure a DXA scan is available prior to starting study medication and to allow more flexibility in the timing of the DXA scan at baseline, the DXA scan can be performed between screening and baseline before study eligibility has been confirmed. Furthermore, it has been clarified that absence of pregnancy needs to be confirmed prior to performing the scan.

Time and Event Schedule
9.1.2.2 Baseline Visit (Day 1)

Rationale: To allow more flexibility in the timing of the DXA scans, but still ensure sufficient time between two consecutive DXA scans to evaluate potential changes, the time windows for the planned study visit scans at Week 24, 48 and 96 and technical rescans have been adjusted.

Time and Event Schedule
9.1.3 Double-blind Treatment Phase
9.1.4 Open-label Single-arm Phase
9.1.6.1 Early Study Treatment Discontinuation Visit

Rationale: The assessment of parathyroid hormone and 25-hydroxy vitamin D at the early study

treatment discontinuation visit (if applicable) has been added for completeness.

Time and Event Schedule
9.1.6.1 Early Study Treatment Discontinuation Visit

Rationale: Since drug dispensation at baseline covers the treatment period up to Week 4, drug accountability at the Week 2 visit has been removed.

SYNOPSIS
Time and Event Schedule
3.1 Overview of Study Design
9.1.3 Double-blind Treatment Phase

Rationale: For clarification, the conditions when the use of lidocaine is disallowed have been specified.

4.2 Exclusion Criteria
8.1 Disallowed and Cautioned Concomitant Therapy

Rationale: For clarification it has been specified that in case of persistent low level viremia between 50 and 400 HIV-1 RNA copies/mL, study drugs may be discontinued at the investigator's discretion and the subject should subsequently be withdrawn from the study.

9.2.2.2 Subjects Eligible for Resistance Testing

Rationale: For clarification, it has been specified that subjects will be given the opportunity to receive D/C/F/TAF treatment after Week 96 in order to collect long-term safety and efficacy data on D/C/F/TAF.

SYNOPSIS
3.2 Study Design Rationale
6 DOSAGE AND ADMINISTRATION

Rationale: Minor modifications and clarifications to the text.

SYNOPSIS
Time and Event Schedule
DEFINITIONS OF TERMS
1.3 Cobicistat (Tybost®)
3.1 Overview of Study Design
8.1 Disallowed and Cautioned Concomitant Therapy
9.1.1 Overview
9.1.2.2 Baseline Visit (Day 1)
9.1.6.1 Early Study Treatment Discontinuation Visit
9.2.2.1 Virologic Failure
9.2.2.2 Subjects Eligible for Resistance Testing
9.4.2 Clinical Laboratory Tests
11.1 Analysis Objectives and Endpoints
11.8 Data Monitoring Committee
Attachment 4 Management of Dyslipidemia

SYNOPSIS

A Phase 3, randomized, active-controlled, double-blind study to evaluate efficacy and safety of darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) once daily fixed dose combination regimen versus a regimen consisting of darunavir/cobicistat fixed dose combination coadministered with emtricitabine/tenofovir disoproxil fumarate fixed dose combination in antiretroviral treatment-naïve human immunodeficiency virus type 1 infected subjects.

EudraCT NUMBER: 2015-000754-38

OBJECTIVES AND HYPOTHESIS

Primary Objective

The primary objective is to demonstrate noninferiority in efficacy of a D/C/F/TAF fixed dose combination (FDC) tablet versus darunavir/cobicistat (DRV/COBI) FDC coadministered with emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) FDC in human immunodeficiency virus type 1 (HIV-1) infected, antiretroviral (ARV) treatment-naïve adult subjects, as determined by the proportion of virologic responders defined as having HIV-1 RNA <50 copies/mL at Week 48 (FDA-defined snapshot analysis), with a maximum allowable difference of 10%.

Secondary Objectives

The secondary objectives of this study are:

- To evaluate superiority of a D/C/F/TAF FDC tablet versus DRV/COBI FDC coadministered with FTC/TDF FDC as determined by the proportion of virologic responders defined as having HIV-1 RNA <50 copies/mL at Week 48 (FDA-defined snapshot analysis), in case noninferiority is established;
- To evaluate the immunologic response (CD4+ cell count) of the 2 treatment arms through Week 48;
- To evaluate the incidence of grade 3 and 4 adverse events (AEs), serious adverse events (SAEs), and premature discontinuations due to AEs in the 2 treatment arms through Week 48;
- To evaluate the change from baseline in serum creatinine, estimated glomerular filtration rate (eGFR) based on creatinine clearance ($eGFR_{creatinine}$, by Cockcroft-Gault and by Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] formulas) and eGFR based on cystatin C clearance ($eGFR_{cystatin\ C}$, by CKD-EPI) in the 2 treatment arms at Week 48;
- To evaluate the change from baseline in renal biomarkers at Week 48;
- To assess the development of viral resistance in the 2 treatment arms through Week 48;
- To evaluate the steady-state pharmacokinetics of DRV and TAF;
- To evaluate long-term efficacy, resistance, and safety of the D/C/F/TAF FDC regimen (Week 96 and beyond).

Objectives of a bone investigation substudy performed at selected study sites:

- To evaluate the safety in the 2 treatment arms as determined by the percentage change from baseline in hip and spine bone mineral density (BMD) and change from baseline in T-score at Week 48;
- To evaluate the change from baseline in bone biomarker levels at Week 48.

Hypothesis

Null hypothesis: D/C/F/TAF FDC is inferior to DRV/COBI FDC coadministered with FTC/TDF FDC by at least 10% with respect to the proportion of subjects having HIV-1 RNA <50 copies/mL at Week 48 (as defined by the FDA-defined snapshot analysis).

Alternative hypothesis: D/C/F/TAF FDC is noninferior to DRV/COBI FDC coadministered with FTC/TDF FDC by less than 10% with respect to the proportion of subjects having HIV-1 RNA <50 copies/mL at Week 48 (as defined by the FDA-defined snapshot analysis).

OVERVIEW OF STUDY DESIGN

Study TMC114FD2HTX3001 is a 96-week multicenter, Phase 3 study consisting of a 48-week randomized, double-blind active-controlled treatment period, to evaluate a D/C/F/TAF FDC versus DRV/COBI FDC coadministered with FTC/TDF FDC in ARV treatment-naïve HIV-1 infected adult subjects, followed by an open-label single-arm D/C/F/TAF treatment period for all subjects up to Week 96 to asses long-term efficacy, resistance, and safety.

A target of 670 subjects will be randomly assigned in this study with 335 subjects planned per treatment arm.

Prior to or at the baseline visit (Day 1), subjects who meet all eligibility criteria will be randomized in a 1:1 ratio to 1 of the following 2 treatment arms:

- D/C/F/TAF Arm: Regimen of a single tablet containing DRV 800 mg/ COBI 150 mg/ FTC 200 mg/ TAF 10 mg (D/C/F/TAF FDC) once daily, (n=335)
  + DRV/COBI FDC-matching and FTC/TDF FDC-matching placebo tablets once daily;
- Control Arm : Regimen of DRV 800 mg/ COBI 150 mg FDC coadministered with FTC 200 mg/ TDF 300 mg FDC once daily, (n=335)
  + D/C/F/TAF FDC-matching placebo tablet once daily.

Randomization will be stratified by HIV-1 RNA level (≤100,000 copies/mL or >100,000 copies/mL) and by CD4+ cell count (<200 cells/µL or ≥200 cells/µL) at screening.

Subjects will be treated for 96 weeks, and will return for study visits at Weeks 2, 4, 8, 12, 24, 36, 48, every 12 weeks thereafter until and including a Week 96 visit.

After Week 48, subjects will continue to take their blinded study drug and attend visits every 12 weeks until all subjects have reached Week 48, the database for the primary analysis has been locked, and treatment assignments have been unblinded. Provided the results from the primary analysis do not preclude (further) exposure of subjects to D/C/F/TAF, all subjects will return for an unblinding visit and will receive the D/C/F/TAF FDC tablet treatment during an open-label single-arm treatment phase up to Week 96. Subjects from the control arm who switch to the D/C/F/TAF regimen after the 48-week double-blind treatment will be required to return to the clinic for an additional visit 3 to 7 weeks after the unblinding visit.

After Week 96, subjects will be given the opportunity to continue D/C/F/TAF treatment during an extension phase until the D/C/F/TAF FDC tablet becomes commercially available and is reimbursed, or can be accessed through another source in the country where he/she is living, or until the sponsor terminates clinical development. During the extension phase subjects will attend visits every 6 months.

Subjects who prematurely discontinue, either during the double-blind treatment phase (from Day 1 to Week 48) or during the single-arm D/C/F/TAF treatment phase (between Week 48 and Week 96) will be

required to return to the clinic within 72 hours of stopping study treatment for the early study treatment discontinuation (ESTD) visit.

In addition, a 30-day follow-up (FU) visit will be required for any subject who has an ongoing AE or SAE at the time of his/her last study visit (unless consent is withdrawn).

Thus, the study will include a screening period of approximately 30 days (up to maximum 6 weeks) starting from the signature of the informed consent form (ICF), double-blind active-controlled treatment for at least 48 weeks, an open-label single-arm D/C/F/TAF treatment up to Week 96 and an extension phase. A 30-day FU visit may take place as described above.

Assessment and reporting of drug adherence and accountability, concomitant medications, and AEs, laboratory evaluations for efficacy and safety (viral load, CD4+ cell count, biochemistry, hematology, urinalysis, urine chemistry), vital signs and (complete or symptom-directed) physical examinations will be performed at each visit, except drug accountability at Week 2. At screening, a 12-lead electrocardiogram (ECG) and an HIV-1 genotype test will be performed. Urine for assessments of selected renal biomarkers, including retinol binding protein and beta-2-microglobulin, will be collected at baseline and at several visits during the study.

Screening genotype testing will be performed for all subjects to assess sensitivity to DRV, TDF and FTC. Further HIV-1 protease (PR) and reverse transcriptase (RT) genotype/phenotype testing will be performed at later time points for subjects that are eligible for resistance testing (subjects with virologic rebound, virologic nonresponse, and discontinuations with last available viral load measurement ≥400 copies/mL). If resistance to the study drugs is documented, study drugs may be discontinued.

Pharmacokinetic assessments (sparse sampling) will be performed for all subjects (single sample from Weeks 4 through 48 or the ESTD visit, except at Weeks 8 and 36 visits, when 2 samples will be collected ≥2.5 hours apart).

A bone investigation substudy will be performed at selected study sites, to assess bone biomarkers, including C-type collagen sequence (CTX), procollagen type 1 N-terminal propeptide (P1NP), parathyroid hormone (PTH) and 25-hydroxy vitamin D, and dual energy x-ray absorptiometry (DXA) scans, in at least 170 subjects (85 subjects per treatment arm) who provide informed consent for the substudy.

The safety and tolerability, as well as efficacy, of the enrolled subjects and treatment regimens will be monitored by an independent Data Monitoring Committee (DMC). In addition to the Week 48, Week 96 and final analyses, formal DMC analyses will be performed for monitoring purposes, including a futility analysis for lack of (non-inferior) efficacy and a blinded sample size re-estimation.

SUBJECT POPULATION

Approximately 670 subjects will be randomized in a 1:1 ratio to 1 of the 2 treatment arms.

The key inclusion and exclusion criteria are summarized below.

Key Inclusion Criteria
Subjects must be ARV treatment-naïve (never treated with an ARV including post-exposure prophylaxis and pre-exposure prophylaxis); no prior use of any approved or experimental anti-HIV drug for any length of time.
Screening plasma HIV-1 RNA level ≥1,000 copies/mL
CD4+ cell count >50 cells/μL.
Screening HIV-1 genotype report must show full sensitivity to DRV, TDF and FTC.
Screening $eGFR_{creatinine}$ ≥70 mL/min according to the Cockcroft-Gault formula for creatinine clearance.

Key Exclusion Criteria
Subject has been diagnosed with a new AIDS-defining condition within the 30 days prior to screening.
Subject has proven or suspected acute hepatitis within 30 days prior to screening.
Subject is hepatitis C or hepatitis B positive
Subject has a history of cirrhosis.

DOSAGE AND ADMINISTRATION

Prior to the baseline visit (Day 1), eligible subjects will be randomized in a 1:1 ratio to the investigational treatment arm (D/C/F/TAF FDC tablet) or the active control arm (DRV/COBI FDC coadministered with FTC/TDF FDC).

- **D/C/F/TAF Arm (n=335):**

  Regimen of a single-tablet containing DRV 800 mg/ COBI 150 mg/ FTC 200 mg/ TAF 10 mg (D/C/F/TAF FDC) once daily
  + DRV/COBI FDC-matching and FTC/TDF FDC-matching placebo tablets once daily;

- **Control Arm (n=335):**

  Regimen of DRV 800 mg/ COBI 150 mg FDC coadministered with FTC 200 mg/ TDF 300 mg FDC once daily
  + D/C/F/TAF FDC-matching placebo tablet once daily.

All baseline tests and procedures must be completed prior to the administration of the first dose of study treatment. Initiation of study treatment must take place within 24 hours after the baseline visit.

The investigational medication, D/C/F/TAF FDC tablets, the control DRV/COBI FDC tablets and the D/C/F/TAF FDC- and DRV/COBI FDC–matching placebo tablets (identical in physical appearance), will be manufactured, packaged and provided by the sponsor. The control FTC/TDF FDC tablets and matching placebo tablets will be manufactured, packaged by Gilead Sciences, Inc. (GSI) and provided to the sponsor for distribution.

All study drugs and matching placebo tablets must be administered orally, once daily in the morning with food, at approximately the same time each day. Study drugs should be taken on site with food during study site visits (except Week 8 and Week 36), after all safety assessments that require fasting are taken. If subjects notice that they 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 missed their dose >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 do not last longer than 4 consecutive weeks. The sponsor should be notified when such temporary interruption occurs.

After Week 48, subjects will continue to take their blinded study drug and attend visits every 12 weeks until all subjects have reached Week 48 and treatment assignments have been unblinded. Provided the results from the primary analysis do not preclude (further) exposure of subjects to D/C/F/TAF, all subjects will return for an unblinding visit and will receive the D/C/F/TAF treatment during an open-label single-arm treatment phase up to Week 96. In order to collect long-term safety and efficacy data on D/C/F/TAF, subjects will be given the opportunity to continue the D/C/F/TAF treatment after Week 96 during an extension phase until the D/C/F/TAF FDC tablet becomes commercially available and is reimbursed, or can be accessed through another source in the country where he/she is living, or until the sponsor terminates clinical development.

EVALUATIONS

Efficacy

Samples for determination of plasma HIV-1 RNA viral load, immunologic parameters, and for HIV-1 genotype/phenotype resistance testing will be taken at the time points specified in the Time and Events Schedule.

Pharmacokinetics

Pharmacokinetic assessments (sparse sampling) will be performed for all subjects at the time points specified in the Time and Events Schedule.

Plasma concentrations of DRV, COBI and TAF of samples from subjects in the D/C/F/TAF treatment arm will be analyzed under the responsibility of the sponsor, using validated analytical methods. Plasma concentrations of FTC and/or TFV of samples from subjects in the D/C/F/TAF treatment arm and plasma concentrations of the ARVs in the control arm may be determined, using validated analytical methods, at the sponsor's discretion.

Safety

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:

- AEs;
- Clinical laboratory tests (including biochemistry, hematology, urinalysis, urine chemistry, renal biomarkers);
- Vital signs;
- Physical examination (complete or symptom-directed);
- Bone investigations (bone biomarkers and DXA scans of spine and hip) in subjects participating in the bone investigation substudy;
- Follow-up on specific toxicities.

Treatment Adherence

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

STATISTICAL METHODS

The following analyses will be performed:

- Independent DMC analyses for monitoring purposes, including a formal futility analysis for lack of (non-inferior) efficacy and a blinded sample size re-estimation.
- The primary analysis: once all subjects have completed the Week 48 assessments or discontinued earlier.
- The Week 96 analysis: once all subjects have completed the Week 96 assessments or discontinued earlier.

- The final analysis: once all subjects have completed the extension phase and the 30-day FU visit (if applicable), or discontinued earlier.

Additional statistical analyses may be done as needed to prepare for interactions with regulatory authorities.

Primary Endpoint

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.

Secondary Endpoints

The secondary endpoints of this study are:

- The proportion of subjects with HIV-1 RNA <50 copies/mL at Week 96 as defined by the FDA snapshot analysis;
- The proportion of subjects with HIV-1 RNA <20 and <200 copies/mL at Weeks 48 and 96 as defined by the FDA snapshot analysis;
- The proportion of subjects with HIV-1 RNA <20, <50, and <200 copies/mL at Weeks 48 and 96 as defined by the time to loss of virologic response (TLOVR) algorithm;
- The change from baseline in $\log_{10}$ HIV-1 RNA at Weeks 48 and 96;
- The change from baseline in CD4+ cell count at Weeks 48 and 96;
- The change from baseline in serum creatinine, $eGFR_{creatinine}$ (by Cockcroft-Gault and by CKD-EPI) and $eGFR_{cystatin\ C}$ (by CKPD-EPI) at Weeks 48 and 96;
- The proportion of subjects experiencing grade 3 and 4 AEs, SAEs, and premature discontinuations due to AEs through Weeks 48 and 96.
- The change from baseline in renal biomarkers at Week 48 and 96;
- The development of viral resistance through Weeks 48 and 96;
- Pharmacokinetic parameters (by population pharmacokinetic analysis) for DRV and TAF.

The endpoints of the bone investigation substudy are:

- The percentage change from baseline in hip and spine BMD and change from baseline in T-score at Weeks 24, 48, and 96;
- The change from baseline in bone biomarkers at Weeks 24, 48, and 96.

Subject Information

- The intent-to-treat (ITT) population will include all the subjects who were randomized and received ≥1 dose treatment in the study. Subjects will be grouped according to the treatment arm (D/C/F/TAF or control) to which they were randomized. The ITT analysis set is the primary analysis set for efficacy analysis. Efficacy data up to the last dose date of the randomized study treatment will be included.

  The safety analysis (including all data collected up to 30 days after subjects permanently discontinue their study treatment) is also performed on this analysis set.
- Since an analysis on the ITT population may not be conservative in a noninferiority setting, an analysis based on the per protocol (PP) population will also be performed to investigate the impact of excluding subjects with major protocol violations and to evaluate the robustness of the primary

analysis results. The PP population will include all subjects who (1) are randomized into the study, (2) have received ≥1 dose of treatment in the study, and (3) without any major protocol deviation that is considered to potentially affect efficacy outcomes (eg, inadequate baseline resistance profile, use of concomitant medication interfering with antiviral efficacy, inadequate adherence to drug intake). Specific details will be provided in the Statistical Analysis Plan. The PP analysis set is the secondary analysis set for efficacy analysis.

- The pharmacokinetic analysis set will include all subjects who are randomized to the D/C/F/TAF arm (and the control arm, if applicable) and have received ≥1 dose of investigational treatment in the study, and for whom plasma concentration data of any analytes of interest are available.

Sample Size Determination

A sample size of 670 subjects (335 subjects in D/C/F/TAF arm and 335 subjects in the control arm) will yield 90% power. It is assumed that both treatment arms have a response rate of 80% (HIV-1 RNA <50 copies/mL at Week 48 as defined by the FDA snapshot analysis), that the noninferiority margin is 10%, and that the significance level of the test is at a 1-sided, 0.025 level.

A minimum of 170 subjects (85 per treatment arm) is targeted to be included in the bone investigation substudy. Assuming a 4% inter-subject variability in BMD and a 1-sided alpha level of 2.5%, 85 subjects per treatment arm is sufficient to detect at least an absolute difference of 2% between the treatment arms with 90% power.

Statistical Analyses

Efficacy

- The primary analysis will consist of a noninferiority evaluation of the D/C/F/TAF FDC tablet (investigational treatment arm) versus DRV/COBI FDC coadministered with FTC/TDF FDC (control arm), with respect to the proportion of subjects with HIV-1 RNA <50 copies/mL at Week 48 after the start of treatment in this study (as defined by the FDA snapshot analysis). It will be concluded that the D/C/F/TAF FDC tablet is not inferior to the control regimen if the lower bound of the 2-sided 95% confidence interval (CI) of the difference between treatment arms (D/C/F/TAF arm - control arm) in the response rate is greater than -10% (ie, a margin of 10% is applied to noninferiority assessment). The difference (with associated 95% confidence interval) will be constructed using the stratum-adjusted Mantel-Haenszel difference in proportions, where the stratification factors (HIV-1 RNA level [≤100,000 copies/mL or >100,000 copies/mL] and CD4+ cell count [<200 cells/µL or ≥200 cells/µL] at screening) determine the strata.

  If noninferiority of the D/C/F/TAF arm to control arm is established, the lower bound of the 95% CI will be compared to 0; if the lower bound of the 95% CI is greater than 0, then superiority of D/C/F/TAF over the control arm will be established.

- The proportion of subjects with HIV-1 RNA <20 and <200 copies/mL at Week 48 as defined by the FDA snapshot analysis will be analyzed using the same method as for the primary efficacy endpoint to compare treatment arms.

- Confirmed virologic response defined as HIV-1 RNA <20, <50, and <200 copies/mL at Week 48 determined by the TLOVR algorithm will be analyzed using the same method as for the primary efficacy endpoint to compare treatment arms.

- The changes from baseline in CD4+ cell count at Week 48 and 96 will be summarized using descriptive statistics. The differences in changes from baseline in CD4+ cell count at Week 48 between the 2 treatment arms and the associated 95% confidence intervals will be constructed using

analysis of covariance (ANCOVA), including CD4+ cell count at baseline as continuous covariate in the model.

- Screening HIV-1 PR/RT genotype analysis will be performed for all subjects. Post-screening HIV-1 PR/RT genotype/phenotype testing will be available from subjects who are eligible for resistance testing (subjects with virologic rebound, virologic nonresponse, and discontinuations with last available viral load measurement ≥400 copies/mL). The number and type of amino acid changes, of HIV-1 PR (including IAS-USA PI RAMs and IAS-USA primary PI mutations), and RT (including IAS-USA NRTI RAMs and IAS-USA NNRTI RAMs), as well as specific mutations associated with resistance to DRV, FTC, and TDF will be tabulated. Available fold change (FC) in 50% effective concentration (EC_{50}) of ARVs will be tabulated. In subjects with paired screening or baseline and post-baseline genotypes/phenotypes, development of resistance will be analyzed.

Pharmacokinetic Analyses

The plasma concentration data of DRV, TAF, and COBI of subjects randomized to the D/C/F/TAF treatment arm will be evaluated. Plasma concentration data for each analyte may be subjected to population pharmacokinetic modeling, if appropriate population pharmacokinetic models are available. Model specifications will be described in separate report(s), as applicable.

The pharmacokinetics of other ARVs in the D/C/F/TAF arm (eg, FTC and TVF) and their metabolites, as well as the ARVs in samples from subjects in the control arm, may be analyzed, if deemed necessary, upon sponsor's request.

Descriptive statistics will be calculated for the plasma concentrations of DRV, COBI, and TAF by visit and for the derived pharmacokinetic parameters (as available), and also for any of the other ARVs in the study analyzed upon sponsor's request, if applicable. Summary statistics include n, mean, SD, coefficient of variation (CV), geometric mean, median, minimum and maximum.

Safety Analyses

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

Summaries (number and percentage of subjects) of treatment-emergent AEs (by system organ class [SOC] and preferred term [PT]) will be provided by treatment arm. Additional summaries will include summaries for AEs by severity grade (with special attention to grade 3 or 4 AEs), investigator's assessment of relationship to treatment, SAEs, and AEs leading to discontinuation of study treatment.

Laboratory data will be summarized by treatment arm and 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.

The changes from baseline in serum creatinine, $eGFR_{creatinine}$ (by Cockcroft-Gault and by CKD-EPI) and $eGFR_{cystatin\ C}$ (by CKPD-EPI) at Weeks 48 and 96 will be summarized by treatment arm and using descriptive statistics. The difference in changes from baseline at Week 48 in serum creatinine between the 2 treatment arms will be tested using ANCOVA, including baseline serum creatinine in the model.

Selected renal biomarkers, including retinol binding protein and beta-2-microglobulin, will be summarized by treatment arm and visit using descriptive statistics. The difference in change from baseline in these biomarkers at Week 48 between 2 treatment arms will be tested using the Wilcoxon rank-sum test.

Descriptive statistics of vital signs (pulse rate, systolic and diastolic blood pressure) 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.

Bone Investigation Substudy

Baseline, post-baseline, and the percent change from baseline at Weeks 24, 48, and 96 for selected bone biomarkers, including CTX, P1NP, PTH and 25-hydroxy vitamin D, will be summarized by treatment arm and visit using descriptive statistics. The within-treatment comparison will be done using Wilcoxon signed-rank test. The comparison between the 2 treatment arms at Weeks 24 and 48 will be performed using the Wilcoxon rank-sum test.

Percent change from baseline in spine and hip BMD at Weeks 24, 48, and 96, as well as the change from baseline in BMD T-score will be summarized by treatment arm and visit using descriptive statistics. The between-treatment differences at Weeks 24 and 48 will be estimated using ANCOVA model, including baseline BMD value and other clinically relevant factors (if deemed necessary) in the model. The within-treatment comparison will be done using paired t-test.

