Janssen Research & Development *

Statistical Analysis Plan
(Week 96 Analysis)

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

Protocol TMC114FD2HTX3001; Phase 3

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

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

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AMENDMENT HISTORY

Not applicable.

ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ARV	antiretroviral
AST	aspartate aminotransferase
ATC	Anatomic and Therapeutic Class
ATV	atazanavir
AUC_{24h}	area under the plasma concentration-time curve over the 24h dosing interval
BIS	bone investigation substudy
BMD	bone mineral density
BMI	body mass index
CI	confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{0h}	Pre-dose (trough) plasma concentration
COBI	cobicistat
DAIDS	Division of AIDS
D/C/F/TAF	darunavir/cobicistat/emtricitabine/tenofovir alafenamide
DMC	Data Monitoring Committee
DPS	Data Presentation Specifications
DRV	darunavir
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
$eGFR_{cr}$	eGFR for creatinine clearance
$eGFR_{cyst}$	eGFR for cystatin C clearance
ESTD	early study treatment discontinuation
FDA	Food and Drug Administration
FDC	fixed-dose combination
FTC	emtricitabine
GSI	Gilead Sciences, Inc.
HIV-1	human immunodeficiency virus type 1
ITT	Intent-to-Treat
LLOQ	Lower limit of quantification
LPV	lopinavir
MedDRA	Medical Dictionary for Regulatory Activities
NCEP	National cholesterol education program
PK	pharmacokinetic(s)
RAM	resistance-associated mutation
RNA	ribonucleic acid
rtv	ritonavir
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate
TD	target detected
TND	target not detected
WHO	World Health Organization

1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the Week 96 analysis that will be performed after the last subject enrolled in the open-label extension phase completes the Week 96 visit, or prematurely discontinues from the study. The final analysis will be described in a separate SAP.

1.1. Trial Objectives

The primary objective of this study was to demonstrate non-inferiority in efficacy of a D/C/F/TAF FDC tablet versus DRV/COBI FDC co-administered 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%.

The secondary objectives of this study were:

- To evaluate superiority of a D/C/F/TAF FDC tablet versus DRV/COBI FDC co-administered 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 non-inferiority 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;
- 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;

Objectives of a bone investigation sub-study 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.

The secondary objectives to be assessed in the study single arm treatment phase:

- To evaluate long-term safety, resistance, and efficacy of the D/C/F/TAF regimen (until Week 96 and beyond);

1.2. Trial Design

This is a randomized, double-blind active-controlled, multicenter, Phase 3 study to evaluate efficacy and safety of D/C/F/TAF once daily fixed dose combination regimen versus a regimen consisting of DRV/COBI FDC combined with FTC/TDF FDC in ARV treatment-naïve HIV-1 infected adult subjects.

The aim of this study was to include 670 subjects that were to be randomly assigned with 335 subjects planned per treatment group. Subjects who met all eligibility criteria were 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 was 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 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 consists of 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 of the protocol 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.

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 tables once daily [g]	D/C/F/TAF FDC	D/C/F/TAF FDC	**ESTD [f] and 30-day FU visit [h]**
	Treatment arm 2 (Control) (n=335): DRV/COBI FDC coadminsitered with FTC/TDF FDC once daily [g] D/C/F/TAF FDC-matching placebo tablet once daily [g]			

[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).

1.3. Statistical Hypotheses for Trial Objectives

The primary efficacy endpoint of this study was the proportion of subjects who have HIV-1 RNA <50 copies/mL at Week 48 as defined by the FDA Snapshot analysis. Thus, no formal statistical hypothesis is to be tested in the Week 96 SAP.

1.4. Sample Size Justification

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 was 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 non-inferiority 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) was targeted to be included in the bone investigation sub-study. 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 1.

Table 1: 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%

1.5. Randomization and Blinding

Randomization

Central randomization was implemented in conducting this study. Subjects were assigned to 1 of 2 treatment groups in a 1:1 ratio based on computer-generated randomization schedule implemented in the interactive web response system (IWRS) before the study. 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. Based on the algorithm, the IWRS assigned a unique treatment code, which dictated the treatment assignment and matching study drug kit for the subject.