Treatment Adherence

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

TIME AND EVENT SCHEDULE

PERIOD		Double-blind Active-controlled Treatment Period[c,d]								Open-label Single-arm D/C/F/TAF Treatment Period[f]			Extension Period[h]	ESTD[i]	30-Day FU[j]
Visit	**Screening[a]**	**Baseline Day 1[b]**	**Week 2**	**Week 4**	**Week 8**	**Week 12**	**Week 24**	**Week 36**	**Week 48[d] and Unblinding Visit[e]**	**3-7 weeks after Unblinding Visit[g]**	**Every 12 weeks**	**Week 96**	**Every 6 months**		
Study Procedures															
Screening/Administrative															
Informed consent[k]	X														
Medical history	X														
12-Lead ECG (local)	X														
Height	X														
HBV and HCV testing	X														
Serum pregnancy test[l]	X														
FSH test[m]	X														
Inclusion/exclusion criteria	X														
Check clinical status[n]		X													
Study Drug Administration															
Randomization[o]		X													
Adherence (log booklet)[p]		X	X	X	X	X	X	X	X[q]	X	X	X		X	
Drug dispensation & accountability		X		X	X	X	X	X	X[q,r]	X[s]	X	X	X[t]	X[s]	
Safety Evaluations															
Adverse events	X	X	X	X	X	X	X	X	X[q]	X	X	X	X	X	X
Vital signs and weight	X	X	X	X	X	X	X	X	X[q]	X	X	X	X	X	X[u]
Complete physical examination	X	X					X		X					X	
Symptom-directed physical examination			X	X	X	X		X	X[v]	X	X	X	X		X
Concomitant medications	X	X	X	X	X	X	X	X	X[q]	X	X	X	X	X	X

PERIOD		Double-blind Active-controlled Treatment Period[c,d]								Open-label Single-arm D/C/F/TAF Treatment Period[f]			Extension Period[h]	ESTD[i]	30-Day FU[j]
Visit	Screening[a]	Baseline Day 1[b]	Week 2	Week 4	Week 8	Week 12	Week 24	Week 36	Week 48[d] and Unblinding Visit[e]	3-7 weeks after Unblinding Visit[g]	Every 12 weeks	Week 96	Every 6 months		
Clinical Laboratory Evaluations[w]															
Chemistry profile[x]	X	X	X	X	X	X	X	X	X[q]	X	X	X	X	X	X
Metabolic profile[y]		X					X		X[q]			X			
Hematology profile[z]	X	X	X	X	X	X	X	X	X[q]	X	X	X	X	X	X
Cystatin C and $eGFR_{cystatin\ C}$	X	X	X	X	X	X	X	X	X[q]	X					
$eGFR_{creatinine}$[aa]	X	X	X	X	X	X	X	X	X[q]	X	X	X	X	X	X
Urinalysis and urine chemistry[bb]	X	X	X	X	X	X	X	X	X[q]	X	X	X	X	X	X
Urine pregnancy test[k]		X	X	X	X	X	X	X	X[q]	X	X	X	X	X	X
Renal biomarkers[cc]		X	X	X		X	X		X[q]	X	X	X		X	
Efficacy Evaluations															
Plasma HIV-1 RNA[dd]	X	X	X	X	X	X	X	X	X[q]	X	X	X	X	X	X
CD4+ cell count	X	X	X	X	X	X	X	X	X[q]	X	X	X	X	X	X
HIV-1 genotype/phenotype[ee]	X	X	X	X	X	X	X	X	X[q]	X	X	X	X	X	
PBMC sample[ff]		X					X		X[gg]			X		X	
Pharmacokinetic Evaluations															
Pharmacokinetic sample[hh]			X	X	X	X	X	X	X[ff]					X	
Other															
Plasma sample storage[ii]		X	X	X	X	X	X	X	X	X		X		X	
Bone investigation substudy															
DXA scans[jj]		X					X		X[gg]			X		X	
Bone biomarkers[ll]		X	X	X		X	X		X[kk]	X	X[kk]	X		X	

DXA: dual energy x-ray absorptiometry; ECG: electrocardiogram; eGFR: estimated glomerular filtration rate; ESTD: Early Study Treatment Discontinuation visit; FSH: follicle-stimulating hormone; FU: Follow-up; HBV: hepatitis B; HCV: hepatitis C; HIV-1: human immunodeficiency virus type 1; ICF: informed consent form; PBMC: peripheral blood mononuclear cells; RNA: ribonucleic acid.

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

[b] The baseline visit (Day 1) cannot proceed until the investigator has received all results of the screening visit and subject eligibility has been confirmed. Subjects will be dispensed investigational drug on the baseline visit; initiation of treatment with the investigational drug must take place within 24 hours after the baseline visit.

[c] All study visits are to be scheduled relative to the baseline visit date and are to occur at the end of Weeks 2, 4, 8, 12, 24, 36, 48, and every 12 weeks thereafter until the unblinding visit. The visit window is ±2 days of the protocol-specified visit date at Week 2, ±7 days of the protocol-specified date through Week 48, and every 12 weeks thereafter until the unblinding visit.

[d] After Week 48, subjects will continue to take their blinded study drug and attend visits every 12 weeks until all subjects have reached Week 48.

[e] Once all subjects have reached Week 48 and unblinded treatment assignments have been provided to the investigators, all subjects will return to the clinic for an unblinding visit, preferably at the next planned visit. At the unblinding visit, provided the results from the primary analysis do not preclude (further) exposure of subjects to D/C/F/TAF, all subjects will discontinue their blinded study drugs and will receive the D/C/F/TAF FDC tablet in a single-arm treatment period up to Week 96.

[f] Study visits during the open-label single-arm D/C/F/TAF treatment period are to be completed within ±7 days of the protocol-specified visit date.

[g] Subjects from the control arm who switch to the D/C/F/TAF treatment after the 48-week double-blind treatment will be required to return to the clinic for an additional visit 3 to 7 weeks after the unblinding visit. If this additional visit would take place within a ±4 week window of a normal planned schedule visit, the additional visit can take place during this planned visit.

[h] Visits in the extension period will occur every 6 months, until the D/C/F/TAF treatment becomes commercially available and is reimbursed, or can be accessed through another source in the country where he/she is living, or until the sponsor terminates clinical development. Study visits during the extension period are to be completed within ±14 days of the protocol-specified visit date.

[i] ESTD visit to occur within 72 hours of last dose of study treatment for subjects who prematurely discontinue, either during the double-blind treatment period (from Day 1 to Week 48), or during the open-label single-arm D/C/F/TAF treatment period (between Week 48 and Week 96).

[j] Required for any subject who has an ongoing AE or SAE at the time of his/her study visit (unless consent is withdrawn); ±7 days window may be used.

[k] Signing of the ICF needs to be done before the first study-related activity.

[l] Females of childbearing potential only. 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 throughout the study. Findings during these unscheduled visits or assessments need to be reported in the eCRF.

[m] FSH test for female subjects who have stopped menstruating for at least 2 years but do not have documentation of ovarian failure.

[n] If a subject's clinical status changes (including available laboratory results or receipt of additional medical records) after screening but before the first dose of study drug is given such that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation in the study.

[o] Randomization should be performed during the baseline visit, provided that all screening procedures have been completed and subject eligibility has been confirmed.

[p] Dispensation of the study medication log booklet at the baseline visit, in which study medication intakes need to be recorded; checking of the log booklet and discussion with the subject by the investigator or designated study personnel at all subsequent visits.

[q] At Week 48, every 12 weeks following Week 48 until unblinding, and the unblinding visit.

[r] The first open-label study drug dispensation will occur at the unblinding visit.

[s] Drug accountability only; study drug will not be dispensed at this visit.

[t] Subjects might return to the clinic more frequently during the extension period for drug dispensation only.

[u] Weight only.

[v] A symptom-directed physical examination (physical examination of body parts for which symptoms have been reported by the subject) will be performed as needed at the every 12 weeks visits between Week 48 and the unblinding visit.

[w] Study drugs should be taken on site with food during all visits up to Week 96 after all laboratory assessments which require fasting are performed (except for the Week 8 and 36 visits, where fasting is not required).

[x] Chemistry profile: alpha1-acid glycoprotein (AAG), alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), total bilirubin, direct and indirect bilirubin, total protein, albumin, creatine phosphokinase (CPK), bicarbonate, blood urea nitrogen (BUN), chloride, creatinine, glucose, phosphorus, potassium, sodium, uric acid, amylase (reflex lipase testing is performed in subjects with total amylase >1.5xULN). At baseline, Weeks 24, 48, and 96, analyses of glucose will be done as part of the fasting metabolic assessments and not as part of the chemistry profile.

[y] Fasting metabolic profile (total, high-and low-density lipoprotein [HDL and LDL] cholesterol, triglycerides, glucose). If a subject has not fasted prior to the visit, the visit may proceed, but subject must return within 72 hours in a fasted state to have a blood draw for the metabolic assessments.

[z] Hematology profile: hemoglobin, hematocrit, red blood cell (RBC) count and parameters (mean corpuscular hemoglobin [MCH], MCH concentration and mean corpuscular volume), white blood cell (WBC) count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), platelet count.

[aa] At screening only $eGFR_{creatinine}$ by Cockcroft-Gault, at other visits during the treatment and extension phase also $eGFR_{creatinine}$ by CKD-EPI.

[bb] Urine chemistry (quantitative measurement): creatinine, sodium, phosphate, glucose, protein, albumin.
Urinalysis by dipstick: specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase, and microscopic analysis if needed.

[cc] Urine sample for selected renal biomarkers (including retinol binding protein and beta-2-microglobulin) should be collected fasted. If the subject has not fasted prior to the visit, the visit may proceed, but the subject must return within 72 hours in a fasted state to provide a urine sample for renal biomarkers. Required on the ESTD visit if the last test was more than 12 weeks before the ESTD visit.

[dd] Leftover blood samples from the viral load determinations could be used for protocol-related testing (virology, safety, pharmacokinetic analysis) at additional time points.

[ee] At screening, only genotypic analysis of the HIV-1 (protease [PR] and reverse transcriptase [RT]) will be conducted for all subjects. Genotype/phenotype testing at later time points will be requested by the study virologist, based on subject's viral load.

[ff] A PBMC sample will be taken for storage for exploratory analysis (eg to characterize archived viral resistance) if deemed necessary by the study virologist.

[gg] Sample only to be taken at Week 48.

[hh] At Weeks 2, 4, 12, 24, 48, and the ESTD visit, subjects will have a single pharmacokinetic blood sample collected at least 30 minutes to maximum 4 hours postdose. At the Week 8 and 36 visits, 2 pharmacokinetic samples will be collected with at least 2.5 hours in between sampling. The first pharmacokinetic sample should be taken between 1 and 4 hours postdose (dosing may occur prior to the study site visit).

[ii] Plasma samples drawn will be frozen and stored. Plasma storage samples will be banked for possible additional protocol-related testing (virology, safety, pharmacokinetic analysis).

Bone investigation substudy at selected sites only (provided the necessary approvals have been obtained and informed consent is provided for the substudy)**:**

[jj] DXA scan of spine and hip: to be performed between screening and baseline (+2 weeks), at Weeks 24, 48, 96 and at the ESTD visit (±2 weeks) (only to be performed at ESTD if the last scan is more than 12 weeks from the date of the ESTD visit and the ESTD visit takes place before Week 96). A rescan for technical reasons is allowed within 2 weeks for the baseline visit, and within 4 weeks for all other visits. The time interval between the evaluable DXA scans at baseline and Week 24, baseline and Week 48, baseline and Week 96 is recommended to be at least 20, 44, and 92 weeks, respectively.

[kk] To be performed every 24 weeks.

[ll] The blood sample for selected bone biomarkers (including CTX, P1NP, PTH and 25-hydroxy vitamin D) is to be collected fasted. If the subject has not fasted prior to the visit, the visit may proceed but the subject must return within 72 hours in a fasted state to draw blood for bone biomarkers. Biomarkers PTH and 25-hydroxy vitamin D should be assessed at Day 1, Week 24, 48, 96, and ESTD (if applicable) only.

Note : During screening, retesting of abnormal laboratory values that may lead to exclusion will be allowed once.

Unscheduled visit(s) may be required for safety reasons, for technical issues, or for confirmation of virologic failure in case of unconfirmed virologic failure (virologic nonresponse or virologic rebound [see Section 9.2.2, Figure 2, and Figure 3]). 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.

ABBREVIATIONS

3TC	lamivudine
AAG	alpha1-acid glycoprotein
ABC	abacavir
ACTG	AIDS Clinical Trial Group
ADR	adverse drug reaction
AE	adverse event
AGEP	acute generalised exanthematous pustulosis
AK	adenylate kinase
AIDS	acquired immunodeficiency syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ARV	antiretroviral
AST	aspartate aminotransferase
ATV	atazanavir
AUC	area under the concentration-time curve
AUC_{inf}	AUC extrapolated to infinity
AUC_{last}	AUC from time of administration up to the last time point with a measurable concentration after dosing
AUC_{tau}	AUC from time of administration up to the end of the dosing interval
BMD	bone mineral density
bPI	boosted protease inhibitor
BUN	blood urea nitrogen
CAD	coronary artery disease
CI	confidence interval
CHD	coronary heart disease
CHMP	Committee for Medicinal Products for Human Use
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{0h}	trough plasma concentration
C_{max}	maximum plasma concentration
C_{xh}	plasma concentrations x hours after dosing
COBI	cobicistat
CPK	creatine phosphokinase
CTX	C-type collagen sequence
CV	coefficient of variation
CYP	cytochrome P450
DAIDS	Division of AIDS
DBP	diastolic blood pressure
D/C/F/TAF	darunavir/cobicistat/emtricitabine/tenofovir alafenamide
DMC	Data Monitoring Committee
DP	diphosphate
DRESS	Drug reaction with eosinophilia and systemic symptoms
DRV	darunavir
DTG	dolutegravir
DXA	dual energy x-ray absorptiometry
EC_{50}	50% effective concentration
E/C/F/TAF	elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide
E/C/F/TDF	elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate
ECG	electrocardiogram
eCRF	electronic case report form
eDC	electronic data capture
EFV	efavirenz
eGFR	estimated glomerular filtration rate
$eGFR_{creatinine}$	eGFR for creatinine clearance

$eGFR_{cystatin\ C}$	eGFR for cystatin C clearance
EOT	end of treatment
ESTD	early study treatment discontinuation
EVG	elvitegravir
FC	fold change
FDA	Food and Drug Administration
FDC	fixed-dose combination
FSH	follicle-stimulating hormone
FTC	emtricitabine
FU	follow-up
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GS-7430 (free base)	TAF (see also below)
GS-7430-02	TAF monofumarate
GS-7430-03	TAF fumarate
GSI	Gilead Sciences, Inc.
HAART	highly-active antiretroviral therapy
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDPE	high-density polyethylene
hERG	human *ether-à-go-go*-related gene
HDL	high-density lipoprotein
HIV-1	human immunodeficiency virus type 1
IAS	International AIDS Society
IB	Investigator's Brochure
IC_{50}	50% inhibitory concentration
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
INR	international normalized ratio
InSTI	integrase strand transfer inhibitor
IRB	Institutional Review Board
ITT	intent to treat
IWRS	interactive web response system
LC-MS/MS	liquid chromatography/mass spectrometry/mass spectrometry
LDL	low-density lipoprotein
LLN	lower limit of normal range
LPV	lopinavir
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
NCEP	National Cholesterol Education Program
NNRTI	non-nucleoside reverse transcriptase inhibitor
NOAEL	no observed adverse effect level
NR	(virologic) nonresponse
NRTI	nucleoside/nucleotide reverse transcriptase inhibitor
P1NP	procollagen type N-terminal propeptide
PBMC	peripheral blood mononucleated cell
PDE	phosphodiesterase
PI	protease inhibitor
PP	per protocol
PQC	Product Quality Complaint
PR	protease
PT	preferred term
PTH	parathyroid hormone

PTT	partial thromboplastin time
QTcB	QT interval corrected for heart rate according to Bazett
QTcF	QT interval corrected for heart rate according to Fridericia
RAL	raltegravir
RAM	resistance-associated mutation
RB	(virologic) rebound
RBC	red blood cell
RBP	retinol binding protein
RNA	ribonucleic acid
RPV	rilpivirine
RT	reverse transcriptase
rtv	low-dose ritonavir
SAE	serious adverse event
SBP	systolic blood pressure
SD	standard deviation
SJS	Stevens-Johnson syndrome
SOC	system organ class
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
t_{max}	time to reach the maximum plasma concentration
TVD	Truvada (emtricitabine/tenofovir disoproxil fumarate)
UGT1A1	uridine diphosphate glucuronosyltransferase 1 family, polypeptide A1
ULN	upper limit of normal range
US	United States of America
VF	virologic failure
WBC	white blood cell
WHO	World Health Organization

DEFINITIONS OF TERMS

Investigational treatment (medication)	D/C/F/TAF FDC tablet
Control/Comparator treatment (regimen, medications)	DRV/COBI FDC coadministered with FTC/TDF FDC
Study treatment (medication)	Any ARV regimen and matching placebo tablets received in the investigational treatment arm or control arm in the current study
Virologic nonresponse (NR)*:	HIV-1 RNA <1 $\log_{10}$ reduction from baseline and ≥50 copies/mL at the Week 8 visit, confirmed at the scheduled or unscheduled visit following Week 8.
Virologic Rebound (RB)*:	• 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 the following scheduled or unscheduled visit; 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.

* Protocol defined for the purpose of the resistance analysis.

1. INTRODUCTION

1.1. Background

Human immunodeficiency virus (HIV) infection is a life-threatening and serious disease that is of major public health interest around the world. In 2012, approximately 35.3 million people were living with HIV-1 worldwide, an estimated 2.3 million people became newly infected with HIV-1 and 1.6 million died from acquired immunodeficiency syndrome (AIDS)-related causes.[34] 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.[21,22,28]

The primary goals of antiretroviral (ARV) therapy for HIV-1 infection are to reduce HIV-associated morbidity and prolong the duration and quality of life, restore and preserve immunologic function, maximally and durably suppress plasma HIV viral load, and prevent HIV transmission. The treatment guidelines suggest that initial therapy for ARV treatment-naïve HIV-1 infected patients consists of 2 nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) and either a non-nucleoside reverse transcriptase inhibitor (NNRTI) (usually efavirenz [EFV]), a boosted protease inhibitor (bPI), or the integrase strand transfer inhibitor (InSTI) raltegravir (RAL).[23,40]

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.[22] 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 ARV therapy, total pill burden, dosing frequency, and safety concerns are among the greatest obstacles to achieving adherence.[8,29,30] 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.[12,20,38]

Currently, 4 highly effective, once-daily tablets are approved for the treatment of HIV-1 infection: Atripla® (EFV/emtricitabine [FTC]/ tenofovir disoproxil fumarate [TDF]), Complera® (rilpivirine [RPV]/FTC/TDF), Stribild® (elvitegravir [EVG]/ cobicistat [COBI]/ FTC/TDF or E/C/F/TDF) and Triumeq® (abacavir [(ABC]/lamivudine [3TC]/dolutegravir (DTG]). There remains a need for simplified PI-based ARV regimens that combine potent and sustained efficacy, favorable tolerability, and minimal long-term toxicity, with practical, convenient dosing.

To address this need, the sponsor is developing an investigational, 4-agent, once-daily fixed-dose combination (FDC) tablet containing the PI darunavir (DRV; developed by the sponsor), the

pharmacokinetic enhancer (booster) COBI (developed by Gilead Sciences, Inc. [GSI]), the NRTI FTC, and the next-generation tenofovir (TFV) prodrug tenofovir alafenamide (TAF; developed by GSI). This FDC tablet, hereafter referred to as the D/C/F/TAF FDC, is intended to be indicated for the treatment of HIV-1 infected adults who are either treatment-naïve or treatment-experienced with no DRV RAMs (V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V).

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.

1.2. Darunavir (PREZISTA®)

DRV (formerly known as TMC114) is an inhibitor of the catalytic activity of HIV-1 protease (PR) with potent in vitro antiviral activity against both wild-type and PI-resistant HIV-1 strains. DRV 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.

DRV has been developed by the sponsor as tablets at different strengths and as an oral suspension. In combination with low-dose ritonavir (rtv) as a pharmacokinetic booster and other ARVs, it has shown significant efficacy in treatment-naïve and treatment-experienced patients. DRV, 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 resistance-associated mutations (RAMs). COBI-boosted DRV is only approved for use in adults.

DRV was first registered in the US (June 2006) and has obtained marketing authorization in the European Union in February 2007. As of 23 December 2014, DRV was registered in more than 99 countries around the world. Adverse drug reactions (ADRs) 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 ARV-treatment-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.

For the most comprehensive nonclinical and clinical information regarding DRV available at the time of protocol writing, refer to the Investigator's Brochure (IB) for D/C/F/TAF and its addendum.[16,17]

1.3. Cobicistat (Tybost®)

COBI (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. COBI has been shown to be a more specific, mechanism-based CYP3A inhibitor than rtv. COBI 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.

COBI, as a single 150-mg tablet, has been developed by 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. COBI 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, ARV treatment-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 ARV-treatment-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, ARV treatment-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.

For the most comprehensive nonclinical and clinical information regarding COBI and COBI/DRV FDC, available at the time of protocol writing, refer to the IB for D/C/F/TAF and its addendum.[16,17]

1.4. Emtricitabine (Emtriva®)

FTC 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. FTC 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 European Union, 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. FTC 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).

For further nonclinical and clinical information regarding FTC, refer to the Prescribing Information for FTC.[31,35]

1.5. Tenofovir Alafenamide

1.5.1. General Information

TAF (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, see also Section 1.7) 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 (DP), 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.

TDF is a first generation oral prodrug of TFV that has been studied extensively in clinical studies for the treatment of HIV-1 infection and has demonstrated antiviral activity against both wild-type and nucleoside resistant strains of HIV-1. The majority of clinical and laboratory adverse events (AEs) in clinical studies of TDF were of mild intensity and the frequencies of these events in patients who received TDF have been similar to those in patients in the comparator arm.

Under the trade name Viread®, TDF is marketed by GSI as a once-daily tablet (300 mg) and as a powder (1 g contains 40 mg TDF). In combination with other HIV-1 ARVs, it is indicated for the treatment of HIV-1 infection in adults and in pediatric patients at least 2 years of age. In addition, it is indicated for the treatment of hepatitis B virus (HBV) infection in adults and in pediatric patients at least 12 years of age. TDF has received marketing approval for the treatment of HIV-1 infection in 149 countries. TDF has also been coformulated and marketed in several coformulations with other HIV-1 ARV drugs, such as FTC/TDF FDC (Truvada®; [TVD]).

For the most comprehensive nonclinical and clinical information regarding TAF and the D/C/F/TAF FDC tablet, refer to the latest version of the IB for D/C/F/TAF and its addendum.[16,17] For further information regarding TDF and FTC/TDF FDC, refer to the Prescribing Information for TDF and FTC/TDF FDC.[32,33,36,37]

1.5.2. Preclinical Pharmacology and Toxicology

Primary Pharmacodynamics

TAF is metabolized to TFV, a nucleotide analog, which is not dependent on an intracellular nucleoside kinase activity for the first step in the conversion to the active metabolite, TFV-DP. The cellular enzymes responsible for TFV metabolism to the active diphosphorylated form are adenylate kinase (AK) and nucleotide diphosphate kinase, which are highly active and ubiquitous. AK exists as multiple isozymes (AK1 to AK4), with the phosphorylation of TFV mediated most efficiently by AK2.

The intracellular metabolism of TAF and TFV are consistent with the 600-fold enhancement in anti-HIV activity in cell culture of TAF over TFV. Metabolism of TAF was also studied in different human blood lymphocyte subpopulations, CD4+ and CD8+ T-cells, NK cells, B-cells

and macrophages/monocytes. TAF is metabolized inside host cells to the active metabolite TFV-DP. Concentration of the active metabolite TFV-DP was substantial in all cell populations.

Safety Pharmacology

TAF monofumarate (GS-7430-02) has been evaluated to determine potential effects on the central nervous system, renal system, cardiovascular and gastrointestinal systems. Single doses did not induce pharmacologic effects on the central nervous system of the rat (1,000 mg/kg), the renal system of the rat (1,000 mg/kg), or the cardiovascular system of the dog (100 mg/kg). TAF monofumarate (at 1,000 mg/kg reduced distal transit and increased stomach weights starting 2 hours after dosing with reversibility beginning by 6 hours after dosing. The no observed adverse effect level (NOAEL) for gastrointestinal motility was 100 mg/kg. The 50% inhibitory concentration (IC_{50}) of TAF fumarate (GS-7340-03) on hERG potassium current was estimated to be greater than 10 µM.

1.5.3. Preclinical Pharmacokinetics

All preclinical pharmacokinetic experiments in this section were performed using TAF monofumarate, and all study data described in this section reflect the dosage of the monofumarate. For reference, 100 mg of TAF monofumarate is equivalent to 80 mg of the GS-7340 free base (TAF).

Plasma pharmacokinetics of the intact prodrug, TAF, following oral administration of TAF monofumarate in dogs and monkeys demonstrated rapid absorption with peak plasma concentrations between 0.25 and 0.5 hours.

Peak TFV plasma concentrations occurred following TAF absorption, with TFV time to maximum plasma concentration (t_{max}) between 0.25 to 1.7 hours in rats, dogs, and monkeys. TFV plasma concentrations declined with a terminal half-life of 11.2 to 16.4 hours in rats (fasted), >24 hours in dogs (fasted), and 8.1 to 12.5 hours in rhesus monkeys.

The tissue distribution and recovery of [14C] radiolabeled TAF monofumarate was examined in beagle dogs. Radioactivity was detected in all tissues except brain, with the majority present in the contents of the gastrointestinal tract, liver, kidney, and large intestine. Tissue concentrations were the highest in kidney, PBMCs, liver, large intestine, and bile. Significant concentrations of TFV-related radioactive material were observed in lymph nodes from all 4 sites, suggesting that TAF may be selectively cleaved to TFV in the cells of the lymphoreticular system.

The primary route of elimination of TFV is renal excretion of unchanged drug. Following oral administration of TAF monofumarate, approximately 15% of a radiolabeled dose is recovered in dog urine in 24 hours. TFV was the major species present in the urine (90%), with about 3.4% of TAF also present. Biliary excretion of TFV in dogs and fecal elimination of TFV in rats and dogs are negligible.

TFV was the only species found in the intestinal contents and feces. In human systems, TAF is metabolized by hydrolytic cleavage and, to a lesser extent, by CYP3A4 catalyzed oxidation. As a result of the limited metabolism of TAF by CYP3A4 inhibition or induction of this enzyme should have little consequence on TAF exposure in vivo. TAF has limited potential to alter CYP enzyme activity through inhibition and does not inhibit UGT1A1 function. In addition, TAF is not an activator of either the aryl hydrocarbon receptor or human pregnane-X-receptor. These features combined with the relatively low plasma exposures of TAF in humans suggest that the potential of TAF to cause or be affected by clinically relevant drug-drug interactions is very low.

1.5.4. Nonclinical Toxicology

TAF monofumarate was evaluated in mice, rats, dogs, and monkeys for treatment periods up to 9-months and was negative in genetic toxicology studies. There was no effect on fetal viability or fetal development in pregnant rats administered doses of TAF monofumarate up to 200 mg/kg/day or in pregnant rabbits administered TAF monofumarate up to 100 mg/kg/day (the highest doses tested).

In chronic studies in rats, bone (atrophy of metaphyseal cancellous bone) and kidneys (karyomegaly) were the primary target organs after 26 weeks of treatment. TAF monofumarate also appeared to increase biochemical markers of bone turnover and decrease serum 1,25-dihydroxy- and 25-hydroxyvitamin D3 at doses of 25 mg/kg/day and above. In chronic studies in dogs after 9 months of treatment with TAF monofumarate, the primary target organs were kidney and bone.

TAF monofumarate had no discernible electrocardiograph effect at the low dose of 2 mg/kg/day and slightly prolong PR intervals at 6 and 18/12 mg/kg/day. Additionally, at Week 39, TAF monofumarate appeared to reversibly reduce heart rate with an associated mild QT prolongation. At Week 39, decreases in serum T3 were noted for animals receiving 18/12 mg/kg/day but was reversible at the 3-month recovery period. Minor hematologic and biochemistry parameters changes were observed but remained within normal historical ranges with the following exceptions: aspartate aminotransferase (AST) (~100% increase) and total bilirubin (~40% increase). There were no clear treatment-related effects observed in monkeys following 28 days of treatment including no changes in mitochondrial function.

The data from the 6-month rat study determined a NOAEL of 25 mg/kg/day (TFV exposure: area under the concentration-time curve [AUC]=3,758 ng·h/mL); the 9-month dog study defined a NOAEL of 2 mg/kg/day (TFV AUC=1,180 ng·h/mL), and the 28-day nonhuman primate study defined a NOAEL of 30 mg/kg/day (TFV AUC = 5,870 ng·h/mL). In conjunction with the nonclinical data with TDF and the clinical experience with TDF and TAF, these toxicology studies support studies in humans of doses up to 150 mg/day (120 mg free base, the highest anticipated human dose) for chronic treatment.

At the time of the rodent toxicity studies, the bioassay could not detect plasma TAF, possibly due to instability in the matrix.

Because of the lack of exposure to the prodrug in mice and rats and achievable TFV exposures less than previously tested in chronic and carcinogenicity studies with TDF, carcinogenicity studies in mice and rats with TAF are currently not planned.

TAF has not been evaluated in perinatal-postnatal reproductive toxicology studies. Reproductive tissues were examined in repeat-dose toxicology studies in the rat, dog, and monkey. There were no clearly treatment-related histologic alterations or changes in organ weights in the rat and the dog following chronic daily dosing, or in the monkey.

The TAF fumarate oral rat fertility study (TX-120-2012) data indicate dose-related decreases in body weight gain in males and females occurred but no drug related changes occurred in male or female fertility endpoints at doses up to 160 mg free base equivalents/kg/day.

1.5.5. Clinical Studies

Clinical studies entailing the use of TAF for the treatment of HIV include:

- GS-120-1101, a Phase 1-2 study of the pharmacokinetics and antiviral activity of GS-7340 (50 mg and 150 mg) in HIV-infected subjects (completed);
- GS-US-120-0104, a Phase 1b study of the pharmacokinetics and antiviral activity of GS-7340 (8 mg, 25 mg, 40 mg) in HIV-infected subjects (completed);
- GS-US-311-0101, a Phase 1 healthy volunteer study evaluating the drug interaction potential between once-daily FTC/GS-7340 FDC and EFV or COBI-boosted DRV (completed);
- GS-US-120-0107, a Phase 1, partially-blinded, randomized, placebo- and positive-controlled study to evaluate the effect of GS-7340 on the QT/QTc interval in healthy subjects (completed);
- GS-US-120-0108, a Phase 1, open-label, parallel-design study to evaluate the pharmacokinetics of GS-7340 in subjects with severe renal impairment (completed);
- GS-US-120-0109, a Phase 1 study to evaluate the pharmacokinetics, metabolism and excretion of GS-7340 (completed);
- GS-US-120-0114, a Phase 1 study to evaluate the pharmacokinetics of TAF in subjects with normal and impaired hepatic function (completed);
- GS-US-120-0117, a Phase 1 study to evaluate the pharmacokinetic drug interaction potential between RPV and TAF in healthy subjects (completed);
- GS-US-120-0118, a Phase 1 pharmacokinetic study to evaluate the drug interaction potential of TAF with a bPI or unboosted integrase inhibitor in healthy subjects (completed).

Clinical trials entailing the use of TAF for the treatment of chronic HBV infection:

- GS-US-320-0101, a Phase 1b randomized, open-label, active-controlled study to assess the safety, viral kinetics and anti-HBV activity of GS-7340 in treatment-naïve adults with chronic hepatitis HBV infection (completed);
- GS-US-320-1228, a Phase 1 single dose study to investigate the pharmacokinetics, safety and tolerability of TAF in healthy Japanese and non-Japanese subjects (completed).

The first proof-of-concept study, GS-120-1101, as well as GS-US-120-0104 and GS-US-292-0101 were performed using TAF monofumarate. All subsequent studies were performed using TAF fumarate, with the exception of GS-US-311-0101 Cohort 4, which used TAF monofumarate for the GS-7340 single-agent 8-mg tablet.

GS-120-1101 was a Phase 1-2 randomized double-blind, active-controlled, dose escalation study of the safety, tolerance, pharmacokinetics, and antiviral activity of TAF in ARV-naïve subjects who were chronically infected with HIV-1. The subjects were randomized to receive 14 days of monotherapy, fasting, with TAF monofumarate 50 mg once daily, 150 mg once daily, or TDF 300 mg once daily (n=10 per group). TAF was rapidly absorbed into the systemic circulation, and following attainment of maximum plasma concentration (C_{max}), was eliminated rapidly with a short plasma half-life (20 to 40 minutes). Compared with TDF, TAF monofumarate 50 mg provided a ~16-fold lower TFV C_{max} (207 ng/mL versus 13 ng/mL), approximately 2-fold longer elimination half-life (26 versus 48 hours) and lower overall systemic TFV exposure (AUC_{inf} 1,814 versus 383 ng.h/mL). TAF monofumarate 150 mg provided lower C_{max} (42 ng/mL), but comparable AUC_{inf} (1,740 ng.h/mL) as TDF. In PBMCs, TFV was detectable earlier, more frequently, and in higher concentrations following dosing of TAF monofumarate. The intracellular delivery of TFV is approximately 30-fold greater for TAF monofumarate versus TDF. The decrease from baseline to Day 14 in plasma HIV-RNA levels was greater for groups treated with TAF monofumarate 50 mg (p=0.02757) or 150 mg (p=0.0010) than the group treated with TDF 300 mg. The median changes from baseline in plasma HIV-1 RNA after 14 days of monotherapy were -0.96, -1.65, and -1.68 $\log_{10}$ copies/mL, respectively, for TDF 300 mg, TAF monofumarate 50 and 150 mg.

A second proof-of-concept study, GS-US-120-0104, evaluated monotherapy, fasting, with 3 lower doses of TAF or TDF 300 mg, or placebo, administered for 10 days. Potent antiviral activity was achieved in treatment-naïve HIV-1 infected subjects, with mean (± standard deviation [SD]) change from baseline in HIV-1 RNA of -0.95±0.45, -1.53±0.40, -1.7±0.22, and -0.81±0.66 $\log_{10}$ copies/mL at TAF 8 mg, 25 mg, 40 mg, and TDF 300 mg, respectively (data unblinded only at dose level). Mean viral load declines for both the 25- and 40-mg doses were statistically better than the 8-mg dose. TAF AUC was best associated with antiviral activity despite its short plasma half-life (~30 minutes). TFV AUC were 97%, 87%, and 80% lower at TAF 8 mg, 25 mg, and 40 mg, respectively, compared to TDF administration. When compared to 40 mg and historical 120-mg data, TAF 25 mg provided near maximum activity (predicted to be ~-1.7 to 1.8 $\log_{10}$ copies/mL). From this pharmacokinetic/pharmacodynamic analysis, a target

dose of TAF 20-25 mg monotherapy was expected to provide near maximum activity and ~90% reduction in circulating TFV.

GS-US-311-0101 was a multi-dose Phase 1 study evaluating the drug interaction potential between once-daily FTC/TAF (200/40 mg) FDC and EFV (Cohort 1), between FTC/TAF (200/25 mg) FDC and COBI (150 mg)-boosted DRV (800 mg) (Cohorts 2 and 3), and between TAF 8 mg and COBI 150 mg (Cohort 4). Following multiple dosing of FTC/TAF plus EFV, no clinically relevant changes in TAF and TFV exposures were observed, indicating the lack of significant influence of the CYP pathway. Following multiple dosing of FTC/TAF plus DRV/COBI, the TAF exposure was unchanged but TFV C_{max} and AUC_{tau} were 3.2-fold higher, as compared with FTC/TAF only. Pharmacokinetic results indicated that when dosed with COBI, TAF C_{max} and AUC_{last} were 2.8- and 2.6-fold higher, respectively, while TFV C_{max} and AUC_{tau} were 3.3-fold higher.

Study GS-US-120-0107 was a Phase 1, partially-blinded, randomized, placebo- and positive-controlled study to evaluate the effect of TAF on the QT/QTc interval in healthy subjects. This was a negative thorough QTc study. No effect of TAF was observed on the QTcF interval (ie, no QTc interval prolongation >10 ms at any time point postdose and assay sensitivity was confirmed via the positive control [moxifloxacin]). As such, these findings satisfy the guidelines set forth in the International Conference on Harmonization (ICH) E14 guidance and support the conclusion that there is no significant effect of TAF on the QT/QTc interval.[7]

Study GS-US-120-0108 was a Phase 1, open-label, parallel-design study to evaluate the pharmacokinetics of TAF in subjects with severe renal impairment. TAF was well tolerated in the study. Subjects with severe renal impairment had approximately <2-fold higher TAF and 5 to 6-fold higher TFV systemic exposures as assessed by AUC relative to subjects with normal renal function. TFV exposures in subjects with severe renal impairment are comparable to those with normal renal function receiving 300 mg TDF once daily as well as severely renally impaired subjects (clearance <50 mL/min) receiving TDF 300 mg twice weekly. Given the extensive safety data available for TDF at a dose of 300 mg, TFV exposures in severely renally impaired subjects similar to those associated with TDF 300 mg are deemed appropriate for further study of TAF in HIV-infected subjects without TAF dose modification.

Results from Study GS-US-120-0109, a Phase 1 pharmacokinetics, metabolism and excretion study (in 8 healthy male subjects) demonstrated that TAF is eliminated in both feces and urine, with total mean (±SD) recovery of 84.4%±2.45%. TAF and its metabolites are eliminated in both feces and urine. The predominant species detected in feces and urine is TFV, accounting for 31.4%±10.4% and 22.2% ±4.47% of the total radioactive dose. These human data are consistent with the established preclinical profile of TAF. Following administration of TAF, plasma [14C] radioactivity showed a time-dependent profile with TAF as the most abundant species in the initial few hours and uric acid in the remaining period. The whole blood-to-plasma concentration ratio of [14C] radioactivity increased from 0.511 at 0.25 hours postdose to 2.32 at 216 hours postdose, suggesting a relatively slower clearance of [14C] radioactivity from blood cells relative to the plasma [14C] radioactivity time-course. In addition to TFV and uric acid, additional low

quantities of metabolites were formed, including xanthine, hypoxanthine, and adenine. They are identical to the endogenous products of purine metabolism and therefore should not cause any safety risk. TAF 25-mg tablets administered together with tracer dose of [14C] radiolabeled TAF as a single oral tablet, were well tolerated.

GS-US-120-0114 was a Phase 1 study to evaluate the pharmacokinetics of TAF in subjects with normal and impaired hepatic function. No clinical relevant changes in TAF or TFV pharmacokinetics were observed in subjects with mild to moderate hepatic impairment compared to the normal matched control subjects following administration of a single dose of TAF 25 mg. The results of this study indicate that no dose adjustment of TAF is necessary in subjects with mild to moderate hepatic impairment. Single doses of TAF 25 mg were generally well tolerated in subjects with mild or moderate hepatic impairment and in subjects with normal hepatic function.

GS-US-120-0117 was a Phase 1 study to evaluate the pharmacokinetic drug interaction potential between single doses of RPV and TAF in healthy subjects. The study concluded that TAF and RPV coadministration does not result in clinically relevant changes in RPV, TAF, or TFV exposure, and no dose adjustments are necessary. Single doses of TAF 25 mg, TAF 25 mg plus RPV 25 mg, and RPV 25 mg were generally well tolerated in these healthy subjects.

GS-US-120-118 was a Phase 1 study to evaluate the drug interaction potential of TAF with the ritonavir-boosted PIs ATV, DRV, and lopinavir (LPV), or with the unboosted InSTI DTG. Results of the study showed that coadministration of FTC+TAF with DTG did not result in clinically relevant changes in TAF or TFV exposure. Coadministration of FTC+TAF with ATV/rtv or LPV/rtv resulted in increased TAF and TFV exposures. Coadministration of FTC+TAF with DRV/rtv did not result in clinically relevant changes in TAF, but resulted in increased TFV exposure.

GS-US-320-0101 was a Phase 1b study of TAF in otherwise healthy HBV-infected subjects, exploring the differences in short-term antiviral activity between doses of TAF (8 , 25, 40, and 120 mg) with respect to the time weighted average change from baseline through Week 4 in serum HBV DNA ($\log_{10}$ IU/mL). Results in all treatment cohorts demonstrated viral suppression over a treatment duration of 4 weeks, with no perceivable differences in the potency of TAF at lower doses compared to higher doses. Viral suppression with TAF was also comparable to that with TDF. TAF was safe and well tolerated. The safety profile for TAF did not differ among dose groups and was similar to that of TDF.

GS-US-320-1228 was a Phase 1 single dose study to investigate the pharmacokinetics, safety and tolerability of TAF in healthy Japanese and non-Japanese subjects. The study found that the pharmacokinetics of TAF and TFV following administration of TAF 25 mg are comparable between Japanese and non-Japanese subjects and support dosing of 25 mg in Japanese subjects, TAF 25 mg was safe and well tolerated in this study.

1.6. Comparator Drug

The control treatment in this study consists of the bPI regimen DRV/COBI FDC (see Section 1.3) coadministered with FTC/TDF FDC (TVD).

Truvada® (Emtricitabine/tenofovir disoproxil fumarate FDC)

For information on FTC, see Section 1.4. TDF is a first generation oral prodrug of TFV that has been studied extensively in clinical studies for the treatment of HIV-1 infection and has demonstrated antiviral activity against both wild-type and nucleoside resistant strains of HIV-1. Under the trade name Viread®, TDF is marketed by GSI as a once-daily tablet (300 mg) and as a powder (1 g contains 40 mg TDF). TDF has also been coformulated and marketed in several coformulations with other HIV-1 ARV drugs, such as FTC/TDF FDC (TVD). TVD, in combination with other ARVs, is indicated for the treatment of HIV-1 infection in adults and in pediatric patients 12 years of age or older.

The most frequently reported adverse reactions considered possibly or probably related to FTC and/or TDF were nausea (12%) and diarrhea (7%) in an open-label, randomized clinical trial (GS-01-934). The safety profiles of FTC and TDF in this study were consistent with the previous experience with these agents when each was administered with other ARV agents.[32,36]

For further information regarding TDF and FTC/TDF FDC, refer to the Prescribing Information for TDF and FTC/TDF FDC.[32,33,36,37]

1.7. Overall Rationale and Risks Assessment for the Study

The success of HAART and the apparent benefits of maximally suppressed viremia have shifted clinical attention towards ARV agents that optimize long-term safety and tolerability. This medical need becomes clearer as the HIV-positive population ages; morbidity and mortality are increasingly driven by non-AIDS associated comorbidities, and these age-associated comorbidities are observed earlier than in the non-HIV-1 infected population despite the best current chronic therapy.[5,6] In addition, young, newly infected patients are diagnosed earlier, initiate therapy earlier, and look ahead towards lifelong therapy, often more than 50 years.[24]

Incomplete adherence to ARV regimens is a critical factor contributing to the development of viral resistance and treatment failure and is thus a primary barrier to successful long-term treatment. Studies have shown that once-daily single-tablet regimens improve adherence, treatment satisfaction, and virologic outcomes for patients infected with HIV-1.[1,10,14,18] Due to a longer duration of high adherence, patients taking single-tablet regimens also have better clinical outcomes, such as fewer hospitalizations, when compared with multiple pill regimens.[27]

To improve care for HIV-infected patients and maximize tolerability, safety, clinical efficacy, and adherence, the sponsor is developing DRV with COBI, FTC and TAF into a FDC tablet (D/C/F/TAF). This new formulation would provide an additional single tablet option, in particular for subjects requiring PI-based regimens, and would be an attractive new once-daily

simplified regimen. The D/C/F/TAF FDC tablet also represents a new alternative for individuals intolerant to currently available combination tablet regimens, and may promote better adherence to bPI-based regimens. Additionally, compared with TDF, the use of TAF in the D/C/F/TAF FDC tablet is postulated to provide greater delivery to lymphatic tissues of TFV and higher intracellular levels of the active phosphorylated moiety TFV-DP, more effective suppression of residual viral replication in a wider range of reservoir and anatomic sanctuaries of HIV, greater and faster viral load reduction during initial therapy, and lower systemic levels of TFV.[4,18]

The principal anticipated drug-drug interaction upon administration of the 4-drug combination is the intended inhibition of CYP3A activity by COBI and the consequent increase in DRV exposure to levels similar to those observed using rtv as a boosting agent. The DRV/COBI 800/150 mg once-daily regimen with other ARV agents has already been established for use in HIV-1 infected patients. DRV and COBI concentrations are not anticipated to be affected by FTC or TAF. For TAF regimens including a pharmacokinetic enhancer (rtv or COBI), a 10 mg dose TAF is used as opposed to a TAF 25 mg dose currently in development for use with other (non-boosted) ARV agents (see also Section 3.3).

Administration of DRV with COBI as a pharmacokinetic enhancer, FTC, and TAF in a single tablet is not expected to change the antiviral activity and, by extension, the resistance profiles of DRV, FTC, and TAF.

The combination of D/C/F/TAF is not anticipated to exacerbate known toxicities or lead to new toxicities compared to DRV/COBI FDC coadministered with FTC/TDF FDC. DRV and FTC have established clinical safety profiles with no significant toxicities observed. Liver toxicity related to COBI, which was observed preclinically, has not been observed clinically to date. Standard liver enzyme assays will be used to monitor for these potential adverse effects. Minimal mononuclear cell infiltration in the posterior uvea has been observed at the highest dose of TAF (12 to 18 mg/kg) in dogs. More than 3,000 HIV-positive subjects have been exposed to TAF as part of the Phase 2 and 3 E/C/F/TAF clinical development program by GSI and no AEs consistent with posterior uveitis in humans have been reported. 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.

The primary nonclinical toxicities for TAF are renal and bone toxicity. Based on available data from the ongoing COBI and E/C/F/TDF tablet clinical development programs, decreases in eGFR are anticipated due to the known effects of COBI on the renal tubular excretion of creatinine, without an impact on the renal glomerular function. Studies GS-US-292-0102 and GS-US-236-0118 showed that the E/C/F/TDF tablet, as well as ATV/COBI or DRV/COBI + background regimens were safe and well tolerated in subjects with mild renal impairment (eGFR 50 to 89 mL/min).[16] The combination of D/C/F/TAF is not anticipated to have an effect on actual glomerular filtration rate, monitoring of creatinine along with other standard clinical tests for renal and bone disorders is planned in all clinical studies with the

D/C/F/TAF FDC tablet. The eligibility criteria for study TMC114FD2HTX3001 with the D/C/F/TAF FDC tablet allow the inclusion of subjects with a screening eGFR of ≥70 mL/min. Changes from baseline in serum creatinine, in eGFR based on creatinine clearance ($eGFR_{creatinine}$) and in eGFR based on cystatin C clearance ($eGFR_{cystatin\ C}$) will be measured in this study. In addition, a renal management algorithm to optimally evaluate and determine the benefit/risk balance for continued participation of subjects whose $eGFR_{creatinine}$ would decrease <50 mL/min is also included in the study protocol. As recent data suggest that the combined use of COBI and TDF might increase proteinuria (expected to be less with TAF), this study will also assess the effects of the D/C/F/TAF FDC tablet on proteinuria, albuminuria, beta-2-microglobulinuria, and urine retinol-binding protein (RBP).

In addition, assessment of bone mineral density (BMD) is included in the study protocol as a substudy, and follow-up per local medical practice at the discretion of the investigator will be recommended in case a decrease from baseline of >7% in the hip region or >5% in the spine region is demonstrated. Selected bone biomarkers, including C-type collagen sequence (CTX), procollagen type N-terminal propeptide (P1NP), parathyroid hormone (PTH), and 25-hydroxy vitamin D, will be monitored in the substudy.

Two clinical studies to date have been performed with the D/C/F/TAF FDC tablet regimen (GS-US-299-0101 in healthy volunteers [N=102], and GS-US-299-0102 in ARV treatment-naïve HIV-1 infected subjects [N=153]).[16] No new or unexpected adverse drug reactions were identified in these studies.

The aim of study TMC114FD2HTX3001 is to evaluate the efficacy and safety of the D/C/F/TAF FDC tablet in ARV treatment-naïve HIV-1 infected subjects. The active control in this randomized, double-blind, comparative study is DRV/COBI FDC coadministered with FTC/TDF FDC.

Week 48 is the primary analysis time point. An additional analysis will be performed when all subjects have completed the Week 96 visit or discontinued earlier. Final analysis will be conducted when all subjects have completed the extension phase or discontinued earlier (see also Section 3.1).

2. OBJECTIVES AND HYPOTHESIS

2.1. Objectives

Primary Objective

The primary objective is to demonstrate noninferiority in efficacy of a D/C/F/TAF FDC tablet versus DRV/COBI FDC coadministered with FTC/TDF FDC in HIV-1 infected, ARV treatment-naïve adult subjects, as determined by the proportion of virologic responders defined as having HIV-1 RNA <50 copies/mL at Week 48 (FDA-defined snapshot analysis), with a maximum allowable difference of 10%.

Secondary Objectives

The secondary objectives of this study are:

- To evaluate superiority of a D/C/F/TAF FDC tablet versus DRV/COBI FDC coadministered with FTC/TDF FDC as determined by the proportion of virologic responders defined as having HIV-1 RNA <50 copies/mL at Week 48 (FDA-defined snapshot analysis), in case noninferiority is established;
- To evaluate the immunologic response (CD4+ cell count) of the 2 treatment arms through Week 48;
- To evaluate the incidence of grade 3 and 4 AEs, serious adverse events (SAEs), and premature discontinuations due to AEs in the 2 treatment arms through Week 48;
- To evaluate the change from baseline in serum creatinine, $eGFR_{creatinine}$ (by Cockcroft-Gault and by Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] formulas) and $eGFR_{cystatin\ C}$ (by CKD-EPI) in the 2 treatment arms at Week 48;[9,19]
- To evaluate the change from baseline in renal biomarkers at Week 48;
- To assess the development of viral resistance in the 2 treatment arms through Week 48;
- To evaluate the steady-state pharmacokinetics of DRV and TAF;
- To evaluate long-term efficacy, resistance, and safety of the D/C/F/TAF regimen (Week 96 and beyond).

Objectives of a bone investigation substudy performed at selected study sites:

- To evaluate the safety in the 2 treatment arms as determined by the percentage change from baseline in hip and spine BMD and change from baseline in T-score at Week 48;
- To evaluate the change from baseline in bone biomarker levels at Week 48.

2.2. Hypothesis

Null hypothesis: D/C/F/TAF FDC is inferior to DRV/COBI FDC coadministered with FTC/TDF FDC by at least 10% with respect to the proportion of subjects having HIV-1 RNA <50 copies/mL at Week 48 (as defined by the FDA-defined snapshot analysis).

Alternative hypothesis: D/C/F/TAF FDC is noninferior to DRV/COBI FDC coadministered with FTC/TDF FDC by less than 10% with respect to the proportion of subjects having HIV-1 RNA <50 copies/mL at Week 48 (as defined by the FDA-defined snapshot analysis).

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a 96-week multicenter, Phase 3 study consisting of a 48-week randomized, double-blind active-controlled treatment period, to evaluate a D/C/F/TAF FDC tablet versus DRV/COBI FDC coadministered with FTC/TDF FDC in ARV treatment-naïve HIV-1 infected adult subjects,

followed by an open-label single-arm D/C/F/TAF treatment period for all subjects up to Week 96 to asses long-term efficacy, resistance, and safety.