Blinding

Subjects continued to take their blinded study drug and to attend visits every 12 weeks following Week 48 until treatment assignment was unblinded. After unblinding, 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 were required to return to the clinic for an additional visit 3 to 7 weeks after the unblinding visit.

2. GENERAL ANALYSIS DEFINITIONS

2.1. Treatment Arms

Following notations for the treatment arms in the single arm treatment phase will be used:

- **Initial D/C/F/TAF Arm**: subjects who received D/C/F/TAF FDC treatment at baseline of the treatment phase
- **Late Switch to D/C/F/TAF Arm**: subjects who were on DRV/COBI FDC+ FTC/TDF FDC treatment and switched to D/C/F/TAF treatment during the single arm treatment phase

2.2. Visit Windows

2.2.1. Trial Phases

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

Trial phase	Start date	End date
Screening	Minimum of Date of signing the informed consent and Date of the screening visit	1 day before start of treatment
Comparative Treatment Phase	Date of the first intake (after randomization)	For ongoing subjects, in order of priority: – Week 48 visit date; if missing then; – Projected Week 48 visit date, where projected Week 48 visit date = baseline visit date + (7 *48) <u>In case of withdrawal use</u>: – Minimum(last intake date of study drug, study withdrawal date) +2 days
Extended double-blind treatment phase (up to Switch)	Comparative treatment phase end date +1 day	If a subject switches prior to Week 96: – Minimum(Date of last double-blind intake +2 days, Start Date of first Open Label D/C/F/TAF intake) If a subject never switches prior to Week 96: – Week 96 visit date; if missing then; – Projected Week 96 visit date, where projected Week 96 visit date = baseline visit date + (7 *96) <u>In case of withdrawal prior to switching use</u>: Minimum (last intake date of study drug, study withdrawal date) + 2 days
Single Arm treatment phase (Switch to Week 96) *	Extended double-blind treatment phase end date +1 day	– Week 96 visit date; if missing then; – Projected Week 96 visit date, where projected Week 96 visit date = baseline visit date + (7 *96) <u>In case of withdrawal after switch use</u>: – Minimum (last intake date of study drug, study withdrawal date) + 2 days
Follow-up	Maximum (end date of extended double-blind treatment phase, end date of single arm treatment phase) +1 day	Trial termination date for all groups (date of last contact)

* The 3-7 WEEKS AFTER UNBLINDING visit will be handled as follows:
- All efficacy assessments collected at this visit will be attributed to the DRV/COBI FDC + FTC/TDF FDC regimen
- All safety assessments collected at this visit will be attributed to the D/C/F/TAF FDC regimen

Data up to each subject's Week 96 visit are in scope for this analysis; in addition DXA data (DP domain) up to Week 96 visit+28 days, and if applicable, any (confirmatory) viral load or genotype/phenotype results immediately subsequent to Week 96 (up to 6 weeks) will also be included in this analysis.

2.2.2. Analysis Time points

All visits/assessments will be allocated to the following time points as per the table below, based on the number of days in the study, calculated as "assessment date – start date of comparative treatment phase + 1 day" for Comparative Treatment, Extended Double-blind Treatment/Single Arm Treatment and Follow-up phase and "assessment date – start date of Comparative Treatment phase" for Screening phase.

The following time intervals will be used for reporting of efficacy as well as safety data:

Phase	Visit	Target day	Analysis time point	Time interval (days)
Screening	1	-∞	Screening	< Day 0
Comparative Treatment Phase	2	1	Baseline [a]	<=Day 1
	3	15	Week 2	Day 2 – Day 21
	4	29	Week 4	Day 22 – Day 42
	5	57	Week 8	Day 43 – Day 70
	6	85	Week 12	Day 71 – Day 126
	7	169	Week 24	Day 127 – Day 210
	8	253	Week 36	Day 211 – Day 294
	9	337	Week 48	Day 295 – Day 378
Extended Double-blind & Single Arm Treatment phase	10	421	Week 60	Day 379 – Day 462
	11	505	Week 72	Day 463 – Day 546
	12	589	Week 84	Day 547 – Day 630
	13	673	Week 96	Day 631 – Day 714
Follow-up	14	31	Follow-up	Day 1 onwards

[a] Except for DXA, only the record closest to target day 1 will be allocated to analysis time point 'Baseline', all records prior to day 1 are assigned to 'Screening'. For DXA, a scan up to 28 days post baseline visit can be allocated to the analysis time point 'Baseline'.