A target of 670 subjects will be randomly assigned in this study with 335 subjects planned per treatment arm.

Prior to or at the baseline visit (Day 1), subjects who meet all eligibility criteria will be randomized in a 1:1 ratio to 1 of the following 2 treatment arms:

- D/C/F/TAF Arm: Regimen of a single tablet containing DRV 800 mg/ COBI 150 mg/ FTC 200 mg/ TAF 10 mg (D/C/F/TAF FDC) once daily, (n=335)
  + DRV/COBI FDC-matching and FTC/TDF FDC-matching placebo tablets once daily;
- Control Arm : Regimen of DRV 800 mg/ COBI 150 mg FDC coadministered with FTC 200 mg/ TDF 300 mg FDC once daily, (n=335)
  + D/C/F/TAF FDC-matching placebo tablet once daily.

Randomization will be stratified by HIV-1 RNA level (≤100,000 copies/mL or >100,000 copies/mL) and CD4+ cell count (<200 cells/µL or ≥200 cells/µL) at screening.

Subjects will be treated for 96 weeks, and will return for study visits at Weeks 2, 4, 8, 12, 24, 36, 48, every 12 weeks thereafter until and including a Week 96 visit.

After Week 48, subjects will continue to take their blinded study drug and attend visits every 12 weeks until all subjects have reached Week 48, the database for the primary analysis has been locked, and treatment assignments have been unblinded. Provided the results from the primary analysis do not preclude (further) exposure of subjects to D/C/F/TAF, all subjects will return for an unblinding visit and will receive the D/C/F/TAF FDC tablet treatment during an open-label single-arm treatment phase up to Week 96. Subjects from the control arm who switch to the D/C/F/TAF regimen after the 48-week double-blind treatment will be required to return to the clinic for an additional visit 3 to 7 weeks after the unblinding visit.

After Week 96, subjects will be given the opportunity to continue D/C/F/TAF treatment during an extension phase until the D/C/F/TAF FDC tablet becomes commercially available and is reimbursed, or can be accessed through another source in the country where he/she is living, or until the sponsor terminates clinical development. During the extension phase subjects will attend visits every 6 months.

Subjects who prematurely discontinue, either during the double-blind treatment phase (from Day 1 to Week 48) or during the single-arm D/C/F/TAF phase (between Week 48 and Week 96) will be required to return to the clinic within 72 hours of stopping study treatment for the early study treatment discontinuation (ESTD) visit.

In addition, a 30-day follow-up (FU) visit will be required for any subject who has an ongoing AE or serious adverse event (SAE) at the time of his/her last study visit (unless consent is withdrawn).

Thus, the study will include a screening period of approximately 30 days (up to maximum 6 weeks) starting from the signature of the informed consent form (ICF), double-blind active-controlled treatment for at least 48 weeks, an open-label single-arm D/C/F/TAF treatment up to Week 96 and an extension phase. A 30-day FU visit may take place as described above.

The primary analysis of this study will be performed when all subjects have completed the Week 48 visit or discontinued earlier. An additional analysis will be performed when all subjects have completed the Week 96 visit. The final analysis will be performed once all subjects have completed the extension phase (and the 30-day FU visit if applicable), or discontinued earlier.

The safety and tolerability, as well as efficacy, of the enrolled subjects and treatment regimens will be monitored by an independent Data Monitoring Committee (DMC). Refer to Section 11.8 for details. In addition to the Week 48, Week 96, and final analyses, formal DMC analyses will be performed for monitoring purposes, including a futility analysis for lack of (non-inferior) efficacy and a blinded sample size re-estimation.

A diagram of the study design is provided in Figure 1.

Assessment and reporting of drug adherence and accountability, concomitant medications, and AEs, laboratory evaluations for efficacy and safety (viral load, CD4+ cell count, biochemistry, hematology, urinalysis, urine chemistry), vital signs and (complete or symptom-directed) physical examinations will be performed at each visit, except for drug accountability at Week 2. At screening, a 12-lead electrocardiogram (ECG) and an HIV-1 genotype test will be performed. Urine for assessments of selected renal biomarkers, including RBP and beta-2-microglobulin, will be collected at baseline and at the time points specified in the Time and Event Schedule.

Screening genotype testing will be performed for all subjects to assess sensitivity to DRV, TDF and FTC. Further HIV-1 PR and RT genotype/phenotype testing will be performed at later time points for subjects that are eligible for resistance testing (subjects with virologic rebound, virologic nonresponse, and discontinuations with last available viral load measurement ≥400 copies/mL). If resistance to the study drugs is documented, study drugs may be discontinued.

Pharmacokinetic assessments (sparse sampling) will be performed for all subjects (single sample from Weeks 4 through 48 or the ESTD visit, except at Weeks 8 and 36 visits, when 2 samples will be collected ≥2.5 hours apart).

A bone investigation substudy will be performed at selected study sites, to assess bone biomarkers and dual energy x-ray absorptiometry (DXA) scans, in at least 170 subjects (85 subjects in each treatment arm) who provide informed consent for the substudy.

To determine BMD of the hip and spine, consenting subjects will have DXA scans performed at the time points specified in the Time and Event Schedule. In subjects participating in the DXA substudy, blood will be collected for assessment of bone biomarkers at the time points specified in the Time and Event Schedule.

Figure 1: Schematic Overview of the Study

Baseline (Day 1)[a] — **Week 24** DMC[b] — **Week 48**[c,d] Primary analysis — **Week 96**[e] Analysis

Screening	**Double-Blind Treatment Phase**[f]	**Single-arm Treatment Phase**[c,d,f]	**Extension Phase**[e]	**Follow-up**
≤30 days prior to baseline	**Treatment arm 1 (Test)** (n=335): D/C/F/TAF FDC once daily[g] DRV/COBI FDC-matching and FTC/TDF FDC-matching placebo tablets once daily[g] **Treatment arm 2 (Control)** (n=335): DRV/COBI FDC coadministered with FTC/TDF FDC once daily[g] D/C/F/TAF FDC-matching placebo tablet once daily[g]	D/C/F/TAF FDC	D/C/F/TAF FDC	**ESTD**[f] **and 30-day FU visit**[h]

[a] Following the baseline visit, subjects will return for study visits at Weeks 2, 4, 8, 12, 24, 36, 48, and every 12 weeks thereafter until and including a Week 96 visit.

[b] Formal DMC interim analyses will be performed for monitoring purposes, including a futility analysis for lack of (non-inferior) efficacy and a blinded sample size re-estimation.

[c] Subjects will continue to take their blinded study drug and to attend visits every 12 weeks following Week 48 until treatment assignment is unblinded.

[d] After unblinding, provided the results from the primary analysis do not preclude (further) exposure of subjects to D/C/F/TAF, all subjects will receive D/C/F/TAF treatment during a single-arm treatment phase up to Week 96. Subjects from the control arm who switch to the D/C/F/TAF regimen after the 48-week double-blind treatment will be required to return to the clinic for an additional visit 3 to 7 weeks after the unblinding visit.

[e] After Week 96, subjects will be given the opportunity to continue D/C/F/TAF treatment during an extension phase until the D/C/F/TAF FDC tablet becomes commercially available and is reimbursed, or can be accessed through another source in the country where he/she is living, or until the sponsor terminates clinical development. During the extension phase subjects will attend visits every 6 months.

[f] Subjects who prematurely discontinue, either during the double-blind treatment phase (from Day 1 to Week 48) or during the single-arm D/C/F/TAF treatment phase (between Week 48 and Week 96) will be required to complete the ESTD assessments within 72 hours of stopping study treatment.

[g] All study drugs and matching placebo tablets must be administered orally, once daily in the morning with food, at approximately the same time each day.

[h] Any subject who has an ongoing AE or SAE at the time of his/her last study visit will be required to return to the clinic 30 days after the completion their his/her study visit for a 30-day FU visit (unless consent is withdrawn).

3.2. Study Design Rationale

Control, Blinding, Randomization and Stratification

A bPI in combination with 2 NRTIs, an established regimen for treatment-naïve HIV-infected patients, is the active control treatment in this study. The active control treatment consists of the DRV/COBI FDC (PREZCOBIX/REZOLSTA) coadministered with FTC/TDF FDC (TVD). In addition, since TAF is substituted by TDF in the comparator treatment, the active control treatment will allow a direct comparison of these 2 ARVs for safety assessments.

Blinded treatment will be used to reduce potential bias during data collection and evaluation of clinical endpoints.

Randomization will be used to minimize bias in the assignment of subjects to treatment arms, to increase the likelihood that known and unknown subject attributes (eg, demographic or baseline characteristics) are evenly balanced across treatment arms, and to enhance the validity of statistical comparisons across treatment arms. Equal randomization will be done because this requires a lower total sample size to attain the same power versus randomization with unequal division.

Two stratification factors (HIV-1 RNA level [≤100,000 copies/mL or >100,000 copies/mL] and CD4+ cell count [<200 cells/µL or ≥200 cells/µL] at screening) will be applied in the randomization process and will subsequently be used in the statistical analysis as covariates in the models. Since previous publications have shown that baseline viral load can be a predictive factor for outcome, this will ensure a balanced distribution of subjects across treatment arms.[11,15]

Study Period and Primary Analysis Time Point

A double-blind, active-controlled treatment duration up to 48 weeks was chosen to evaluate the sustained efficacy, tolerability and safety of the D/C/F/TAF FDC tablet regimen in the selected population. To assure continued follow-up of the study participants and gain further safety information, subjects who prematurely discontinue study treatment during the double-blind treatment period will be asked to remain in the study and attend the ESTD (and 30-day FU visit, if applicable).

In addition, to further assure continued treatment of the study participants and collect further extended safety data, provided the results from the primary analysis do not preclude (further) exposure of subjects to D/C/F/TAF, subjects of both treatment arms will receive the D/C/F/TAF FDC tablet in an open-label single-arm treatment phase and attend visits every 12 weeks up to Week 96. In order to collect long-term safety and efficacy data on D/C/F/TAF, subjects will be given the opportunity to continue D/C/F/TAF treatment after Week 96 during an extension phase and attend visits every 6 months, until D/C/F/TAF becomes commercially available and is reimbursed, or can be accessed through another source in the country where they are living, or until the sponsor terminates clinical development.

The primary analysis of this study will be performed when all subjects have completed the Week 48 visit or discontinued earlier. An additional analysis will be performed when all subjects have completed the Week 96 visit.

Primary analysis at Week 48, double-blind active-controlled treatment duration of 48 weeks and longer term follow-up up to 96 weeks are in line with FDA *Guidance for Industry Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment (draft guidance June 2013)*.

Toxicity Management

The combination of D/C/F/TAF is not anticipated to exacerbate known toxicities or lead to new toxicities (see also Section 1.7). Measures and guidelines for the monitoring and management of specific toxicities with DRV, COBI, FTC, TAF or TDF are included in this protocol (see Section 9.5). The presented toxicity management guidelines are applicable throughout the entire study starting from baseline through the 96-week treatment period and the extension phase.

Safety and Efficacy Monitoring

All individual components of the investigational regimen are well-established or authorized. Yet, the combination as such and the single-tablet formulation used in this study are new. Therefore, an independent DMC will be established and monitor the safety and efficacy information, to ensure the safety of the subjects enrolled in this study, and to allow regular assessment of the risk/benefit profile of the applied therapy schemes (see also Section 11.8).

3.3. Dose Selection Rationale

DRV 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).[16]

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).[16] 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 FDC 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.

4. SUBJECT POPULATION

Approximately 670 subjects will be randomized in a 1:1 ratio to 1 of the 2 treatment arms.

Screening for eligible subjects will be performed within approximately 30 days (up to maximum 6 weeks) before administration of the study drug. Signing of the ICF needs to be done before the first study-related activity.

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 should consult with the appropriate sponsor representative before enrolling a subject in the study. No exemptions or waivers related to inclusion or exclusion criteria will be granted.

For a discussion of the statistical considerations of subject selection, refer to Section 11.3, Sample Size Determination.

4.1. Inclusion Criteria

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

1. Subject must be medically stable on the basis of physical examination, medical history, vital signs, and 12-lead ECG performed at screening. If there are abnormalities, they must be consistent with the underlying illness in the study population. This determination must be recorded in the subject's source documents and initialed by the investigator.

2. Subjects must have documented HIV-1 infection.

3. Subjects must be ARV treatment-naïve (never treated with an ARV including post-exposure prophylaxis and pre-exposure prophylaxis); no prior use of any approved or experimental anti-HIV drug for any length of time.

4. Screening plasma HIV-1 RNA level ≥1,000 copies/mL.

5. CD4+ cell count >50 cells/µL.

6. Screening HIV-1 genotype report must show full sensitivity to DRV, TDF and FTC.

7. Screening $eGFR_{creatinine}$ ≥70 mL/min according to the Cockcroft-Gault formula for creatinine clearance.[9]

8. Screening hepatic transaminases (alanine aminotransferase [ALT] and AST) ≤5 x upper limit of the normal range (ULN).

9. Screening direct bilirubin ≤1.5 x ULN.

   Note: Subjects with documented Gilbert's Syndrome may have total bilirubin up to 5 x ULN.

10. Adequate hematologic parameters at screening: platelets ≥50,000 /µL, hemoglobin ≥8.5 g/dL, absolute neutrophil count ≥1,000/µL.

11. Screening serum amylase ≤2 x ULN (subjects with serum amylase >2 x ULN will remain eligible if serum lipase is ≤2 x ULN).

12. For the other clinical laboratory tests performed at screening and not specified in the inclusion criteria above, the test results should be within normal reference ranges. If the results of the serum chemistry panel, hematology, or urinalysis are outside the normal reference ranges, the subject may be included only if the investigator judges the abnormalities or deviations from normal to be not clinically significant or to be appropriate and reasonable for the population under study. This determination must be recorded in the subject's source documents and initialed by the investigator.

13. Women of childbearing potential, must agree to practice sexual abstinence or use adequate reliable contraceptive methods as per local regulations and as per applicable Prescribing Information guidance, from screening until 90 days after end of treatment (EOT) (or longer, if dictated by local regulations). The investigator will counsel subjects on the use of contraceptive methods to avoid pregnancy.

    - Women receiving oral contraceptives or patch contraceptives should consider other/ additional methods of contraception (see also Section 8.1).
    - Women who are not heterosexually active must have periodic confirmation of continued abstinence from heterosexual intercourse and have regular pregnancy testing while taking study drugs; the investigator should counsel subjects on adequate reliable

contraceptive methods for avoiding pregnancy if they choose not to continue abstinence. 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 throughout the study.

- The use of birth control methods does not apply if the male partner has been vasectomized minimally 2 months prior to screening.
- The use of birth control methods does not apply for women of nonchildbearing potential, ie:
    - who have been 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.
    - who are surgically sterile (have had a total hysterectomy or bilateral oophorectomy, tubal ligation/bilateral tubal clips without reversal operation, or otherwise are incapable of becoming pregnant).

14. A woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction until 90 days after EOT (or longer, if dictated by local regulations).

15. Men with a female partner of childbearing potential must agree to use adequate reliable contraceptive methods (see also Inclusion Criterion 13) during the study until 90 days after EOT (or longer, if dictated by local regulations).
    - 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 tested study treatment and for up to 90 days after EOT.

16. Men must agree not to donate sperm during the study until 90 days after EOT (or longer, if dictated by local regulations).

17. Each subject (or their legally acceptable representative) must sign an ICF indicating that he or she understands the purpose of and procedures required for the study and are willing to participate in the study.

18. Subject must be able to swallow tablets.

19. Subject must be a man or woman ≥18 years of age.

4.2. Exclusion Criteria

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

1. Subject has been diagnosed with a new AIDS-defining condition (see Attachment 2) within the 30 days prior to screening.

2. Subject has proven or suspected acute hepatitis within 30 days prior to screening.

3. Subject is hepatitis C antibody positive; however, spontaneously cured hepatitis C virus (HCV) infection and subjects cured of HCV infection after treatment (with documented sustained virologic response, ie, undetectable HCV RNA 24 weeks after the last dose of HCV treatment), are allowed to participate.

4. Subject is hepatitis B surface antigen (HBsAg) positive.

5. Subject has a history of cirrhosis.

6. Subject has a history of malignancy within the past 5 years or ongoing malignancy other than cutaneous Kaposi's sarcoma, basal cell carcinoma, resected, noninvasive cutaneous squamous carcinoma or anal, penile or cervical intra-epithelial neoplasia.

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

8. Subject has known allergies, hypersensitivity, or intolerance to D/C/F/TAF FDC, DRV/COBI FDC, and TDF/FTC FDC, or their excipients.

9. Subject is unlikely to comply with the protocol requirements, based on clinical judgment.

10. Participation in any other clinical study without prior approval from the sponsor.

11. Subject is a woman who is pregnant (positive serum pregnancy test), or breast-feeding, or planning to become pregnant while enrolled in this study or within 90 days after the last dose of study drug.

12. Subject is a man who plans to father a child while enrolled in this study or within 90 days after the last dose of study drug.

13. Subject has a current condition (including but not limited to alcohol or substance use) judged by the investigator to potentially compromise the subject's safety and/or adherence to the study protocol.

14. Subject has any condition 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.

15. Subject is an 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.

16. Subject is receiving therapy with any of the disallowed drugs in Table 1 and for whom it is impossible to have these discontinued at least 30 days prior to baseline.

Table 1: Exclusionary Concomitant Medications

Drug Class	Agents Disallowed[a,b]
Alpha adrenergic receptor antagonist	Alfuzosin
Analeptic	Modafenil
Anti-anginals	Ranolazine
Anti-arrhythmics	Amiodarone, Quinidine, Dronedarone, systemic Lidocaine (IV or IM) used as anti-arrhythmic
Anticoagulants	Rivaroxaban, Apixaban, Dabigatran etexilate
Anticonvulsants	Phenobarbital, Phenytoin, Carbamazepine, Oxcarbazepine
Antigout	Colchicine (in patients with renal or hepatic impairment)
Anti-HCV drugs	Telaprevir, Boceprevir, Simeprevir, fixed dose combination tablet containing Ombitasvir, Paritaprevir, and Ritonavir copackaged with Dasabuvir
Antihistamines	Astemizole, Terfenadine
Antimycobacterials	Rifampin, Rifapentine, Rifabutin
Antineoplastics	Everolimus
Antipsychotics/Neuroleptics	Pimozide, Quetiapine, Sertindole
Antiretrovirals	Any antiretroviral drug that is not part of the study regimen
Calcium channel blockers	Bepridil
Corticosteroids: systemic	All agents, including dexamethasone with the exception of short-term (less than 1 week) use of prednisone as a steroid burst
Endothelin receptor antagonists	Bosentan
Ergot derivatives	Ergotamine, Ergonovine, Dihydroergotamine, Methylergonovine, Ergometrine
Gastrointestinal motility agents	Cisapride
Herbal supplements	St. John's Wort, Echinacea
HMG-CoA reductase inhibitors	Simvastatin, Lovastatin
Immunosuppressants	Everolimus
Inhaled β-agonists	Salmeterol
Phosphodiesterase (PDE)-5 inhibitors	Avanafil, Use of any other PDE-5 inhibitor in the treatment of pulmonary arterial hypertension
Platelet aggregation inhibitor	Ticagrelor
Sedatives/Hypnotics	Midazolam (oral), Triazolam; with the exception of one-time use for procedures

[a] Administration of any of the above medications must have been discontinued at least 30 days prior to baseline (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.

[b] This list of disallowed concomitant medication may not be exhaustive. Refer to the current local Prescribing Information for these medications, where available, for additional and up-to-date information.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a subject's clinical status changes (including available laboratory results or receipt of additional medical records) after screening but before the first dose of study drug is given such that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation in the study. Section 17.4, Source Documentation, describes the required documentation to support meeting the enrollment criteria.

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. All HIV-infected subjects should be advised to take the necessary precautions to reduce the risk of transmitting HIV.
2. Since reproductive risks have been noted with some HIV-1 ARVs, non-vasectomized heterosexually active males and/or females of childbearing potential having heterosexual intercourse must agree to use a highly effective method of birth control (see Section 4.1 for details).
3. A woman using oral contraceptives should use an additional birth control method (see inclusion criterion).

5. TREATMENT ALLOCATION AND BLINDING

Treatment Allocation

Procedures for Randomization and Stratification

Central randomization will be implemented in conducting this study. Subjects will be assigned to 1 of 2 treatment groups based on a computer-generated schedule, constructed via random permuted blocks implemented in the interactive web response system (IWRS) and prepared before the start of the study by or under the supervision of the sponsor. Stratified randomization minimizes the imbalance in the distribution of the number of subjects across treatment groups within the levels of each individual stratification factor: HIV-1 RNA level (≤100,000 copies/mL or >100,000 copies/mL) and CD4+ cell count (<200 cells/µL or ≥200 cells/µL) at screening. The IWRS will assign a unique treatment code, which will dictate the treatment assignment and matching study drug kit for the subject.

The randomization and baseline visit (Day 1) cannot proceed until the investigator has received all results of the screening visit and subject eligibility has been confirmed in IWRS, which should occur within approximately 30 days after the screening visit (for further details, see Section 9.1.2.1). Randomization should be performed on the same day as the baseline visit (Day 1), provided that all screening procedures have been completed and subject eligibility has been confirmed.

Blinding

The investigator will not be provided with randomization codes. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the blind for an individual subject.

Data that may potentially unblind the treatment assignment (ie, pharmacokinetic data) will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized. This can include making special provisions, such as segregating the data in question from view by the investigators, clinical team, or others as appropriate until the time of database lock and unblinding.

Under normal circumstances, the blind should not be broken until all subjects have reached Week 48 and the database for the Week 48 analysis is finalized. Otherwise, the blind should be broken only if specific emergency treatment/course of action would be dictated by knowing the treatment status of the subject. In such cases, the investigator may in an emergency determine the identity of the treatment by contacting the IWRS. It is recommended that the investigator contacts the sponsor or its designee if possible to discuss the particular situation, before breaking the blind. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the sponsor must be informed as soon as possible. The date, time, and reason for the unblinding must be documented by the IWRS, in the appropriate section of the electronic case report form (eCRF) and in the source document. The documentation received from the IWRS indicating the code break must be retained with the subject's source documents in a secure manner.

In order to distinguish samples from subjects randomized to the D/C/F/TAF treatment arm from those of subjects in the control group, the bioanalytical lab will be unblinded to the treatment groups. However, the sponsor will remain blinded from the origin of the samples that have been analyzed, as well as from the outcome of the analyses, until locking of the database has been performed for the primary analysis.

Subjects who have had their treatment assignment unblinded should continue to return for scheduled evaluations to receive the D/C/F/TAF FDC tablet in an open-label single-arm treatment phase.

6. DOSAGE AND ADMINISTRATION

Prior to the baseline visit (Day 1), eligible subjects will be randomized in a 1:1 ratio to the investigational treatment arm (D/C/F/TAF FDC tablet) or the active control arm (DRV/COBI FDC coadministered with FTC/TDF FDC) (see also Figure 1).

- **D/C/F/TAF Arm (n=335):**

  Regimen of a single-tablet containing DRV 800 mg/ COBI 150 mg/ FTC 200 mg/ TAF 10 mg (D/C/F/TAF FDC tablet) once daily
  + DRV/COBI FDC-matching and FTC/TDF FDC-matching placebo tablets once daily;

- **Control Arm (n=335):**

  Regimen of DRV 800 mg/ COBI 150 mg FDC coadministered with FTC 200 mg/ TDF 300 mg FDC once daily
  + D/C/F/TAF FDC-matching placebo tablet once daily.

All baseline tests and procedures must be completed prior to the administration of the first dose of study treatment. Initiation of study treatment must take place within 24 hours after the baseline visit.

The investigational medication, D/C/F/TAF FDC tablets, the control DRV/COBI FDC tablets and the D/C/F/TAF FDC- and DRV/COBI FDC–matching placebo tablets (identical in physical appearance), will be manufactured, packaged and provided by the sponsor. The control FTC/TDF FDC tablets and matching placebo tablets will be manufactured, packaged by GSI and provided to the sponsor for distribution.

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

All study drugs and matching placebo tablets must be administered orally, once daily in the morning with food, at approximately the same time each day. Study drugs should be taken on site with food during study site visits (except Week 8 and Week 36), after all safety assessments that require fasting are taken. If subjects notice that they 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 missed their dose >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 do not last longer than 4 consecutive weeks. The sponsor should be notified when such temporary interruption occurs.

After Week 48, subjects will continue to take their blinded study drug and attend visits every 12 weeks until all subjects have reached Week 48 and treatment assignments have been unblinded. Provided the results from the primary analysis do not preclude (further) exposure of subjects to D/C/F/TAF, all subjects will return for an unblinding visit and will receive the D/C/F/TAF FDC tablet in an open-label single-arm treatment phase until Week 96. In order to collect long-term safety and efficacy data on D/C/F/TAF, subjects will be given the opportunity to continue D/C/F/TAF treatment after Week 96 during an extension phase until the D/C/F/TAF

FDC tablet becomes commercially available and is reimbursed, or can be accessed through another source in the country where he/she is living, or until the sponsor terminates clinical development.

7. TREATMENT COMPLIANCE

Adherence to study medication intake (investigational medication, ARV regimen in the control arm and matching placebo tablets) will be assessed by pill counts. For this purpose, 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.

The investigator or designated study personnel will maintain a log of all study drugs (investigational medication and ARVs in the control arm) dispensed and returned. Drug supplies for each subject will be inventoried and accounted for throughout the study (see also Section 14.5).

In addition, adherence to study medication (investigational medication, ARV regimen in the control arm and matching placebo tablets) intake will be monitored by the investigator using study medication log booklets. At the baseline visit (Day 1), subjects will be given a study medication log booklet, in which they are to record their study medication intakes. Subjects should be instructed to bring their log booklet, and these will be checked and discussed with the subject by the investigator or designated study personnel at each visit up to Week 96.

If a subject's medication intake is not according to the protocol, it will be the investigator's responsibility to take the necessary measures to ensure future compliance to the protocol.

8. PRESTUDY AND CONCOMITANT THERAPY

Prestudy therapies administered up to 30 days before 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 the investigational medication (D/C/F/TAF FDC tablet, ARVs in the control arm, or matching placebo tablets) must be recorded in the eCRF. Recorded information will include a description of the type of the drug, treatment period, dosing regimen, route of administration, and its indication. Modification of an effective preexisting therapy should not be made for the explicit purpose of entering a subject into the study if such modification of treatment is not clinically acceptable. Any change in dosage of the medication must also be reported in the eCRF.

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

Data on concomitant medication will be collected up to the last FU visit, even after withdrawal of a subject. Concomitant therapies should be recorded beyond the last FU visit only in conjunction with SAEs that meet the criteria outlined in the study protocol.

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

8.1. Disallowed and Cautioned Concomitant Therapy

Females of childbearing potential must use effective birth control methods (as outlined in Section 4.1, see also Section 4.3) during the entire study and for at least 90 days after the last intake of study medication. Subjects receiving oral contraceptives or patch contraceptives should consider other methods of contraception, as concentrations of ethinyl estradiol, norgestimate or norethindrone may increase or decrease on coadministration with the investigational medication. The use of any oral, injectable and implantable hormonal contraceptives should be recorded in the concomitant therapy section of the eCRF. Applicable procedures and treatment guidance based on Prescribing Information should be respected.

Because the concomitant use of some medications or herbal supplements may result in altered exposure to the investigational medication or the concomitant medication, due to pharmacokinetic interactions, certain medications or supplements are excluded or are to be used with caution while taking the study medication. Guidance on dose adjustments for these concomitant medications, if applicable, is provided in Table 2.

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 prior to discussion with the medical monitor, the investigator must notify the sponsor as soon as becoming aware.

Table 2: Concomitant Therapy: Disallowed and Cautioned Use

Drug Class	Agents Disallowed[a]	Use Discouraged or to be Used With Caution[a]
Alpha adrenergic receptor antagonist	Alfuzosin	
Analeptic	Modafinil	
Analgesics		Tramadol, Propoxyphene: Concentrations may increase with study drug(s); clinical monitoring is recommended.
Anti-anginals	Ranolazine	

Drug Class	Agents Disallowed[a]	Use Discouraged or to be Used With Caution[a]
Anti-arrhythmics	Amiodarone, Quinidine, Dronedarone, systemic Lidocaine (IV or IM) used as anti-arrhythmic	Flecainide, Propafenone, Mexilitine, Digoxin Disopyramide: Concentrations may increase with study drug(s) resulting in a potential for cardiac arrhythmias; caution is warranted and therapeutic drug monitoring of antiarrhythmics is recommended when available. The lowest dose of Digoxin should be administered and dose should be titrated. Serum digoxin concentrations should be monitored to assist in the titration.
Antibacterials		Concentrations of telithromycin may increase with study drug(s). Clinical monitoring is recommended. Clarithromycin: Concentrations may increase with study drug(s); consider an alternative; if coadministration cannot be avoided, consult the local Prescribing Information for further dosing recommendations.
Anticoagulants	Rivaroxaban, Apixaban, Dabigatran etexilate	Warfarin: Concentrations may be affected by study drug(s); frequent international normalized ratio (INR) monitoring is recommended.
Anticonvulsants	Phenobarbital, Phenytoin, Carbamazepine, Oxcarbazepine	Clonazepam, Ethosuximide, Concentrations may increase with study drug(s). Divalproex, Lamotrigine: Concentrations may be affected by study drug(s). Clinical monitoring is recommended.
Antidepressants		Bupropion: Concentrations may be affected by study drug(s). Subjects receiving bupropion should be monitored for adequate clinical response. Selective serotonin reuptake inhibitors, eg, Trazodone, Paroxetine, Sertraline: A dose reduction may be required. Dosing should be titrated in conjunction with clinical monitoring. Tricyclics: Concentrations may increase with study drug(s). Concentration monitoring is recommended to ensure adequate clinical response.

Drug Class	Agents Disallowed[a]	Use Discouraged or to be Used With Caution[a]
Antifungals		Ketoconazole, Fluconazole, Posaconazole, Itraconazole: Concomitant use with study drug(s) may result in an increase in concentrations. Daily dose of ketoconzazole and itraconazole should be restricted to 200 mg. Voriconazole: Plasma concentrations may be increased or decreased in the presence of DRV/COBI, and should not be administered unless an assessment of the benefit/risk ratio justifies the use. Subjects receiving antifungals should be monitored for adequate clinical response. Note: topical administration of antifungals is allowed.
Antigout	Colchicine (in patients with renal or hepatic impairment)	Colchicine: Concentrations may increase with study drug(s). Dose reductions of colchicine may be required. Treatment for gout-flare: 0.6 mg (1 tablet) x 1 dose, followed by 0.3 mg (half tablet) 1 hour later. Treatment course to be repeated no earlier than 3 days. Prophylaxis of gout-flare: If the original regimen was 0.6 mg twice daily, the regimen should be adjusted to 0.3 mg once daily. If the original regimen was 0.6 mg once daily, the regimen should be adjusted to 0.3 mg once every other day. Treatment of familial Mediterranean fever: Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice daily).
Anti-HCV drugs	Telaprevir, Boceprevir, Simeprevir, fixed dose combination tablet containing Ombitasvir, Paritaprevir, and Ritonavir copackaged with Dasabuvir	Sofosbuvir, Ledipasvir, Daclatasvir
Antihistamines	Astemizole, Terfenadine	
Antimalarials		Artemether/Lumefantrine: Use with caution.
Antimycobacterials	Rifampin, Rifapentine, Rifabutin	
Antineoplastics	Everolimus	Dasatinib, Nilotinib, Vinblastine, Vincristine: Caution should be exercised.
Antipsychotics/Neuroleptics	Pimozide, Quetiapine, Sertindole	Perphenazine, Risperidone, Thioridazine: A dose decrease may be needed.
Antiretrovirals	Any ARV drug that is not part of the study regimen	
β-Blockers		Carvedilol, Metoprolol, Timolol: Clinical monitoring is recommended when coadministering β -blockers and a lower dose of the β -blocker should be considered.

Drug Class	Agents Disallowed[a]	Use Discouraged or to be Used With Caution[a]
Calcium channel blockers	Bepridil	Felodipine, Nifedipine, Nicardipine, Verapamil, Diltiazem, Amlodipine: Concentrations may increase with study drug(s). Caution is warranted and careful clinical monitoring is recommended.
Contraceptives		Ethinylestradiol, Norethindrone, Norgestimate: Concentrations of contraceptives may decrease or increase with study drug(s). Alternative methods of nonhormonal contraception are recommended.
Corticosteriods: inhaled/nasal		Concomitant use of inhaled fluticasone and study drug(s) may increase plasma concentrations of fluticasone and/or decrease concentrations of COBI and/or DRV. Alternatives should be considered, particularly for long term use.
Corticosteroids: systemic	All agents, including dexamethasone with the exception of short term (less than 1 week) use of prednisone as a steroid burst	Use of Prednisone as a steroid burst (maximum 1 week of use) should be monitored appropriately.
Endothelin receptor antagonists	Bosentan	
Ergot derivatives	Ergotamine, Ergonovine, Dihydroergotamine, Methylergonovine, Ergometrine	
Gastrointestinal motility agents	Cisapride	
Herbal/Natural supplements	St. John's Wort, Echinacea	
HMG-CoA reductase inhibitors	Simvastatin, Lovastatin	Atorvastatin, Rosuvastatin, Pravastatin: Concentrations may increase with study drug(s). Titrate atorvastatin, pravastatin or rosuvastatin dose carefully and use the lowest necessary dose while monitoring for safety. Pitavastatin: Caution should be exercised when coadministering pitavastatin.
Immunosuppressants	Everolimus	Cyclosporine, Sirolimus, Tacrolimus: Concentrations may increase with study drug(s). Therapeutic monitoring should be considered.
Inhaled β-agonist	Salmeterol	
Opiates		Methadone: Concentrations may increase with study drug(s). Concentration monitoring is recommended to ensure adequate clinical response; a methadone dose adjustment may be required. Buprenorphine/Naloxone: Concentrations of buprenorphine or its active metabolite may be affected by study drug(s). Careful clinical monitoring is recommended.

Drug Class	Agents Disallowed[a]	Use Discouraged or to be Used With Caution[a]
PDE-5 inhibitors	Avanafil, Use of any other PDE-5 inhibitor in the treatment of pulmonary arterial hypertension	Sildenafil, Vardenafil, Taladafil: It is recommended that a single dose of Sildenafil ≤25 mg in 48 hours, Vardenafil ≤2.5 mg in 72 hours, or Taladafil ≤10 mg in 72 hours be coadministered.
Platelet aggregation inhibitor	Ticagrelor	
Sedatives/Hypnotics	Midazolam (oral), Triazolam; with the exception of one-time use for procedures	Buspirone, Clorazepate, Diazepam, Estazolam, Flurazepam, Zolpidem: A dose decrease may be needed for these drugs. Coadministration of parenteral midazolam should be done in a setting that ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dose reduction for parenteral midazolam should be considered, especially if more than a single dose of midazolam is administered.

[a] This list of disallowed concomitant medication or concomitant medications with specific precautions may not be exhaustive. Refer to the current local Prescribing Information for these medications, where available, for additional and up-to-date information.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The Time and Events Schedule summarizes the frequency and timing of efficacy, pharmacokinetic and safety measurements applicable to this study. The protocol procedures are described in detail in Sections 9.2 through 9.5.

It is the responsibility of the investigator to follow the screening procedures and ensure that each subject is eligible for the study before enrollment. Please see Sections 5 and 6 for details on randomization and assigned treatment, and Section 9.1.2 for details on pretreatment procedures.

Following the baseline visit (Day 1), subjects will return for study visits at the end of Weeks 2, 4, 8, 12, 24, 36, 48, every 12 weeks thereafter until and including a Week 96 visit. All study visits are to be scheduled relative to the baseline/Day 1 visit date. Some flexibility in the planning of the visits is allowed, however, the total treatment duration at the end of the treatment period should be 96 weeks. The study visit at Week 2 is to be completed within ±2 days of the protocol-specified visit date based on the baseline (Day 1). The other study visits through Week 96 are to be completed within ±7 days of the protocol-specified visit date. For further details, see Section 9.1.3.

After Week 48, subjects will continue to take their blinded study drug and attend visits every 12 weeks until all subjects have reached Week 48 and treatment assignments have been unblinded. Provided the results from the primary analysis do not preclude (further) exposure of

subjects to D/C/F/TAF, all subjects will return for an unblinding visit and will receive the D/C/F/TAF FDC tablet in an open-label single-arm treatment phase. Subjects from the control arm who switch to the D/C/F/TAF regimen after the 48-week double-blind treatment will be required to return to the clinic for an additional visit 3 to 7 weeks after the unblinding visit. If this additional visit would take place within a ±4 week window of a normal planned schedule visit, the additional visit can take place during this planned visit. For further details, see Section 9.1.4.

After Week 96, subjects will be given the opportunity to continue D/C/F/TAF treatment during an extension phase until the D/C/F/TAF FDC tablet becomes commercially available and is reimbursed, or can be accessed through another source in the country where he/she is living, or until the sponsor terminates clinical development. During the extension phase subjects will attend visits every 6 months. The visits during the extension phase are to be completed within ±14 days of the protocol-specified visit date. For further details, see Section 9.1.5.

Subjects who prematurely discontinue treatment, either during the double-blind treatment phase (from Day 1 to Week 48) or during the open-label single-arm treatment phase (between Week 48 and Week 96) will be required to complete the ESTD visit assessments within 72 hours of stopping study treatment.

In addition, a 30-day FU visit will be required for any subject who has an ongoing AE or SAE at the time of his/her last study visit (unless consent is withdrawn) and must be scheduled within ± 7 days of the protocol-specified visit date. For further details, see Section 9.1.6.2.

For laboratory assessments that need to be performed fasted (no food or drinks, except water, for at least 8 hours prior to blood or urine collection)while the subject has not fasted prior to the visit, the visit may proceed, but the subject must return within 72 hours in a fasted state to provide the necessary sample(s) for the assessments.

The total blood volume to be collected from each subject from screening through the Week 96 visit will be approximately 585 mL and 640 mL, for subjects participating only in the main study and for subjects also participating in the bone investigation substudy, respectively.

Repeat or unscheduled samples may be required for safety reasons, for technical issues with the samples, or for confirmation of virologic failure (VF) in case of unconfirmed FV (virologic nonresponse or virologic rebound). 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. 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. Findings during these unscheduled visits or assessments need to be reported in the eCRF.

Plasma 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. No human genetic testing will be performed. See also Section 16.2.5.

9.1.2. Pre-treatment Phase

9.1.2.1. Screening Visit

Subjects will be screened within 30 days before randomization to determine eligibility for participation in the study. The screening period may be extended on a case-by-case basis after discussion and approval by the sponsor. However, no extensions beyond 6 weeks will be allowed. The following evaluations will be performed and documented at screening.

- Obtain written informed consent.
- Obtain medical history including history of HIV-1 disease-related events and prior medications within 30 days of the screening visit.
- Complete physical examination (urogenital/anorectal examinations will be performed at the discretion of the investigator).
- Vital signs measurement (blood pressure and pulse) and weight.
- 12-lead ECG performed supine.
- Height.
- Midstream urine sample collection for the following laboratory procedures:
  - Urine chemistry (quantitative measurement): creatinine, sodium, phosphate, glucose, protein, albumin.
  - Urinalysis by dipstick: specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, and leukocyte esterase.
- Blood sample collection for the following laboratory analyses:
  - Serum pregnancy test (females of childbearing potential only). If the test is positive, the subject will not be enrolled.
  - FSH test is required for female subjects who have stopped menstruating for at least 2 years but do not have documentation of ovarian hormonal failure.
  - Chemistry profile: alpha 1-acid glycoprotein (AAG), alkaline phosphatase (ALP), AST, ALT, gamma-glutamyl transferase (GGT), total bilirubin, direct and indirect bilirubin, total protein, albumin, creatine phosphokinase (CPK), bicarbonate, blood urea nitrogen (BUN), chloride, creatinine, glucose, phosphorus, potassium, sodium, uric acid, and amylase (reflex lipase testing is performed in subjects with total amylase >1.5 x ULN).
  - Cystatin C and $eGFR_{cystatin}$ according to the CKD-EPI formula.

- $eGFR_{creatinine}$ ≥70 mL/min according to the Cockcroft-Gault formula for creatinine clearance; for details, see Section 9.5.4.
- Hematology profile: hemoglobin, hematocrit, red blood cell (RBC) count and parameters (mean corpuscular hemoglobin [MCH], MCH concentration and mean corpuscular volume [MCV]), white blood cell (WBC) count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), and platelet count.
- CD4+ cell count.
- Plasma HIV-1 RNA.
- HIV-1 PR/RT genotype.
- HBV and HCV testing (HBsAg, HCV antibody, and HCV RNA).

- Review of AEs and concomitant medications.

Retesting of abnormal laboratory values that may lead to exclusion will be allowed once. Retesting will take place during an unscheduled visit in the screening period. The investigator may consider the subject eligible if the previously abnormal laboratory test result is within protocol acceptable range on a repeat testing in the central laboratory.

Subjects meeting all of the inclusion criteria and none of the exclusion criteria will return to the clinic within 30 days after the screening visit for the baseline (Day 1) assessments.

9.1.2.2. Baseline Visit (Day 1)

The investigator must have received all results from the screening visit before proceeding with the baseline visit. Once eligibility has been confirmed, the investigator will randomize the subject using IWRS during the baseline visit. The subject must complete all baseline procedures before being dispensed the study drug. The following procedures are to be completed and documented at the baseline visit.

- Review of AEs and changes in concomitant medications.
- Review of clinical status and available data.
- Complete physical examination (urogenital/anorectal examinations will be performed at the discretion of the investigator).
- Vital signs measurement (blood pressure and pulse) and weight.
- Midstream urine sample collection for the following laboratory procedures:
  - Urinalysis and urine chemistry (see also Section 9.1.2.1).
  - Urine renal biomarkers (fasted, ie, no food or drinks except water, at least 8 hours prior to urine collection): RBP and beta-2-microglobulin. If the subject has not fasted prior to the visit, the visit may proceed, but the subject must return within 72 hours in a fasted state to provide a urine sample for renal biomarkers.

  - Urine pregnancy test (females of childbearing potential only). If the urine pregnancy test is positive at baseline, study drug will not be dispensed. The positive result will be confirmed with a serum pregnancy test. If the serum pregnancy test is positive, the subject will not be able to participate.

- Blood sample collection for the following laboratory analyses:
  - Chemistry profile (see also Section 9.1.2.1). At baseline, glucose will be performed as part of the metabolic profile.
  - Metabolic profile (collected fasted): total, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, triglycerides, glucose. If the subject has not fasted prior to the visit, the visit may proceed, but the subject must return within 72 hours in a fasted state to have a blood draw for the metabolic assessments.
  - Hematology profile (see also Section 9.1.2.1).
  - Cystatin C and $eGFR_{cystatin}$ according to the CKD-EPI formula.
  - $eGFR_{creatinine}$ according to the Cockcroft-Gault formula and the CKD-EPI formula; for details, see Section 9.5.4.
  - Plasma HIV-1 RNA.
  - CD4+ cell count.
  - HIV-1 resistance testing. HIV-1 PR/RT genotype/phenotype testing will be requested by the study virologist on samples from subjects eligible for resistance testing.
  - Plasma storage samples for possible additional testing.
  - PBMC storage sample for exploratory analysis (eg to characterize archived viral resistance) if deemed necessary by the study virologist.
- Study drug dispensation (D/C/F/TAF FDC and DRV/COBI FDC + FTC/TDF FDC matching placebos or D/C/F/TAF FDC-matching placebo and DRV/COBI FDC + FTC/TDF FDC) in a double-blind fashion:
  - All subjects must initiate dosing with study medication within 24 hours after the baseline visit.
  - 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.
- Dispensation of the study medication log booklet, in which subjects should record their study medication intakes. Subjects should also be instructed to bring their log booklet at each study visit.

In subjects participating in the bone investigation substudy:

- Bone biomarkers (collected fasted, ie, no food or drinks, except water, at least 8 hours prior to sample collection): CTX, P1NP, PTH, and 25-hydroxy vitamin D. If the subject has not

fasted prior to the visit, the visit may proceed but the subject must return within 72 hours in a fasted state to provide a blood sample for bone biomarker assessment.

- DXA scan of spine and hip: The scan is to be performed between the screening and the baseline visit (a window of +2 weeks is allowed). A rescan for technical reasons is allowed within 2 weeks.
  Note: For female subjects absence of pregnancy will be confirmed at screening prior to performing the DXA scan.

9.1.3. Double-blind Treatment Phase

After the baseline visit, subjects will return for study visits at the end of Weeks 2, 4, 8, 12, 24, 36, and 48 (scheduled relative to the baseline visit date). After Week 48, subjects will continue to take their blinded study drug and attend visits every 12 weeks until all subjects have reached Week 48 and treatment assignments have been unblinded. Provided the results from the primary analysis do not preclude (further) exposure of subjects to D/C/F/TAF, all subjects will return to the clinic for an unblinding visit, preferably at the next planned visit.

The time window for the Week 2 visit is ±2 days, and for the visits through the unblinding visit is ±7 days of the protocol-specified visit date. The following procedures are to be completed and documented at each visit.

- Review of AEs and changes in concomitant medications.
- Complete physical examination at **Weeks 24, 48, and at the unblinding visit** (urogenital/anorectal examinations will be performed at the discretion of the investigator).
- Symptom-directed physical examination (physical examination of body parts for which symptoms have been reported by the subject) as needed at **Weeks 2, 4, 8, 12, 36, and every 12 weeks following Week 48 until unblinding.**
- Vital signs measurement (blood pressure and pulse) and weight.
- Midstream urine sample collection for the following laboratory procedures:
  - Urinalysis and urine chemistry (see also Section 9.1.2.1).
  - Urine renal biomarkers (fasted, ie, no food or drinks, except water, at least 8 hours prior to urine collection; if the subject has not fasted prior to the visit, the visit may proceed, but the subject must return within 72 hours in a fasted state to provide a urine sample for renal biomarkers) at **Weeks 2, 4, 12, 24, 48, every 12 weeks following Week 48 until and including the unblinding visit** (see also Section 9.1.2.2).
  - Urine pregnancy test (females of childbearing potential only); positive urine pregnancy tests will be confirmed with a serum test; if this test is positive, the subject will be withdrawn (see also Section 12.4.3).

- Blood sample collection for the following laboratory analyses:
  - Chemistry profile (see also Section 9.1.2.1). At **Weeks 24 and 48**, analysis of glucose will be done as part of the fasting metabolic profile and not as part of the chemistry profile.
  - Metabolic profile (including glucose; collected fasted; if the subject has not fasted prior to the visit, the visit may proceed, but the subject must return within 72 hours in a fasted state to have a blood draw for the metabolic assessments) at **Weeks 24, 48, every 12 weeks following Week 48 until and including the unblinding visit** (see also Section 9.1.2.1).
  - Hematology profile (see also Section 9.1.2.1).
  - Cystatin C and $eGFR_{cystatin}$ according to the CKD-EPI formula.
  - $eGFR_{creatinine}$ according to the Cockcroft-Gault formula, and the CKD-EPI formula (for details, see Section 9.5.4).
  - Plasma HIV-1 RNA.
  - CD4+ cell count.
  - HIV-1 resistance testing. HIV-1 PR/RT genotype/phenotype testing will be requested by the study virologist on samples from subjects eligible for resistance testing.
  - Plasma storage sample for possible additional clinical testing at **Weeks 2, 4, 12, 24, 36, 48, and the unblinding visit**.
  - PBMC storage sample at **Weeks 24 and 48,** for exploratory analysis (eg to characterize archived viral resistance) if deemed necessary by the study virologist.
- Pharmacokinetic sample collection:
  - Blood samples will be collected at least 30 minutes to maximum 4 hours postdose at **Weeks 2, 4, 12, 24, and 48**.
  - Blood samples will be collected at 2 time points with at least 2.5 hours in between sampling at **Weeks 8 and 36**. The first pharmacokinetic sample at these visits should be taken between 1 and 4 hours postdose (dosing may occur prior to the study site visit).
- Document study drug dispensation and accountability (except at Week 2) for all study drugs dispensed.
- Checking of the study medication log booklet for review of treatment adherence.

In subjects participating in the bone investigation substudy:

- Bone biomarkers at **Weeks 2, 4, 12, 24, 48, and Week 72 (if applicable)** (collected fasted, ie, no food or drinks, except water, at least 8 hours prior to sample collection): CTX, P1NP, PTH and 25-hydroxy vitamin D. Biomarkers PTH and 25-hydroxy vitamin D should be assessed at **Weeks 24 and 48** only. If the subject has not fasted prior to the

visit, the visit may proceed but the subject must return within 72 hours in a fasted state to provide a blood sample for bone biomarker assessment.

- DXA scan of spine and hip at **Weeks 24 and 48**. A time window of ±2 weeks and a rescan for technical reasons within 4 weeks are allowed.

9.1.4. Open-label Single-arm Phase

After the unblinding visit, provided the results from the primary analysis do not preclude (further) exposure of subjects to D/C/F/TAF, subjects will receive the D/C/F/TAF FDC tablet in an open-label single-arm treatment phase of the study and will be required to attend visits every 12 weeks. Subjects from the control arm who switch to the D/C/F/TAF treatment after the 48-week double-blind treatment will be required to return to the clinic for an additional visit 3 to 7 weeks after the unblinding visit. If the additional visit would take place within a ±4 week window of a normal planned schedule visit, the additional visit can take place during a planned visit.

The time window for the visits during the open-label single-arm treatment phase is ±7 days of the protocol-specified visit date, except for the additional visit where no extra time window is applicable. The following evaluations are to be completed and documented at each visit.

- Review of AEs and changes in concomitant medications.
- Symptom-directed physical examination (physical examination for which symptoms have been reported by the subject) as needed at **3 to 7 weeks following the unblinding visit** (only for those subjects who switched to D/C/F/TAF), **every 12 weeks following the unblinding visit until and including Week 96.**
- Vital signs measurement (blood pressure and pulse) and weight.
- Midstream urine sample collection for the following laboratory procedures:
  - Urinalysis and urine chemistry (see also Section 9.1.2.1).
  - Urine renal biomarkers (fasted, ie, no food or drinks, except water, at least 8 hours prior to urine collection; if the subject has not fasted prior to the visit, the visit may proceed, but the subject must return within 72 hours in a fasted state to provide a urine sample for renal biomarkers) at **3 to 7 weeks following the unblinding visit** (only for those subjects who switched to D/C/F/TAF), **every 12 weeks following the unblinding visit until and including Week 96** (see also Section 9.1.2.2).
  - Urine pregnancy test (females of childbearing potential only); positive urine pregnancy tests will be confirmed with a serum test. If the test is positive, the subject will be withdrawn (see also Section 12.4.3).
- Blood sample collection for the following laboratory analyses:
  - Chemistry profile (see also Section 9.1.2.1).