Unless specified otherwise, if two visits fall within the same interval, the one closest to the target day will be used for the analysis displays and graphics in order to have only one evaluation per subject per analysis time point. However, all data will be presented in the listings. If distances of both visits to the target day are equal, the visit latest in time will be used. If multiple visits that fall within the same analysis window have the same date/time, the one with the highest sequence number will be used.

2.3. Analysis Sets

2.3.1. Efficacy Analysis Set(s)

2.3.1.1. Intent-to-Treat Analysis Set

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

2.3.1.2. Per Protocol Analysis Set

Since an analysis on the ITT population may not be conservative in a non-inferiority 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. Specific details are provided in Attachment 1.

2.3.2. Safety Analysis Set

The safety analysis (including all data collected up to 30-day follow-up visit) is also performed on the ITT analysis set.

2.3.3. Bone Investigation Sub-study Analysis Set

The bone investigation sub-study (BIS) analysis set will include all subjects who are randomized and have received ≥1 dose of treatment in the study, and have at least one post-reference value either in biomarker or in BMD data. Subjects will be grouped according to the treatment arm (D/C/F/TAF or control) to which they were randomized.

2.4. Definition of Subgroups

2.4.1. Subgroups for Efficacy Analyses

- Adherence based on D/C/F/TAF (i.e., worst D/C/F/TAF adherence from baseline to switch and switch to week 96 for the Initial D/C/F/TAF group, and from switch to week 96 for the Late Switch to D/C/F/TAF group) on drug accountability for both derivations (>95%: adherent, ≤95%: non-adherent, missing/unknown)
- Re-classified (see section 2.5) viral load stratification factor (≤ 100,000, > 100,000 copies/mL)
- Re-classified (see section 2.5) CD4+ count:
  - < 200, ≥ 200 cells/mm^3[200≤ x<350, 350≤x≤500, >500 cells/mm^3]
- Combination of re-classified (see section 2.5) stratification factors:
  - Viral load ≤ 100,000 copies/mL and CD4+ < 200 cells/ mm^3
  - Viral load ≤ 100,000 copies/mL and CD4+ ≥ 200 cells/ mm^3
  - Viral load > 100,000 copies/mL and CD4+ < 200 cells/ mm^3
  - Viral load > 100,000 copies/mL and CD4+ ≥ 200 cells/ mm^3
- Race (American Indian or Alaska Native, Asian, Black or African American, White, Native Hawaiian or other Pacific Islander, Other, Non Black or African American)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Gender (Male, Female)
- Age group:
  - ≤50, >50 years
- Region (Europe, North America)
- WHO Clinical Staging of HIV/AIDS
- HIV-1 subtype (B, non-B)
- Any PI RAMs (primary + secondary) (0-3, 4-6, 7-9, >=10)
- Presence (Yes/No) of one or more:
  - primary and/or DRV RAMs,
  - NRTI RAMs,
  - NNRTI RAMs,
  - M184V/I

Subgroup analyses will be performed on the ITT analysis set.

2.4.2. Subgroups for Safety Analyses

- Age group:
  - ≤50, >50 years
- Re-classified (see section 2.5) viral load stratification factor (≤ 100,000, > 100,000 copies/mL)
- Re-classified (see section 2.5) CD4+ count (< 200, ≥ 200 cells/mm^3)
- Combination of re-classified (see section 2.5) stratification factors:
  - Viral load ≤ 100,000 copies/mL and CD4+ < 200 cells/ mm^3

  - Viral load ≤ 100,000 copies/mL and CD4+ ≥ 200 cells/ mm^3
  - Viral load > 100,000 copies/mL and CD4+ < 200 cells/ mm^3
  - Viral load > 100,000 copies/mL and CD4+ ≥ 200 cells/ mm^3
- Race (American Indian or Alaska Native, Asian, Black or African American, White, Native Hawaiian or other Pacific Islander, Other, Non Black or African American)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Gender (Male, Female)
- Region (Europe, North America)
- WHO Clinical Staging of HIV/AIDS