- Metabolic profile (including glucose; collected fasted; if the subject has not fasted prior to the visit, the visit may proceed, but the subject must return within 72 hours in a fasted state to have a blood draw for the metabolic assessments) at Week 96 (see also Section 9.1.2.1).
- Hematology profile (see also Section 9.1.2.1).
- Cystatin C and $eGFR_{cystatin}$ according to the CKD-EPI formula at **3 to 7 weeks following the unblinding visit** (only for those subjects who switched to D/C/F/TAF) (for details, see Section 9.5.4).
- $eGFR_{creatinine}$ according to the Cockcroft-Gault formula and the CKD-EPI formula (for details, see Section 9.5.4).
- Plasma HIV-1 RNA.
- CD4+ cell count.
- HIV-1 resistance testing. HIV-1 PR/RT genotype/phenotype testing will be requested by the study virologist on samples from subjects eligible for resistance testing.
- Plasma storage sample for possible additional clinical testing at **3 to 7 weeks following the unblinding visit** (only for those subjects who switched to D/C/F/TAF) and at **Week 96**.
- PBMC storage sample at **Week 96** for exploratory analysis (eg to characterize archived viral resistance) if deemed necessary by the study virologist.

- Document study drug dispensation and accountability for all study drugs dispensed.
- Checking of the study medication log booklet for review of treatment adherence.

In subjects participating in the bone investigation substudy:

- Bone biomarkers at **3 to 7 weeks following the unblinding visit** (only for those subjects who switched to D/C/F/TAF) and **every 24 weeks until and including Week 96** (collected fasted, ie, no food or drinks, except water, at least 8 hours prior to sample collection): CTX, and P1NP. Biomarkers PTH and 25-hydroxy vitamin D should be assessed at **Week 96** only. If the subject has not fasted prior to the visit, the visit may proceed but the subject must return within 72 hours in a fasted state to provide a blood sample for bone biomarker assessment.
- DXA scan of spine and hip at **Week 96**. A time window of ±2 weeks and a rescan for technical reasons within 4 weeks is allowed.

9.1.5. Extension Phase

After Week 96 subjects will be given the opportunity to continue D/C/F/TAF treatment during an extension phase until the D/C/F/TAF FDC tablet becomes commercially available and is reimbursed, or can be accessed through another source in the country where he/she is living, or until the sponsor terminates clinical development. During the extension phase subjects will

attend visits every 6 months thereafter. The time window during the extension phase is ±14 days of the protocol-specified visit date. The following evaluations are to be completed and documented at each visit.

- Review of AEs and changes in concomitant medications.
- Symptom-directed physical examination (physical examination of body parts for which symptoms have been reported by the subject) as needed.
- Vital signs measurement (blood pressure and pulse) and weight.
- Midstream urine sample collection for the following laboratory procedures:
  - Urinalysis and urine chemistry (see also Section 9.1.2.1).
  - Urine pregnancy test (females of childbearing potential only); positive urine pregnancy tests will be confirmed with a serum test; if this test is positive, the subject will be withdrawn (see also Section 12.4.3).
- Blood sample collection for the following laboratory analyses:
  - Chemistry profile (see also Section 9.1.2.1).
  - Hematology profile (see also Section 9.1.2.1).
  - $eGFR_{creatinine}$ according to the Cockcroft-Gault formula, and the CKD-EPI formula (for details, see Section 9.5.4).
  - Plasma HIV-1 RNA.
  - CD4+ cell count.
  - HIV-1 resistance testing. HIV-1 PR/RT genotype/phenotype testing will be requested by the study virologist on samples from subjects eligible for resistance testing.
- Document study drug dispensation and accountability for all study drugs dispensed.

9.1.6. Post-treatment Phase

9.1.6.1. Early Study Treatment Discontinuation Visit

Subjects who prematurely discontinue, either during the double-blind treatment phase (from Day 1 to Week 48) or during the open-label single-arm treatment phase (between Week 48 and Week 96) will be required to return to the clinic within 72 hours of stopping study treatment for the ESTD visit.

Any evaluations at the ESTD visit showing abnormal results indicating that there is a possible or probable causal relationship with study drug, need to be followed (as often as deemed prudent by the investigator) until satisfactory clinical resolution or stabilization.

The following procedures are to be completed and documented.

- Review of AEs and changes in concomitant medications.
- Complete physical examination (urogenital/anorectal examinations will be performed at the discretion of the investigator).
- Vital signs measurement (blood pressure and pulse) and weight.
- Midstream urine sample collection for the following laboratory procedures:
  - Urinalysis and urine chemistry (see also Section 9.1.2.1).
  - Urine renal biomarkers: required if the last test was more than 12 weeks before the ESTD visit (fasted, ie, no food or drinks, except water, at least 8 hours prior to urine collection; if the subject has not fasted prior to the visit, the visit may proceed, but the subject must return within 72 hours in a fasted state to provide a urine sample for renal biomarkers) (see also Section 9.1.2.2).
  - Urine pregnancy test (females of childbearing potential only); positive urine pregnancy tests will be confirmed with a serum test. If the test is positive, see Section 12.4.3 for the procedure to follow.
- Blood sample collection for the following laboratory analyses:
  - Chemistry profile (see also Section 9.1.2.1).
  - Hematology profile (see also Section 9.1.2.1).
  - $eGFR_{creatinine}$ according to the Cockcroft-Gault formula, and the CKD-EPI formula (for details, see Section 9.5.4).
  - Plasma HIV-1 RNA.
  - CD4+ cell count.
  - HIV-1 resistance testing. HIV-1 PR/RT genotype/phenotype testing will be requested by the study virologist on samples from subjects eligible for resistance testing.
  - Plasma storage sample for possible additional clinical testing.
  - PBMC storage sample for exploratory analysis (eg, to characterize archived viral resistance) if deemed necessary by the study virologist.
- Pharmacokinetic blood sample.
- Document study drug accountability for all study drugs dispensed.

In subjects participating in the bone investigation substudy:

- Bone biomarkers (collected fasted, ie, no food or drinks, except water, at least 8 hours prior to sample collection): CTX, P1NP, PTH and 25-hydroxy vitamin D. If the subject has not fasted prior to the visit, the visit may proceed but the subject must return within 72 hours in a fasted state to provide a blood sample for bone biomarker assessment.

- DXA scan of spine and hip: only to be performed at ESTD (±2 Weeks) if the last scan is more than 12 weeks from the date of the ESTD visit and the ESTD visit takes place before Week 96. A rescan for technical reasons within 4 weeks is allowed.

9.1.6.2. 30-Day Follow-up Visit

A 30-day FU visit will be required for any subject who has an ongoing AE or SAE at the time of his/her last study visit (unless consent is withdrawn).

A time window of ±7 days of the protocol-specified visit date may be used for this 30-day FU visit. The following evaluations are to be completed and documented.

- Review of AEs and changes in concomitant medications.
- Symptom-directed physical examination (physical examination for which symptoms have been reported by the subject) as needed.
- Weight.
- Midstream urine sample collection for the following laboratory procedures:
  - Urinalysis and urine chemistry (see also Section 9.1.2.1).
  - Urine pregnancy test (females of childbearing potential only); positive urine pregnancy tests will be confirmed with a serum test. If the test is positive, see Section 12.4.3 for the procedure to follow.
- Blood sample collection for the following laboratory analyses:
  - Chemistry profile (see also Section 9.1.2.1).
  - Hematology profile (see also Section 9.1.2.1).
  - $eGFR_{creatinine}$ according to the Cockcroft-Gault formula, and the CKD-EPI formula (for details, see Section 9.5.4).
  - Plasma HIV-1 RNA.
  - CD4+ cell count.

9.2. Efficacy Evaluations

9.2.1. Antiviral Efficacy and Immunologic Change

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 Event Schedule.

Plasma viral load levels will be measured using a validated assay, which will be conducted by the 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 (S)AE.

9.2.2. Resistance Determinations

Samples for HIV-1 genotype/phenotype resistance testing, as well as a PBMC sample will be taken at the time points specified in the Time and Event Schedule. PBMC samples will be taken for storage for exploratory analysis (eg, to characterize archived viral resistance) only if deemed necessary by the study virologist.

9.2.2.1. Virologic Failure

Subjects who are on study medication and who experience a protocol defined confirmed VF, ie, virologic nonresponse (NR) or virologic rebound (RB), as defined below, will be considered to have VF for the purpose of the resistance analysis.

Virologic Nonresponse:

- HIV-1 RNA <1 $\log_{10}$ reduction from baseline and ≥50 copies/mL at the Week 8 visit, confirmed at the following scheduled or unscheduled visit following Week 8.

Subjects (and the resistance testing on samples from these subjects), who meet the criteria for NR will be managed according to the protocol schema provided in Figure 2.

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 the following scheduled or unscheduled visit; 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.

Subjects (and the resistance testing on samples from these subjects), meeting the criteria for RB will be managed according to the schema provided in Figure 3.

9.2.2.2. Subjects Eligible for Resistance Testing

To investigate the emergence of PR/RT resistance, the following subjects will be eligible for genotypic/phenotypic resistance testing:

- Any subject who experiences a protocol defined confirmed VF, ie NR or RB, and has an HIV-1 RNA value ≥400 copies/mL (see Section 9.2.2.1);
- Any subject who discontinues study treatment and has an HIV-1 RNA value ≥400 copies/mL at the last viral load measurement (within 72 hours after discontinuation of the study treatment).

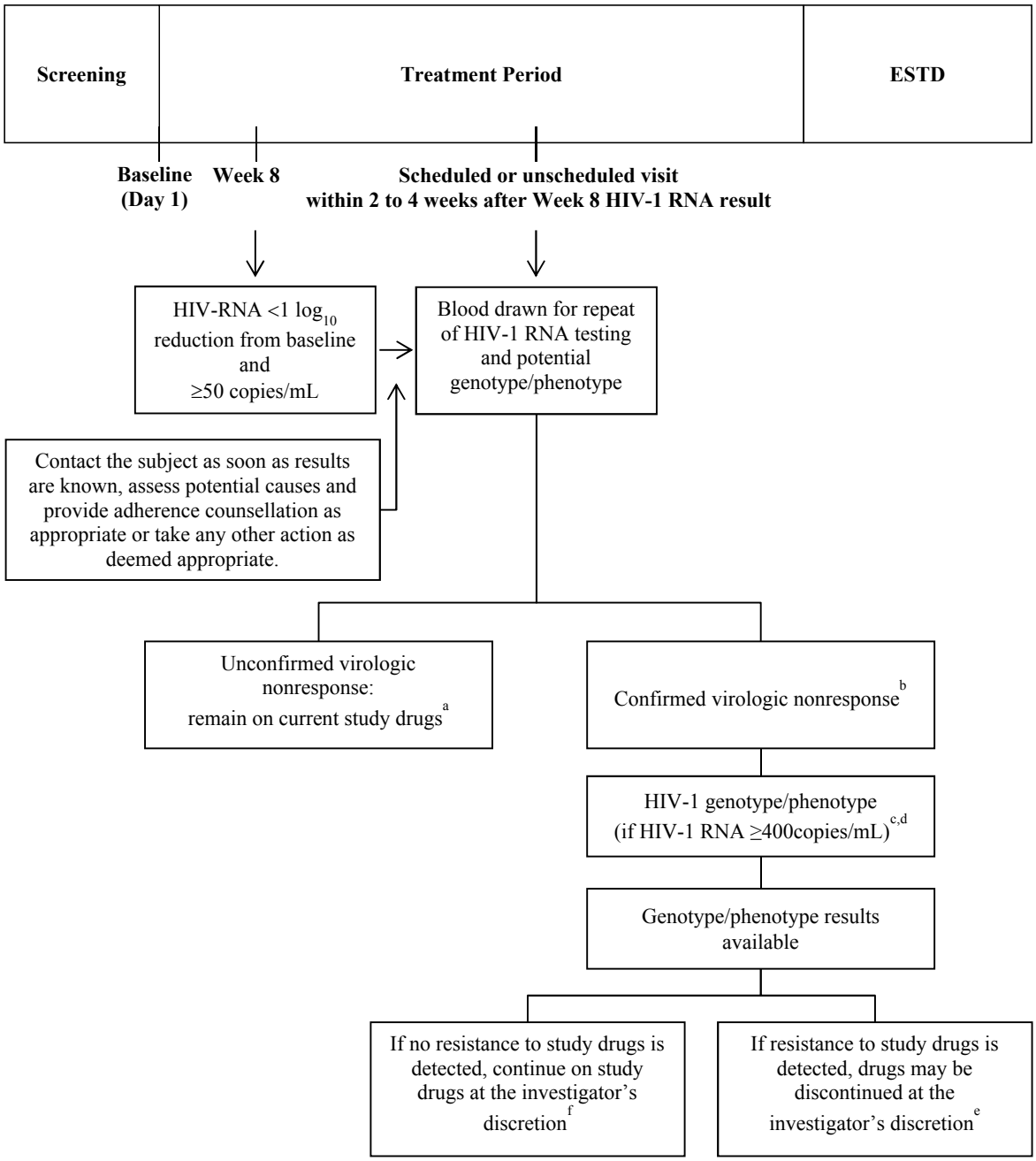
For subjects with confirmed VF (NR or RB), the plasma sample corresponding to the confirmed VF time point will be analyzed if HIV-1 RNA value ≥400 copies/mL. In case of confirmed VF

but with an HIV-1 RNA value <400 copies/mL at the confirmed VF point, resistance testing might then be done at a later time point if HIV-1 RNA value ≥400 copies/mL or at the unconfirmed VF point if HIV-1 RNA value ≥400 copies/mL. In case of persistent low level viremia between 50 and 400 HIV-1 RNA copies/mL, study drugs may be discontinued at the investigator's discretion and the subject will be withdrawn from the study.

An HIV-1 PR/RT genotypic assay will be used to determine the screening genotype for all patients. Further PR/RT genotypic resistance testing will be performed on eligible subjects and phenotypic resistance testing may be done upon request of the study virologist. Baseline phenotyping (and genotyping) may be performed retrospectively on subjects with confirmed VF if they showed evidence of reduced susceptibility after VF to any of the study drugs. Other time points may still be analyzed if deemed necessary by the protocol virologist.

In case of early discontinuation an HIV-1 genotypic resistance report will be forwarded to the investigator in order to assist in the selection of a new ARV regimen.

Figure 2: Virologic Nonresponse Schema



[a] If virologic nonresponse is not confirmed, the subject will remain on its assigned 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 (RT and PR) will be analyzed if HIV-1 RNA ≥400 copies/mL.

[d] If HIV-1 RNA <400 copies/mL, the subject's viral load will be further monitored and resistance testing may be done at a later time point if HIV-1 RNA ≥400 copies/mL or at the unconfirmed virologic failure point if HIV-1 RNA ≥400 copies/mL. In case of persistent low level viremia between 50 and 400 HIV-1 RNA copies/mL,

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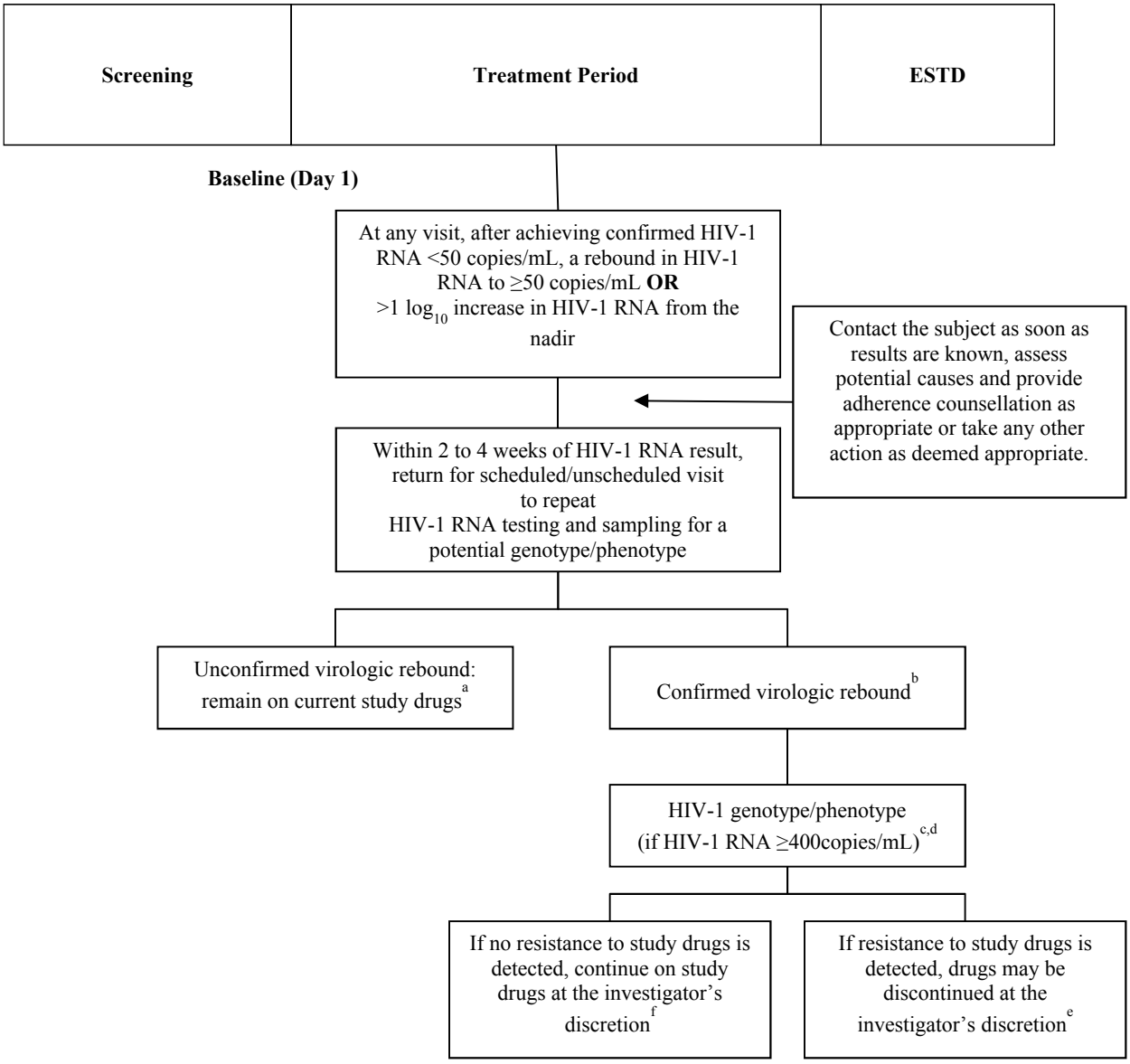
study drugs may be discontinued at the investigator's discretion and the subject will be withdrawn from the study.

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

[f] 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 drugs for an individual subject must inform the sponsor's medical monitor prior to study drug discontinuation.

Figure 3: Virologic Rebound Schema



[a] If virologic rebound is not confirmed, the subject will remain on its current regimen 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 (RT and PR) will be analyzed if HIV-1 RNA ≥400 copies/mL

[d] If HIV-1 RNA <400 copies/mL, the subject's viral load will be further monitored. In this case of HIV-1 RNA <400 copies/mL at the confirmed virologic failure point, resistance testing may then be done at a later time point if HIV-1 RNA ≥400 copies/mL or at the unconfirmed virologic failure point if HIV-1 RNA ≥400 copies/mL. In case of persistent low level viremia between 50 and 400 HIV-1 RNA copies/mL, study drugs may be discontinued at the investigator's discretion and the subject will be withdrawn from the study.

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

[f] 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 drugs for an individual subject must inform the sponsor's medical monitor prior to study drug discontinuation.

9.3. Pharmacokinetics Evaluations

9.3.1. Evaluations

Pharmacokinetic assessments (sparse sampling) will be performed for all subjects at the time points specified in the Time and Event Schedule.

In order to distinguish samples from subjects randomized to the D/C/F/TAF treatment arm from those of subjects in the control group, the bioanalytical lab will be unblinded to the treatment groups. However, the sponsor will remain blinded from the origin of the samples that have been analyzed, as well as from the outcome of the analyses, until locking of the database has been performed for the primary analysis.

Single sparse blood samples will be collected at least 30 minutes to maximum 4 hours post-dose on the Weeks 2 through 48 visits, and the ESTD visit (if applicable). At the Weeks 8 and 36 only, 2 blood samples will be collected at 2 time points at least 2.5 hours apart. The first pharmacokinetic sample for the Week 8 and 36 visits should be taken between 1 and 4 hours post-dose (dosing may occur prior to the study site visit).

All samples for pharmacokinetic analyses will be collected, identified and handled according to the laboratory manual. Exact dates and times of blood sampling, intake time of investigational medication, and whether this was taken with an accompanying meal, for the last 2 doses of investigational medication prior to the pharmacokinetic sampling must be recorded in the eCRF.

Pharmacokinetics of ARVs may also be evaluated using stored plasma samples (see Section 9.1.1), if deemed necessary and upon request of the study pharmacologist.

9.3.2. Analytical Procedures

Plasma concentrations of DRV, COBI and TAF of samples from subjects in the D/C/F/TAF treatment arm will be analyzed under the responsibility of the sponsor, using validated high-performance liquid chromatography-tandem mass spectroscopy (LC-MS/MS) methods.

Plasma concentrations of FTC and/or TFV of samples from subjects in the D/C/F/TAF treatment arm and plasma concentrations of the ARVs in the control arm may be determined, using validated methods, at the sponsor's discretion.

A description of the assays and validation data will be included in separate reports.

Results of bioanalyses will not be made available to the investigators.

9.3.3. Pharmacokinetic Parameters

Based on the individual plasma concentration-time data, using the actual dose taken and the actual intake and sampling times, the following pharmacokinetic parameters may be derived using population pharmacokinetic modeling and Bayesian feedback, if appropriate population pharmacokinetic models are available.

- Trough plasma concentration (C_{0h}) and AUC_{tau} for DRV and COBI;
- Plasma concentrations x hours after dosing (C_{xh}) and AUC_{tau} for TAF;
- C_{0h} and AUC_{tau} for FTC, TVF and their metabolites, or other ARVs in the control arm, if deemed necessary, upon request of the study pharmacologist.

9.4. Safety Evaluations

The study will include the following evaluations of safety and tolerability according to the time points provided in the Time and Event Schedule: AE reporting, clinical laboratory tests (including biochemistry, hematology, urinalysis, urine chemistry, and renal biomarkers), vital signs, physical examinations (complete or symptom-directed), and bone biomarkers and DXA scans of spine and hip (only for subjects participating in the substudy). These protocol procedures are described in Sections 9.4.1 through 9.4.6. In addition to these measurements, guidelines for the management of toxicities are described in Section 9.5.

Any clinically relevant abnormalities occurring at screening (from signing the ICF) and any clinically relevant changes occurring during the study must be recorded in the AE section of the eCRF.

Clinical events and clinically significant laboratory abnormalities will be graded according to the Division of AIDS (DAIDS) grading table (see Attachment 1).

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 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) (for further details, see Section 9.5.1).

Any evaluations at the ESTD visit showing abnormal results indicating that there is a possible causal relationship with study drug, need to be followed by the investigator (as often as deemed prudent) until satisfactory clinical resolution or stabilization. Certain long-term AEs of ARV therapy 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.

Details regarding the Independent Data Monitoring Committee are provided in Section 11.8.

9.4.1. Adverse Events

At each visit, from signing of the ICF, subjects will be asked about any untoward medical occurrences, and these will be recorded as AEs in the AE section of the eCRF. For detailed definitions and reporting procedures of AEs, please see Section 12.

Special attention will be paid to those subjects who discontinue the study for an AE, or who experience a severe AE (at least grade 3), or an SAE. For reported HIV events, further details

will be recorded if these events are AIDS-defining illnesses (see World Health Organization [WHO] Clinical Staging of HIV/AIDS, Attachment 2). For subjects experiencing specific AEs, toxicity management should be done as described in Section 9.5.

9.4.2. Clinical Laboratory Tests

Blood samples for biochemistry, hematology and serum pregnancy testing (females only, at screening only or if urine pregnancy test is positive), and a urine sample for urinalysis by dipstick, urine chemistry, renal biomarkers, and urine pregnancy testing (except at screening) will be collected at the time points specified in the Time and Event Schedule.

For laboratory assessments that need to be performed fasted while the subject has not fasted prior to the visit, the visit may proceed, but the subject must return within 72 hours in a fasted state to provide the necessary sample(s) for the assessments.

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 report, 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 the sponsor an alert form whenever a grade 3 or 4 laboratory abnormality (see Attachment 1) has been 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 medication interruption or discontinuation unless such delay is not consistent with good medical practice.

If a grade 3 or 4 laboratory abnormality is well documented prior to the start of the study and is not considered a safety concern by 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 further details on the management of grade 3 or 4 laboratory toxicities, see Section 9.5.1 and Attachment 3.

The following tests will be performed by the central laboratory:

- Urine chemistry panel: creatinine, sodium, phosphate, glucose, protein, albumin; (quantitative measurement).
- Urinalysis by dipstick: specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, and leukocyte esterase.

If dipstick result is abnormal, urine flow cytometry will be used to analyze sediment. In case of discordance between the dipstick results and the flow cytometric results, the sediment will be examined microscopically.

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

- Urine renal biomarkers: RBP and beta-2-microglobulin (collected fasted).
- Cystatin C.
- Serum Chemistry panel: AAG, ALP, AST, ALT, GGT, total bilirubin, direct and indirect bilirubin, total protein, albumin, CPK, bicarbonate, BUN, chloride, creatinine, glucose, phosphorus, potassium, sodium, uric acid, and amylase (reflex lipase testing is performed in subjects with total amylase >1.5 x ULN), and AAG.