Subgroups for Bone Investigation Analyses:

- Race (American Indian or Alaska Native, Asian, Black or African American, White, Native Hawaiian or other Pacific Islander, Other, Non Black or African American)
- Gender (Male, Female)
- Baseline BMI:
  - Underweight (< 18.5 kg/m^2)
  - Normal range (18.5 – 24.99 kg/m^2)
  - Overweight (25.0 – 29.99 kg/m^2)
  - Obese (≥ 30.0 kg/m^2)
- Age group (≤50, >50 years)
- Current smoking status (Y/N)

2.5. Re-classification of Stratification Factors for Purpose of Analysis

For the purpose of analysis the stratification factors (HIV-1 RNA [≤ 100,000, > 100,000 copies/mL] and CD4+ count [(< 200, ≥ 200 cells/mm^3]) will be re-classified based on the baseline values from the laboratory data. If the baseline data are missing, then the laboratory data at screening will be used. If the laboratory data at screening are missing, then the data from the IVRS/IWRS will be used.

The re-classified stratification factors will be used for analysis. Listings showing the discrepancies between the strata entered at randomization (IVRS/IWRS) and actual screening laboratory data will be presented.

2.6. Reference

For Initial D/C/F/TAF group, reference is the comparative treatment phase baseline as in Week 48 analysis. For the Late Switch group, the references are as follows:

1. Comparative treatment phase baseline (for efficacy this reference will be used for periods before and after the switch; for safety this reference will be used for periods before the switch).
2. Last value prior to the switch will be used as a reference for periods after the switch for both efficacy and safety; for DXA scan, data up to (and including) 28 days after the switch to open label D/C/F/TAF can be used as reference.

3. SUBJECT INFORMATION

3.1. Demographics and Baseline Characteristics

These parameters will not be included in this analysis, because no new subjects were recruited since the Week 48 analysis.

3.2. Disposition Information

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

Tabulation per treatment arm of the number of subjects who have completed the treatment/single arm phase, who are ongoing, and who have discontinued the trial with the reason for discontinuation will be provided. For the Initial D/C/F/TAF group, the tabulation will be presented by time period as follows; baseline to Week 48, Week 48 to Week 96 and overall from baseline to Week 96. For the Late Switch group, the tabulation will be presented by time period as follows; baseline to Week 48, Week 48 to the switch, from the switch to Week 96, and overall from baseline to Week 96.

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

3.3. Treatment Adherence

Treatment adherence based on drug accountability will be summarized by means of descriptive statistics and frequency tabulations. Cumulative treatment adherence will be calculated from baseline to the switch, and again from the switch to Week 96. Cumulative treatment adherence will be determined (derivation i).

The following parameters are derived:

Amount to be taken through switch/Week 96 = (number of days since start of treatment/switch × number of tablets to be taken per day).

Number of days since start of start of treatment/switch is based on (whichever comes sooner):

- last study medication intake (if available) or, in case subject discontinued and last study medication intake is missing, the last visit date prior to withdrawal will be used.
- Switch/Week 96 visit date,

In addition (derivation ii), the cumulative treatment adherence up to time point where not more than one bottle is missing, or if available, up to switch/Week 96, whichever comes sooner, will be calculated.

Actual amount taken = (number of tablets dispensed – number of tablets returned), summed over time points up to the time point of interest.

Level of adherence = (actual amount taken / amount to be taken) × 100%

Treatment adherence is defined as:

- adherent: the level of adherence is >95%,

- non-adherent: the level of adherence is ≤95%.

Additionally, following categories of level of adherence will be defined:

- >95%
-]80%; 95%]
-]65%; 80%]
-]50%; 65%]
- ≤ 50%

Interruptions (for AEs) are not to be taken into account for the calculation of adherence, i.e. they will not be subtracted from the amount to be taken.