At baseline, Weeks 24, 48, every 12 weeks following Week 48 until and including the unblinding visit, and Week 96, analyses of glucose will be done as part of the fasting metabolic assessments and not as part of the chemistry profile.

For the calculation of $eGFR_{creatinine}$ according to the Cockcroft-Gault and CKD-EPI formulas, and $eGFR_{cystatin}$ according to the CKD-EPI formula see Section 9.5.4; the eGFR calculations will be performed by the central laboratory.

- Metabolic panel: total, HDL and LDL cholesterol, triglycerides, glucose, (collected fasted).
- Hematology panel: hemoglobin, hematocrit, RBC count and parameters (MCH, MCH concentration and MCV), WBC count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), and platelet count.
- Pregnancy testing: The screening sample for biochemistry will include a serum pregnancy test for all female subjects of childbearing potential. A urine pregnancy test will be performed locally at all other visits. Positive urine pregnancy tests will be confirmed with a serum pregnancy test. FSH testing is required for female subjects who have stopped menstruating for at least 2 years but do not have documentation of ovarian hormonal failure. The results of the serum and urine pregnancy tests should be recorded in the eCRF and in the subject's medical records.

- Hepatitis testing: A sample will be taken for HBV and HCV testing (HBsAg, HCV RNA, and HCV antibody) at screening. Whenever clinically relevant, the investigator can request additional tests at other visits.
- Bone biomarkers: CTX, P1NP and PTH and 25-hydroxy vitamin D (collected fasted) (only for subjects participating in the bone investigation substudy). Biomarkers PTH and 25-hydroxy vitamin D should be assessed at Day 1, Weeks 24, 48 and 96 only.
- In addition, 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 9.5.2.

9.4.3. Electrocardiogram

An ECG will be taken locally at screening to determine subject eligibility for participation in the study.

During the collection of ECGs, subjects should be in a quiet setting without distractions (eg, television, cell phones). Subjects should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs. If blood sampling or vital sign measurement is scheduled for the same time point as ECG recording, the procedures should be performed in the following order: ECG(s), vital signs, blood draw.

Twelve-lead ECGs will be recorded until 4 regular consecutive complexes are available so that the different ECG intervals (RR if available, PR, QRS and QT) and heart rate can be measured. The QT intervals will be corrected for heart rate according to Bazett's (QTcB) and Fridericia's (QTcF) QT corrections.[3,13]

Any clinically relevant findings at screening must be recorded in the AE section of the eCRF.

9.4.4. Vital Signs

Systolic and diastolic blood pressure (SBP, DBP), pulse rate (supine after at least 5 minutes rest), and weight will be recorded in a quiet setting without distractions, at the time points specified in the Time and Event Schedule.

Blood pressure and pulse/heart rate measurements will be assessed with a completely automated device if possible. 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.

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

9.4.5. Physical Examination

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

A complete physical examination includes skin and mucous membranes, lymph nodes, respiratory system, cardiovascular system, abdomen, central nervous system, peripheral nervous system, musculoskeletal system, genitourinary system and head-neck examination. Urogenital or anorectal examination will be performed at the discretion of the investigator if clinically relevant. Subjects should be undressed during these complete physical examinations, which should be performed by a licensed medical doctor, a physician's assistant or a nurse practitioner in accordance with local guidelines.

The 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 AE section of the eCRF.

9.4.6. Bone Investigation Substudy

A bone investigation substudy will be performed at selected study sites, to assess bone biomarkers and DXA scans, in at least 170 subjects (85 in each treatment arm) who provide informed consent for the substudy.

DXA scans will be performed in subjects participating in the DXA substudy, provided that all necessary local regulatory authority and ethics committee approvals have been obtained. DXA scans will be performed at the time points specified in the Time and Event Schedule and will cover the spine and hip to measure changes in BMD.

A complete description of the procedures for the DXA scans will be provided in the DXA manual.

Reading of the DXA scans will be performed centrally and results will be sent to the investigator. The investigator must review the DXA scan report, document this review and record any clinically relevant findings at baseline and changes occurring during the study in the AE section of the eCRF. The DXA scan reports must be filed with the source documents. For the management of potential bone toxicity, see Section 9.4.6.

In subjects participating in the DXA substudy, blood will be collected for assessment of bone biomarkers (including CTX, P1NP, PTH and 25-hydroxy vitamin D) at the time points specified in the Time and Event Schedule.

9.5. Toxicity Management

The toxicity management guidelines in this section are applicable throughout the entire study, starting from baseline through the 96-week treatment period and the extension phase.

General guidance for the management of toxicities is provided in Section 9.5.1. Guidance for specific toxicities is provided in Sections 9.5.2 through 9.5.9. Please, see also Sections 9.4 and 12 for information on procedures concerning the measurement and reporting of clinically relevant abnormalities and toxicities.

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

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

Grade 1 and 2

Continue study medication at the discretion of the investigator.

Grade 3

- For a grade 3 clinical event or clinically relevant laboratory abnormality, study medication may be continued if the event is considered to be unrelated to study medication.
- For a grade 3 clinical event, or clinically relevant laboratory abnormality confirmed by repeat testing (see Section 9.4.2), that is considered to be related to study medication, study medication 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 asymptomatic grade 3 triglyceride or cholesterol elevations.
- If a laboratory abnormality recurs to ≥ grade 3 following rechallenge with study medication and is considered related to be to study medication, study medication should be permanently discontinued and the subject managed according to local practice. Recurrence of laboratory abnormalities considered unrelated to study medication may not require permanent discontinuation.

Grade 4

- For a grade 4 clinical event or clinically relevant laboratory abnormality confirmed by repeat testing (see Section 9.4.2), that is considered to be related to study medication, study medication 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 asymptomatic grade 4 triglyceride or cholesterol elevations.
- Study medication may be continued without dose interruption for a clinically nonrelevant grade 4 laboratory abnormalities (eg, grade 4 CPK after strenuous exercise, or triglyceride elevation that is nonfasting or that can be medically managed), or a clinical event considered unrelated to study medication.

A schematic overview of these guidelines is provided in Attachment 3 for clinically relevant laboratory toxicities.

9.5.2. Cutaneous Events/Rash

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

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

Management will be at the discretion of the investigator, taking into account the following protocol-defined procedures (see also Table 3), 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 medication interrupted at the investigator's discretion. Safety sampling (to be processed by the central laboratory) at the time of the rash and clinical follow-up for these AEs will be at the discretion of the investigator, however, close clinical follow-up is recommended to monitor for any progression of the AE.

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 x baseline but ≥5 x ULN;

  - fever ≥38°C or 100°F;
  - serum sickness-like reaction;
  - eosinophil count >1,000/mm³.
- 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;
- TEN.

Subjects experiencing a grade 3 or 4 rash or cutaneous event must have their study medication 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 3: Summary of Cutaneous Reaction/Rash Follow-up

DAIDS Toxicity Grade	Definitions	Investigator Action
Grade 1	Localized rash	Subject may continue study medication
Grade 2	Diffuse rash Target lesions	Subject may continue study medication
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 x baseline but ≥5 x ULN) - Fever ≥38°C or 100 F - Serum sickness-like reaction - Eosinophils >1,000/mm³ DRESS and AGEP	Permanently discontinue study medication 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 medication 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

9.5.3. Acute Systemic Allergic Reaction

Management will be at the discretion of the investigator, taking into account the following protocol-defined procedures (see also Table 4), 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 medication or have their study medication 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 or the local Prescribing Information of the ARVs.

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 medication or have their study medication 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 medications. 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 or the local Prescribing Information of the ARVs.

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 medication. 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 medication. Subjects will be treated as clinically appropriate. Standard management should be undertaken.

Table 4: 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 medication
Grade 2	Localized urticaria with intervention indicated, or mild angioedema with no intervention indicated	Subject may continue study medication
Grade 3	Generalized urticaria, or angioedema with intervention indicated, or symptoms of mild bronchospasm	Permanently discontinue study medication
Grade 4	Acute anaphylaxis, or life-threatening bronchospasm, or laryngeal edema	Permanently discontinue study medication

9.5.4. Potential Renal Toxicity

Estimated glomerular filtration rate for creatinine clearance ($eGFR_{creatinine}$ calculated according to the Cockcroft-Gault formula and the CKD-EPI formula), and eGFR for cystatin C clearance ($eGFR_{cystatin\ C}$ calculated according to the CKD-EPI formula) will be followed post-baseline during the treatment phase of the study. The eGFRs calculations will be performed and provided to the investigator by the central laboratory.

During the extension phase of the study, $eGFR_{creatinine}$ according to the Cockcroft-Gault formula for creatinine clearance will be monitored. All subjects with $eGFR_{creatinine}$ <50 mL/min must have serum creatinine re-measured preferably within 3 calendar days of receipt of results. At the time of this repeat serum creatinine assessment, cystatin C will also be measured and the $eGFR_{cystatin}$ will be calculated and compared with the baseline measurement.

- $eGFR_{creatinine}$ according to the Cockcroft-Gault formula:[9]

Male: $$\frac{(140 - \text{age in years}) \times (\text{weight in kg})}{72 \times (\text{serum creatinine in mg/dL})} = eGFR_{cr}\ (\text{mL/min})$$

Female: $$\frac{(140 - \text{age in years}) \times (\text{weight in kg})}{72 \times (\text{serum creatinine in mg/dL})} \times 0.85 = eGFR_{cr}\ (\text{mL/min})$$

- $eGFR_{creatinine}$ and $eGFR_{cystatin}$ according to the CKD-EPI formula:[19]

$eGFR_{creatinine}$

Female:	$S_{cr} \leq 0.7$ mg/dL	$144 \times (S_{cr}/0.7)^{-0.329} \times 0.993^{age}$
	$S_{cr} > 0.7$ mg/dL	$144 \times (S_{cr}/0.7)^{-1.209} \times 0.993^{age}$
Male:	$S_{cr} \leq 0.9$ mg/dL	$141 \times (S_{cr}/0.9)^{-0.411} \times 0.993^{age}$
	$S_{cr} > 0.9$ mg/dL	$141 \times (S_{cr}/0.9)^{-1.209} \times 0.993^{age}$

$eGFR_{cystatin}$

$S_{cyst} \leq 0.8$ mg/L	$133 \times (S_{cyst}/0{,}8)^{-0.499} \times 0.996^{age}$ [x 0.932 if female]
$S_{cyst} > 0.8$ mg/L	$133 \times (S_{cyst}/0{,}8)^{-1.328} \times 0.996^{age}$ [x 0.932 if female]

S_{cr} = serum creatinine (mg/dL), S_{cyst} = serum cystatin C (mg/L)

Any subjects who have an $eGFR_{creatinine}$ (by Cockcroft-Gault) <50 mL/min, and who also experience >20% reduction in $eGFR_{cystatin}$ (by CKD-EPI) 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 drugs. For subjects with $eGFR_{creatinine}$ <50 mL/min who are not discontinued based on toxicity management procedures above and considered to have stable renal function per principal investigator and medical monitor, it is not mandatory to repeat eGFR assessments within 3 days.

All subjects with negative or trace proteinuria at baseline who develop >1+ proteinuria on urinalysis must have a 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 clinic for a scheduled or unscheduled FU 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.

9.5.5. Potential Bone Toxicity

As there is uncertainty surrounding the clinical significance and management of decreases in BMD for HIV-1 positive patients, the sponsor recommends that any subject who has a DXA scan that demonstrates a decrease from baseline of >5% in the spine region or >7% in the hip region should be followed per local medical practice at the discretion of the investigator.

9.5.6. Potential Posterior Uveitis Cases

In a 9-month toxicology study conducted in dogs, some animals administered the highest dose of TAF (12 to 18mg/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.

9.5.7. Hyperglycemia

Grade 3: 13.89–27.75 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 medications 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.

9.5.8. Hypertriglyceridemia and Hypercholesterolemia

Hypertriglyceridemia:	**Grade 3:**	**5.7-11.4 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 medications 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 4). 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 HDL cholesterol, and prior history of cardiovascular disease should be taken into account. Appropriate clinical management of hyperlipidemia in the setting of HIV disease should be started in a timely fashion if applicable.

9.5.9. 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 (see Attachment 1) under Endocrine/Metabolic. The following terms are included: lipohypertrophy, lipoatrophy and gynecomastia.

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

9.6. Sample Collection and Handling

Refer to the Time and Event Schedule for the timing and frequency of all sample collections.

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

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/WITHDRAWAL

10.1. Completion

In the period up to Week 96, a subject will be considered to have completed the study treatment if he or she has continued study medication intake up to Week 96 and has completed assessments at Week 96. Subjects who prematurely discontinue study treatment for any reason before completion of the 96-week treatment period will not be considered to have completed treatment.

In the period after Week 96, subjects will be considered to have completed study treatment 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 in the country where he/she is living, 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 post-Week 96 D/C/F/TAF treatment period.

10.2. Withdrawal From the Study

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

- Lost to follow-up
- Withdrawal of consent
- Subject request to stop study treatment for any reason.
- The investigator or sponsor believes (eg, that for safety or tolerability reasons such as an AE) it is in the best interest of the subject to stop study treatment. The sponsor should be contacted for further discussion and final decision.
- Unacceptable toxicity, as defined in the toxicity management Section 9.5 of this protocol.
- Toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures.
- Pregnancy has been determined in participating female subjects.
- The subject develops clinical hepatitis.
- Discontinuation of the study at the request of the sponsor, DMC, the concerned regulatory agency or Independent Ethics Committee (IEC)/ Institutional Review Board (IRB).

A subject's study treatment may be discontinued if:

- An SAE occurs.
- The subject fails to comply with the protocol or study staff requirements.
- The subject starts disallowed treatment.
- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree.
- The subject requires new onset treatment with one of the medications reported on the list of disallowed medications (see Section 8.1).
- The subject demonstrates VF/viral resistance to any of the ARVs in the HAART regimen; see also Section 9.2.2.1.

If an investigator considers withdrawing a subject from study treatment for 1 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, either during the double-blind active-controlled treatment phase (from Day 1 to Week 48) or during the open-label single-arm D/C/F/TAF treatment phase (from Week 48 up to Week 96), will be required to return to the clinic within 72 hours of stopping study treatment for the ESTD visit.

In addition, a 30-day FU visit will be required for any subject who has an ongoing AE or SAE at the time of his/her last study visit (unless consent is withdrawn).

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, at the final evaluation the Trial Termination section of the eCRF must be completed. Study drug assigned to the withdrawn subject may not be assigned to another subject. Subjects who withdraw will not be replaced.

Subjects who withdraw consent from the bone investigation substudy (see Section 16.2.3) can still continue to participate in the main study.

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:

- Formal independent DMC analyses for monitoring purposes, including a futility analysis for the lack of (non-inferior) efficacy and a blinded sample size re-estimation (see also Section 11.8).
- The primary analysis: once all subjects have completed the Week 48 assessments or discontinued earlier.
- The Week 96 analysis: once all subjects have completed the Week 96 assessments or discontinued earlier.
- The final analysis: once all subjects have completed the extension phase and the 30-day FU visit (if applicable), or discontinued earlier.

Additional statistical analyses may be done as needed to prepare for interactions with regulatory authorities.

11.1. Analysis Objectives and Endpoints

An overview of the objectives and hypothesis tested in this study is provided in Section 2. The analysis endpoints are listed below.

Primary Endpoint

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.

Secondary Endpoints

The secondary endpoints of this study are:

- The proportion of subjects with HIV-1 RNA <50 copies/mL at Week 96 as defined by the FDA snapshot analysis;
- The proportion of subjects with HIV-1 RNA <20 and <200 copies/mL at Weeks 48 and 96 as defined by the FDA snapshot analysis;
- The proportion of subjects with HIV-1 RNA <20, <50, and <200 copies/mL at Weeks 48 and 96 as defined by the time to loss of virologic response (TLOVR) algorithm;
- The change from baseline in $\log_{10}$ HIV-1 RNA at Weeks 48 and 96;
- The change from baseline in CD4+ cell count at Weeks 48 and 96;
- The change from baseline in serum creatinine, $eGFR_{creatinine}$ (by Cockcroft-Gault and by CKD-EPI) and $eGFR_{cystatin\ C}$ (by CKPD-EPI) at Weeks 48 and 96;

- The proportion of subjects experiencing grade 3 and 4 AEs, SAEs, and premature discontinuations due to AEs through Weeks 48 and 96.
- The change from baseline in renal biomarkers at Weeks 48 and 96;
- The development of viral resistance through Week 48 and 96;
- Pharmacokinetic parameters (by population pharmacokinetic analysis) for DRV and TAF.

The endpoints of the bone investigation substudy are:

- The percentage change from baseline in hip and spine BMD and change from baseline T-score in hip and spine, at Weeks 24, 48, and 96;
- The change from baseline in bone biomarkers at Weeks 24, 48, and 96.

11.2. Subject Information

For all subjects who are randomly assigned to study drug and receive at least 1 dose of study drug descriptive statistics will be provided. Demographic and baseline disease characteristics will be summarized using standard descriptive methods (eg, sample size [n], mean, SD, median, minimum, maximum, frequency) as appropriate.

An intent-to-treat (ITT), per protocol (PP) and pharmacokinetic analysis population, will be defined:

- The ITT population will include all the subjects who were randomized and received ≥1 dose treatment in the study. Subjects will be grouped according to the treatment arm (D/C/F/TAF or control) to which they were randomized. The ITT analysis set is the primary analysis set for efficacy analysis. Efficacy data up to the last dose date of the randomized study treatment will be included.

  The safety analysis (including all data collected up to the 30-day FU visit) is also performed on this analysis set.
- Since an analysis on the ITT population may not be conservative in a noninferiority setting, an analysis based on the PP population will also be performed to investigate the impact of excluding subjects with major protocol violations and to evaluate the robustness of the primary analysis results. The PP population will include all subjects who (1) are randomized into the study, (2) have received ≥1 dose of treatment in the study, and (3) without any major protocol deviation that is considered to potentially affect efficacy outcomes (eg, inadequate baseline resistance profile, use of concomitant medication interfering with antiviral efficacy, inadequate adherence to drug intake). Specific details will be provided in the Statistical Analysis Plan. The PP analysis set is the secondary analysis set for efficacy analysis.
- The pharmacokinetic analysis set will include all subjects who are randomized to the D/C/F/TAF arm (and the control arm, if applicable) and have received ≥1 dose of investigational treatment in the study, and for whom plasma concentration data of any analytes of interest are available.

11.3. Sample Size Determination

A sample size of 670 (335 subjects in D/C/F/TAF arm and 335 subjects in the control arm) will yield 90% power. It is assumed that both treatment arms have a response rate of 80% (HIV-1 RNA <50 copies/mL at Week 48 as defined by the FDA snapshot analysis), that the noninferiority margin is 10%, and that the significance level of the test is at a 1-sided, 0.025 level.

A minimum of 170 subjects (85 per treatment arm) is targeted to be included in the bone investigation substudy. Assuming a 4% inter-subject variability in BMD and a 1-sided alpha level of 2.5%, 85 subjects per treatment arm is sufficient to detect at least an absolute difference of 2% between the treatment arms with 90% power. Power calculations are presented in Table 5.

Table 5: BMD at the Lumbar Spine, Power Calculations

	Mean % Change from Baseline	Common Standard Deviation (%)	Power
N=170	2	3.5	96%
		4	90%
	3	3.5	>99%
		4	>99%

11.4. Efficacy Analyses

11.4.1. Primary Analysis

The primary analysis will consist of a noninferiority evaluation of the D/C/F/TAF FDC tablet (investigational treatment arm) versus DRV/COBI FDC coadministered with FTC/TDF FDC (control arm), with respect to the proportion of subjects with HIV-1 RNA <50 copies/mL at Week 48 after the start of treatment in this study (as defined by the FDA snapshot analysis). It will be concluded that the D/C/F/TAF FDC tablet is not inferior to the control regimen if the lower bound of the 2-sided 95% confidence interval (CI) of the difference between treatment arms (D/C/F/TAF arm - control arm) in the response rate is greater than -10% (ie, a margin of 10% is applied to noninferiority assessment). The difference (with associated 95% confidence interval) will be constructed using the stratum-adjusted Mantel-Haenszel difference in proportions, where the stratification factors (HIV-1 RNA level [≤100,000 copies/mL or >100,000 copies/mL] and CD4+ cell count [<200 cells/µL or ≥200 cells/µL] at screening) determine the strata.

If noninferiority of the D/C/F/TAF arm to control arm is established, the lower bound of the 95% CI will be compared to 0; if the lower bound of the 95% CI is greater than 0, then superiority of D/C/F/TAF over the control arm will be established.

11.4.2. Secondary Analyses

Antiviral Efficacy

As secondary analyses, the proportion of subjects with HIV-1 RNA <20 and <200 copies/mL at Week 48 as defined by the FDA snapshot analysis will be analyzed using the same method as for the primary efficacy endpoint to compare treatment arms.

In addition, confirmed virologic response defined as HIV-1 RNA <20, <50, and <200 copies/mL at Week48 determined by the TLOVR algorithm will be analyzed using the same method as for the primary efficacy endpoint to compare treatment arms.

Immunologic Change

The changes from baseline in CD4+ cell count at Week 48, and 96 will be summarized using descriptive statistics. The differences in changes from baseline in CD4+ cell count at Week 48 between the 2 treatment arms and the associated 95% confidence intervals will be constructed using analysis of covariance (ANCOVA), including CD4+ cell count at baseline as continuous covariate in the model.

Resistance

Screening HIV-1 PR/RT genotype analysis will be performed for all subjects. Post-screening HIV-1 PR/RT genotype/phenotype testing will be available from subjects who are eligible for resistance testing (subjects with virologic rebound, virologic nonresponse, and discontinuations with last available viral load measurement ≥400 copies/mL). The number and type of amino acid changes, of HIV-1 PR (including IAS-USA PI RAMs and IAS-USA primary PI mutations), and RT (including IAS-USA NRTI RAMs and IAS-USA NNRTI RAMs), as well as specific, but not limited to, IAS-USA[41] mutations associated with resistance to DRV, FTC, and TDF will be tabulated. Available fold change (FC) in 50% effective concentration (EC_{50}) of ARVs will be tabulated. In subjects with paired screening or baseline and post-baseline genotypes/phenotypes, development of resistance will be analyzed.

11.5. Pharmacokinetic Analyses

The plasma concentration data of DRV, TAF, and COBI of subjects randomized to the D/C/F/TAF treatment arm will be evaluated. Plasma concentration data for each analyte may be subjected to population pharmacokinetic modeling, if appropriate population pharmacokinetic models are available. Model specifications will be described in separate report(s), as applicable.

The pharmacokinetics of other ARVs in the study (eg, FTC, TFV) and their metabolites, as well as the ARVs in samples from subjects in the control arm, may be analyzed, if deemed necessary, upon request of the protocol pharmacologist.

Descriptive statistics will be calculated for the plasma concentrations of DRV, COBI, and TAF by visit and for the derived pharmacokinetic parameters as available, and also for any of the

other ARVs in the study analyzed upon sponsor's request, if applicable. Summary statistics include n, mean, SD, coefficient of variation (CV), geometric mean, median, minimum and maximum.

11.6. Safety Analyses

Adverse Events

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

Summaries (number and percentage of subjects) of treatment-emergent AEs (by SOC and PT) will be provided by treatment arm. Additional summaries will include summaries for AEs by severity grade (with special attention to grade 3 or 4 AEs), investigator's assessment of relationship to treatment, SAEs, and AEs leading to discontinuation of study treatment.

Clinical Laboratory Tests

Laboratory data will be summarized by treatment arm and 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 DAIDS grading table (see Attachment 1) 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 develop grade 3 or 4 toxicities.

Serum Creatinine and Cystatin C

The changes from baseline in serum creatinine, $eGFR_{creatinine}$ (by Cockcroft-Gault and by CKD-EPI) and $eGFR_{cystatin}$ (by CKPD-EPI) at Weeks 48 and 96 will be summarized by treatment arm and using descriptive statistics. The difference in changes from baseline at Week 48 in serum creatinine between the 2 treatment arms will be tested using ANCOVA, including baseline serum creatinine in the model.

Renal Biomarkers

Selected renal biomarkers, including retinol binding protein and beta-2-microglobulin, will be summarized by treatment arm and visit using descriptive statistics. The difference in change from baseline in these biomarkers at Week 48 between 2 treatment arms will be tested using the Wilcoxon rank-sum test.

ECG

ECG assessments were done locally, only at screening and thus not suitable to be analyzed. For definitions of abnormalities of ECG, refer to Attachment 5.

Vital Signs

Descriptive statistics of vital sign (pulse rate, systolic and diastolic blood pressure) 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 summarized. For definitions of abnormalities of vital signs, refer to Attachment 5.

Physical Examination

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

DXA Substudy – Bone Investigations

Baseline, post-baseline, and the percent change from baseline at Weeks 24, 48, and 96 for selected bone biomarkers, including CTX, P1NP, PTH and 25-hydroxy vitamin D, will be summarized by treatment arm and visit using descriptive statistics. The within-treatment comparison will be done using the Wilcoxon signed-rank test. The comparison between the 2 treatment arms at Weeks 24 and 48 will be performed using the Wilcoxon rank-sum test.

Percent change from baseline in spine and hip BMD at Weeks 24, 48, and 96, as well as the change from baseline in BMD T-score will be summarized by treatment arm and visit using descriptive statistics. The between-treatment differences at Weeks 24 and 48 will be estimated using ANCOVA model, including baseline BMD value and other clinically relevant factors (if deemed necessary) in the model. The within-treatment comparison will be done using a paired t-test. A supportive longitudinal repeated measures analysis will be performed on this endpoint to obtain an estimate of the between-treatment difference along with its 95% CI at Week 48. This model will include post-baseline percent change from baseline as a response variable, terms for treatment, visit, the interaction of visit and treatment and the corresponding baseline BMD value as a covariate and other clinically relevant factors (if deemed necessary). An unstructured covariance matrix will be used to model the correlation among repeated measurements.

The BMD T-score will be summarized descriptively. BMD status based on the T-score (normal: ≥-1; osteopenia: from <-1 to -2.5; osteoporosis: <-2.5) will be tabulated.

11.7. Treatment Adherence

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

11.8. Data Monitoring Committee

An independent DMC will be established to monitor the safety and efficacy information to ensure the safety of the subjects enrolled in this study, and to allow regular assessment of the risk/benefit profile of the applied therapy schemes. The details will be provided in a separate DMC charter.

A formal futility analysis for lack of (non-inferior) efficacy of the D/C/F/TAF regimen will be performed, using a conditional power approach, ie, probability of claiming non-inferiority at the completion of the study based on the available interim data. To this end, the available Week 24 data (used as predictor for the primary endpoint), and the Week 48 primary endpoint data (if any) will be used. Further details regarding the derivation of the conditional power and the choice of threshold for the conditional power to stop for futility will be provided in the DMC charter and DMC statistical analysis plan. The futility analysis will be guided by the DMC, and the sponsor and study team will remain blinded. It is not the intention to stop the study early in case of superiority or noninferiority of the D/C/F/TAF regimen versus the control group.

In addition, a blinded sample size re-estimation procedure will be applied to allow for an adjustment in sample size to maintain adequate power in case the overall response rate is anticipated to be different than assumed, eg, due to a higher drop-out rate. Details will be provided in the DMC charter.

The DMC will consist of 2 external medical experts in the relevant therapeutic area and 1 external statistician. The DMC responsibilities, authorities, and procedures will be documented in its charter.

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 AE is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a

medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per 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 AEs starting with the signing of the ICF (refer to Section 12.4.1, All Adverse Events, for time of last AE recording).

An AE does not include the following (see also Section 12.3 and 12.4.3):

- Medical or surgical procedures if the condition that leads to the procedure is an AE.
- 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 AE. 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.

Serious Adverse Event

An SAE based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death; however, death is an outcome of an AE, and not an AE in itself.
- 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. 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 AE 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 AEs/SAEs:

- Complications that occur during hospitalizations are AEs. If a complication prolongs the hospitalization, it is an SAE.
- In-patient hospitalization means 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 diagnosis of an event on the basis of signs, symptoms and/or other clinical information; in such cases, the diagnosis should be documented as the AE and/or SAE and not the individual signs/symptoms.
- A distinction should be made between seriousness and severity of an AE. An AE that is assessed as grade 4 (potentially life-threatening) should not be confused with an SAE. Severity is a category utilized for rating the intensity of an event, and both AEs and SAEs can be assessed as grade 4. An event is defined as 'severe' when it meets the predefined criteria as described the DAIDS toxicity grading table in Attachment 1 (see also Section 12.1.3).

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information at the time the AE is reported.

For D/C/F/TAF FDC tablet, the expectedness of an AE will be determined by whether or not it is listed in the adverse reaction table provided in the IB or its relevant IB addendum.[16,17] For DRV/COBI FDC and FTC/TDF FDC used in the control arm, the expectedness of an AE will be determined by whether or not it is listed in the applicable USPI current at the time the AE is reported.

Adverse Event Associated With the Use of the Drug

An AE 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.

12.1.2. Attribution Definitions

Not Related

An AE that is not related to the use of the drug.

Doubtful

An AE 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 AE 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 AE 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 AE 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 following general categorical descriptors outlined in the DAIDS toxicity grading table in Attachment 1.

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 AEs. An AE that is assessed as grade 4 (potentially life-threatening) should not be confused with an SAE. Severity is a category utilized for rating the intensity of an event, and both AEs and SAEs can be assessed as grade 4. An event is defined as ‘serious’ when it meets 1 of the predefined outcomes described in Section 12.1.1.

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

Laboratory abnormalities are usually not recorded as AEs or SAEs. 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 AE, as

well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, DXA, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE (or SAE) as described in Section 12.1.1. If the laboratory abnormality is part of a syndrome, the syndrome or diagnosis (ie, anemia) must be recorded and not the laboratory result (ie, decreased hemoglobin).

12.3. Special Reporting Situations

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

- Overdose of a sponsor study drug.
- Suspected abuse/misuse of a sponsor study drug.
- Inadvertent or accidental 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).
- Lack of effect reports.
- Pregnancy reports, whether or not maternal exposure to the product occurred (see also Section 12.4.3).
- Reports of adverse reactions in infants following exposure from breastfeeding.

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

12.4. Procedures

12.4.1. All Adverse Events

All AEs and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until completion of the subject's last study-related procedure (which may include contact for follow-up of safety). SAEs, 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 SAE will be reported as SAEs, regardless of whether they are protocol-specific assessments. Anticipated events will be recorded and reported as described in Attachment 6.

All AEs, 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 AE to study therapy. All measures required for AE management must be recorded in the source document and reported according to sponsor instructions.

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (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.
- Any other information that is required to do an emergency breaking of the blind.

12.4.2. Serious Adverse Events

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

Information regarding SAEs 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 SAE should be made by facsimile (fax).

All SAEs 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 an SAE. 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 an SAE, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or AE (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 SAEs. Any AE that results in a prolongation of the originally planned hospitalization is to be reported as a new SAE.
- For convenience the investigator may choose to hospitalize the subject for the duration of the treatment period.

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

12.4.3. 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 SAEs 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 by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required, also if the outcome is post-study.

12.5. 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 on 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 an SAE, the study-site personnel must report the PQC to the sponsor according to the SAE reporting timelines (refer to Section 12.4.2). 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 on 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, DRV/COBI FDC, and the matching placebo 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 (double-blind treatment phase) or debossed (open-label treatment phase), film-coated tablets containing 800 mg of DRV (as 867 mg of darunavir ethanolate), 150 mg of COBI (288.5 mg total weight of COBI on silicon dioxide carrier), 200 mg of FTC, and 10 mg of TAF (as 11.2 mg TAF fumarate). Each D/C/F/TAF FDC tablet in the open-label treatment phase is debossed with “8121” on one side and “JG” on the other side. The D/C/F/TAF FDC tablet cores contain silicon dioxide, croscarmellose sodium, microcrystalline cellulose, magnesium

stearate, polyvinyl alcohol, iron oxide yellow, polyethylene glycol, talc, and titanium dioxide.

- The D/C/F/TAF FDC-matching placebo tablets supplied for this study are identical in physical appearance and contain lactose monohydrate, croscarmellose sodium, microcrystalline cellulose, magnesium stearate, polyvinyl alcohol, iron oxide yellow, polyethylene glycol, talc, and titanium dioxide.
- The DRV/COBI FDC tablets supplied for this study are pink oval shaped, plain-faced, containing, plain faced, film coated tablets containing 800 mg of DRV (as 867 mg of darunavir ethanolate) and 150 mg of COBI (288.5 mg total weight of COBI on silicon dioxide carrier). The DRV/COBI cores contain hypromellose, silicon dioxide, silicified microcrystalline cellulose, crospovidone, magnesium stearate, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide, iron oxide red and iron oxide black.
- The DRV/COBI FDC-matching placebo tablets supplied for this study are identical in physical appearance and contain silicified microcrystalline cellulose, colloidal anhydrous silica, magnesium stearate, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide, iron oxide red and iron oxide black.

The control FTC/TDF FDC tablets and matching placebo tablets will be manufactured, packaged and provided by GSI.

- FTC/TDF FDC tablets are capsule-shaped, film-coated blue tablets that are debossed with “GILEAD” on one side and plain-faced on the other side. The FDC/TDF FDC tablets contain 200 mg of emtricitabine and 300 mg of tenofovir DF. In addition to the active ingredients, the tablets contain microcrystalline cellulose, pregelatinized starch, croscarmellose sodium, lactose monohydrate, magnesium stearate, hypromellose, titanium dioxide, triacetin, and FD&C blue #2/indigo carmine aluminum lake.
- FTC/TDF FDC-matching placebo tablets are identical in physical appearance and contain denatonium benzoate, lactose monohydrate, pregelatinized starch, croscarmellose sodium, magnesium stearate, hypromellose, titanium dioxide, triacetin, and FD&C blue #2/Indigo carmine aluminum lake.

14.2. Packaging

D/C/F/TAF FDC, DRV/COBI FDC, TDF/FTC FDC and the matching placebo tablets will be packaged under responsibility of the sponsor and will allow for blinded administration.

The D/C/F/TAF FDC and –matching placebo 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.

The DRV/COBI FDC and –matching placebo tablets are packaged in HDPE bottles with a child-resistant closure and induction foil seal.

The FTC/TDF FDC and –matching placebo tablets are packaged in white, HDPE bottles with a silica gel desiccant canister or sachet. Each bottle is enclosed with a white, continuous thread, child-resistant screw cap fitted with an induction-sealed, aluminum-faced liner.

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

14.4. Preparation, Handling, and Storage

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

To ensure the stability of D/C/F/TAF FDC tablets, DRV/COBI FDC and FTC/TDF FDC tablets in the control arm, the drug products should not be dispensed into a container other than the container in which it is supplied.

Measures that minimize drug contact with the body should always be considered during handling, preparation, and disposal procedures. Any unused study drug should be disposed of in accordance with local requirements.

Refer to the pharmacy manual/study site investigational product 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, or their legally acceptable representatives where applicable, must be instructed to return all original containers, whether empty or containing study drug.

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. 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.

The monitor will periodically check the supplies of study medication held by the investigator or pharmacist to ensure accountability and appropriate storage conditions of all study drug(s) used.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- IB and IB addendum of D/C/F/TAF;
- IWRS manual;
- Sample ICF;
- eCRF completion guidelines;
- Pharmacy manual/study site investigational product manual;
- Laboratory manual;
- DXA manual (if applicable);
- Contact information page(s).

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 AEs 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 (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct).
- Sponsor-approved ICF (and any other written materials to be provided to the subjects).
- IB (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), 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 AEs 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. The reapproval should be documented in writing (excluding the ones that are purely administrative, with no consequences for subjects, data, or study conduct).

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(s) the subject is authorizing such access, including permission to obtain information about his or her survival status, and agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, if needed, and subsequent disease-related treatments, or to obtain information about his or her survival status.

The subject will be given sufficient time to read the ICF(s) 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.

Subjects willing to participate in the bone investigation substudy at selected study sites must provide informed consent for the substudy.

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

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand D/C/F/TAF FDC, to understand HIV-1 infection, and to understand differential drug responders. No future pharmacogenomic (DNA) research will be conducted. The research may begin at any time during the study or the post-study storage period. See also Section 9.1.1.

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 10.2 Withdrawal From the Use of Samples in Future Research).

16.2.6. Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product, unless explicitly addressed as a specific ethical consideration in Section 16.1, Study-Specific Design Considerations.

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 IRB (and IEC 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 (see Contact Information page(s) provided separately). Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the CRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

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 randomized 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 CRF: 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.

The study medication log booklets will be considered source data.

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 provided for each subject in electronic format.

Electronic Data Capture (eDC) will be used for this study. The study data will be transcribed by study-site personnel from the source documents onto an eCRF, and 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 eCRFs in English. Study-site personnel must complete the eCRF 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. The investigator must verify that all data entries in the eCRFs are accurate and correct.

All eCRF entries, corrections, and alterations must be made by the investigator or other authorized study-site personnel. 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 an eCRF are needed after the initial entry into the eCRF, this can be done in 3 different ways:

- 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).
- Study site manager can generate a query for resolution by the study-site personnel.
- Clinical data manager can generate a query for resolution by the 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 CRFs 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 post-initiation 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 hospital or clinic records (source documents). 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 documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the eCRF are consistent with the original source data. Findings from this review of eCRFs and source documents 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 documentation 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

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 and comparison with the CRFs. 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 the 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 the 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 eCRF data from all study sites that participated in the study, and direct transmission of clinical laboratory data from a central laboratory into the sponsor's database. 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 GCP 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/or disclose the existence of and the results of clinical studies as required by law.

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ATTACHMENTS

Attachment 1: Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events 125
Attachment 2: WHO Clinical Staging of HIV/AIDS 147
Attachment 3: Management of Clinically Significant Laboratory Toxicities 149
Attachment 4: Management of Dyslipidemia 150
Attachment 5: Cardiovascular Safety: Definitions of Abnormalities 154
Attachment 6: Anticipated Events 155

Attachment 1: Division of AIDS 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 (version 2.0, November 2014), or 'DAIDS grading table', is a descriptive terminology to be utilized for AE reporting in this study. A grading (severity) scale is provided for each AE term.

General Instructions

Estimating Severity Grade for Parameters Not Identified in the Grading Table

If the need arises to grade a clinical AE 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 AE 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 AEs. When a single set of parameters is not appropriate for grading specific types of AEs 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 AE, 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 AE could fall under either 1 of 2 grades (eg, the severity of an AE could be either grade 2 or grade 3), select the higher of the 2 grades for the AE.

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.

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] As per Bazett's formula.

DERMATOLOGIC				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Alopecia (scalp only)	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	NA	NA
Bruising	Localized to one area	Localized to more than one area	Generalized	NA
Cellulitis	NA	Non-parenteral treatment indicated (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 9.5.2.	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)

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

NEUROLOGIC				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Acute CNS Ischemia	NA	NA	Transient ischemic attack	Cerebral vascular accident (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

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* *<12 years of age (based on a 1, 2, 3, 4, 6 and 8 kHz audiogram)*	NA >20 dB hearing loss at ≤4 kHz	Hearing aid or intervention not indicated >20 dB hearing loss at >4 kHz	Hearing aid or intervention indicated >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	Profound bilateral hearing loss (>80 dB at 2 kHz and above) OR Non-serviceable hearing (ie, >50 dB audiogram and <50% speech discrimination) 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.

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	pH <7.3 without life-threatening consequences	pH <7.3 with life-threatening consequences
Albumin, Low (g/dL; *g/L*)	3.0 to <LLN *30 to <LLN*	≥2.0 to <3.0 *≥20 to <30*	<2.0 *<20*	NA
Alkaline Phosphatase, High	1.25 to <2.5 x ULN	2.5 to <5.0 x ULN	5.0 to <10.0 x ULN	≥10.0 x ULN
Alkalosis	NA	pH > ULN to ≤7.5	pH >7.5 without life-threatening consequences	pH >7.5 with life-threatening consequences
ALT or SGPT, High *Report only one*	1.25 to <2.5 x ULN	2.5 to <5.0 x ULN	5.0 to <10.0 x ULN	≥10.0 x ULN
Amylase (Pancreatic) or Amylase (Total), High *Report only one*	1.1 to <1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to <5.0 x ULN	≥5.0 x ULN
AST or SGOT, High *Report only one*	1.25 to <2.5 x ULN	2.5 to <5.0 x ULN	5.0 to <10.0 x ULN	≥10.0 x ULN
Bicarbonate, Low (mEq/L; *mmol/L*)	16.0 to <LLN *16.0 to <LLN*	11.0 to <16.0 *11.0 to <16.0*	8.0 to <11.0 *8.0 to <11.0*	<8.0 *<8.0*
Bilirubin ***Direct Bilirubin[14], 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 x ULN See Appendix A. Total Bilirubin for Term and Preterm Neonates	 NA >1 to ≤1.5 mg/dL 1.6 to <2.6 x ULN See Appendix A. Total Bilirubin for Term and Preterm Neonates	 >ULN >1.5 to ≤2 mg/dL 2.6 to < 5.0 x 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 x 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] Direct bilirubin >1.5 mg/dL in a participant <28 days of age should be graded as grade 2, if <10% of the total bilirubin.

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Creatine Kinase, High	3 to <6 x ULN	6 to <10 x ULN	10 to <20 x ULN	≥20 x ULN
Creatinine, High	1.1 to 1.3 x ULN	>1.3 to 1.8 x ULN OR Increase of >0.3 mg/dL above baseline	>1.8 to <3.5 x ULN OR Increase of 1.5 to <2.0 x above baseline	≥3.5 x ULN OR Increase of ≥2.0 x above baseline
Creatinine Clearance[15] 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 x ULN without acidosis	≥2.0 x ULN without acidosis	Increased lactate with pH <7.3 without life-threatening consequences	Increased lactate with pH <7.3 with life-threatening consequences
Lipase, High	1.1 to <1.5 x ULN	1.5 to <3.0 x ULN	3.0 to <5.0 x ULN	≥5.0 x ULN
Lipid Disorders (mg/dL; *mmol/L*) ***Cholesterol, Fasting, High*** *≥18 years of age* *<18 years of age* ***LDL, 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[16], 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*

[15] Use the applicable formula (ie, Cockroft-Gault in mL/min or Schwatrz in mL/min/1.73m^2).
[16] To convert a magnesium value from mg/dL to mmol/L, laboratories should multiply by 0.4114.

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Sodium, High (mEq/L; *mmol/L*)	146 to <150 *146 to <150*	150 to <154 *150 to <154*	154 to <160 *154 to <160*	≥160 *≥160*
Sodium, Low (mEq/L; *mmol/L*)	130 to <135 *130 to <135*	125 to <130 *125 to <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 x 10^9 to <0.650 x 10^9*	500 to <600 *0.500 x 10^9 to <0.600 x 10^9*	350 to <500 *0.350 x10^9 to <0.500 x 10^9*	<350 *<0.350 x 10^9*
Absolute Neutrophil Count (ANC), Low (cells/mm^3; *cells/L*) *>7 days of age* *2 to 7 days of age* *≤1 day of age*	800 to 1,000 *0.800 x 10^9 to 1.000 x 10^9* 1,250 to 1,500 *1.250 x 10^9 to 1.500 x 10^9* 4,000 to 5,000 *4.000 x 10^9 to 5.000 x 10^9*	600 to 799 *0.600 x 10^9 to 0.799 x 10^9* 1,000 to 1,249 *1.000 x 10^9 to 1.249 x 10^9* 3,000 to 3,999 *3.000 x 10^9 to 3.999 x 10^9*	400 to 599 *0.400 x 10^9 to 0.599 x 10^9* 750 to 999 *0.750 x 10^9 to 0.999 x 10^9* 1,500 to 2,999 *1.500 x 10^9 to 2.999 x 10^9*	<400 *<0.400 x 10^9* <750 *<0.750 x 10^9* <1,500 *<1.500 x 10^9*
Fibrinogen, Decreased (mg/dL; *g/L*)	100 to <200 *1.00 to <2.00* OR 0.75 to <1.00 x LLN	75 to <100 *0.75 to <1.00* OR ≥0.50 to <0.75 x LLN	50 to <75 *0.50 to <0.75* OR 0.25 to <0.50 x LLN	<50 *<0.50* OR <0.25 x LLN OR Associated with gross bleeding
Hemoglobin[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, High (not on anticoagulation therapy)	1.1 to <1.5 x ULN	1.5 to <2.0 x ULN	2.0 to <3.0 x ULN	≥3.0 x ULN
Methemoglobin (% hemoglobin)	5.0 to <10.0%	10.0 to <15.0%	15.0 to <20.0%	≥20.0%

[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.

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

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

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 x ULN	1.6 to <2.6 x ULN	2.6 to <5.0 x ULN	≥5.0 x 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 x ULN	1.6 to <2.6 x ULN	2.6 to <5.0 x ULN	≥5.0 x 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 2: 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]). [25,39]

Clinical Stage 1

Clinical Stage 1 consists of 1 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 ≥1 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

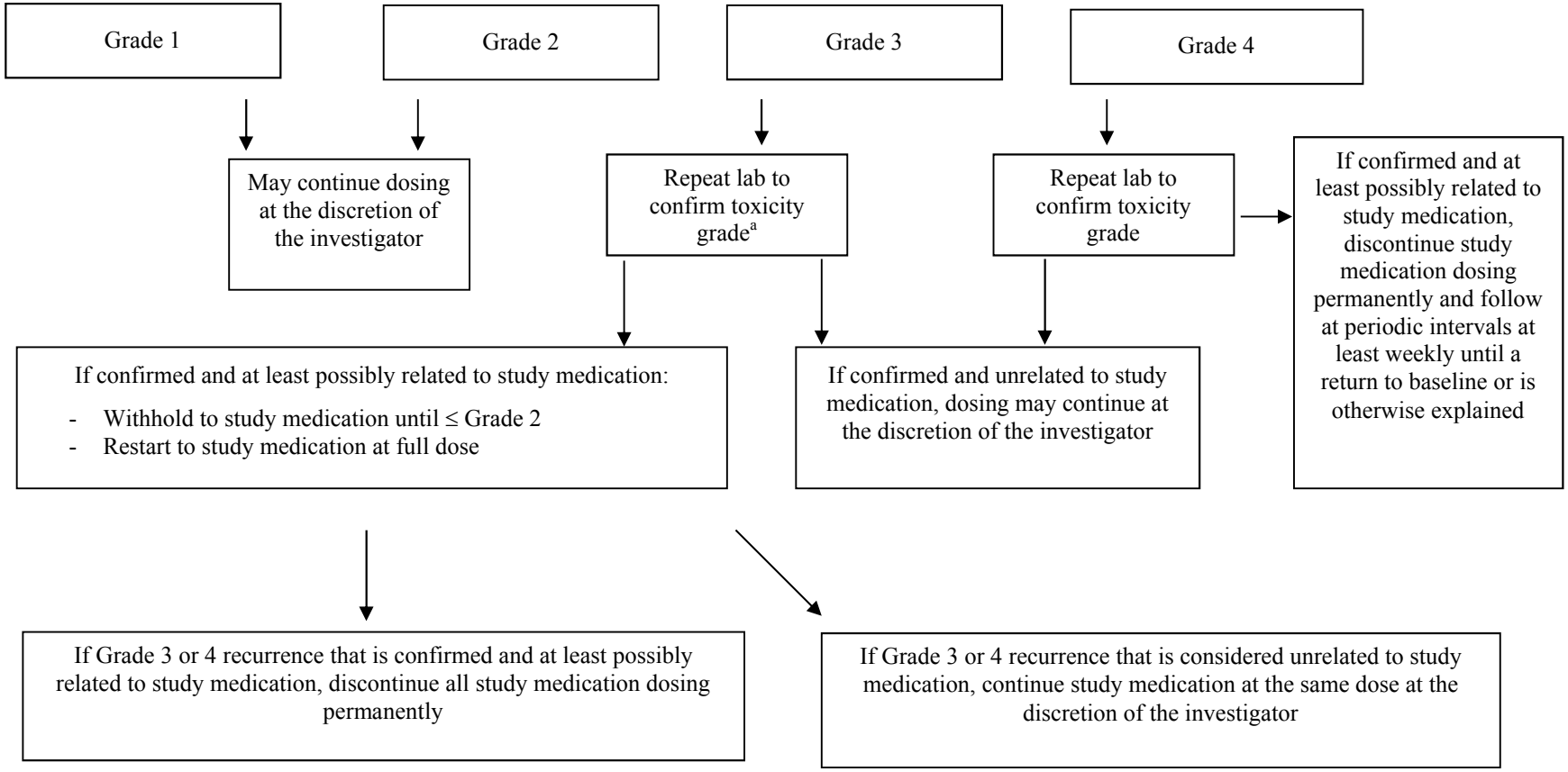
- Unexplained persistent fever (above 37.6°C intermittent or constant, for longer than 1 month)
- Persistent oral candidiasis
- Oral hairy leukoplakia
- Pulmonary tuberculosis (current)
- Severe bacterial infections (such as pneumonia, empyema, pyomyositis, bone or joint infection, meningitis or bacteremia)
- Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis
- Unexplained anemia (<8 g/dL), neutropenia ($<0.5 \times 10^9$/L) or chronic thrombocytopenia ($<50 \times 10^9$/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 3: 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.

Attachment 4: Management of Dyslipidemia

RECOMMENDATIONS

(Adapted from: Guidelines for the evaluation and management of dyslipidemia in human immunodeficiency virus [HIV]-Infected adults receiving ARV therapy: Recommendations of the HIV Medicine Association of the Infectious Disease Society of America and the Adult AIDS Clinical Trials Group.[2])

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 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. 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 prior to 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 6 and Table 7). 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 6 and Table 7). 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 7). 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 6: 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 7: 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 5: 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 AEs related to hypotension/hypertension should be done according to the DAIDS grading table (Attachment 1).

ECG

Abnormality Code	Heart Rate (bpm)	PR (ms)	QRS (ms)	QTc[a] (ms)
Abnormally low	≤50 bpm	N/A	≤50 ms	-
Abnormally high	≥120 bpm	≥210 ms	≥120 ms	-
]450 ms, 480 ms]	-	-	-	450 <QTc ≤480
]480 ms, 500 ms]	-	-	-	480 <QTc ≤500
More than 500 ms	-	-	-	QTc >500

[a] Categories for QTc parameters are defined based on the ICH E14 Guidance.[7]

Attachment 6: 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[26]
† Condition that might be diagnosed presumptively
§ Only among adults and adolescents aged ≥13 years[25]

Reporting of Anticipated Events

These events will be captured on the CRF and in the database, and will be reported to the sponsor as described in Section 12.4.1, All Adverse Events. Any event that meets serious adverse event criteria will be reported to the sponsor within the appropriate timeline as described in Section 12.4.2, Serious Adverse Events. These anticipated events are exempt from expedited reporting as individual single cases to Health Authorities, Investigators and Independent Ethics Committee/Institutional Review Board. 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): M. Opsomer

Institution: Janssen Research & Development

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.

LAST PAGE

SIGNATURES

Signed by	Date	Justification
Magda Opsomer	19Apr2017, 14:43:12 PM, UTC	Document Approval