Within treatment group comparison using McNemar's Exact test comparing adherence (i.e., adherent versus non-adherent) before and after the switch will be calculated. The statistical test will be interpreted at the 5% two-sided significance level.

3.4. Extent of Exposure

Descriptive statistics will be tabulated for the duration of treatment of both treatment groups, in weeks, during the respective active treatment phases, as of reference up to the Week 96 visit or in case of early discontinuation, last study medication intake. In addition, subject-years of exposure will be shown, derived as mean of treatment duration (in weeks) x N) x 7 / 365.25. Tabulation of the distribution of exposure per 4 week intervals will be presented. Additionally, the number (with percentages) of subjects who switched by analysis time point will be provided along with the subject-years of exposure to D/C/F/TAF per analysis time point.

Treatment duration (in weeks) is derived as follows:

(End of phase – reference + 1) / 7

Treatment interruptions will not be taken into account for the above definition.

3.5. Protocol Deviations

All major protocol deviations will be tabulated and listed by treatment arm and overall. The proportion of subjects with one or more major protocol deviation that led to exclusion from the per protocol analysis set (see Attachment 1) will also be tabulated.

3.6. Concomitant Medications

Concomitant medications are defined as any therapy used on or after the same day as the first dose of study agent, including those that started before and continue on after the first dose of study agent. Combination drugs are split up into their respective compounds.

Concomitant therapies will be grouped as follows, using a list of dictionary derived terms provided as metadata. These groups will be tabulated (n, %) per treatment group and analysis phase:

- lipid lowering drugs
- antidiabetic drugs
- antihypertensive drugs
- drugs for cardiovascular disease
- antiosteoporotic drugs

4. EFFICACY

4.1. Analysis Specifications

4.1.1. Level of Significance

No formal statistical tests will be performed. All analyses will be descriptive.

4.1.2. Data Handling Rules

Plasma viral load levels will be measured using the ROCHE COBAS® AmpliPrep/COBAS® Taqman® HIV-1 Test, v2.0, which will be conducted by the central laboratory.

Imputation of left censored HIV-1 RNA values: viral load results recorded as "< 20 HIV-1 RNA copies/mL detected" and "< 20 HIV-1 RNA copies/mL not detected" will be scored at 19.

CD4+ cell count and HIV-1 RNA data collected on treatment (up to the last dose date of study drug) will be used in the analysis.

4.1.3. FDA Snapshot Approach and Time to Loss of Virologic Response Algorithm (TLOVR)

FDA Snapshot approach (applying 20/50/200 copies/mL as threshold): The Snapshot approach will classify subjects into 3 outcome categories: "virologic success", "virologic failure", or "no viral load data in the Week 96 visit window". Several subcategories of the outcome will also be presented in the analysis and are shown below. The categories below are mutually exclusive such that a subject will be included in one (sub)category. If a subject discontinues in the time window but also has an HIV-RNA value in the time window then the viral load value will be used to classify the subject's category.

- Virologic success:
  - Last available HIV RNA <20/50/200 copies/mL in the Week 96 visit window (Week 90-102)
- Virologic failure:
  - Last available HIV RNA ≥20/50/200 copies/mL in the Week 96 visit window (Week 90-102)
  - Virologic failure leading to discontinuation
  - Discontinued due to other reason (i.e., other than AE/death or virologic failure) and last available HIV RNA ≥20/50/200 copies/mL
- No viral load data in the Week 96 visit window:
  - Discontinued due to AE/death (subjects will be classified in this category if discontinued prior to Week 96 window regardless of HIV RNA level)
  - Discontinued due to other reason (i.e., other than AE/death or virologic failure) and the last available HIV RNA <20/50/200 copies/mL (or missing)
  - Missing data during the Week 96 visit window but on study

'Virologic failure' as reason for discontinuing the trial was inadvertently not included in the Study Termination eCRF page. Therefore, whether a subject would be classified into the subcategory 'Virologic failure leading to discontinuation' will be determined by a medical assessment of the comment fields and other specification reasons for discontinuation to determine if anyone discontinued the trial due to lack of efficacy reasons. A current list of comments and other specification reasons are documented in Attachment 5, and will be used to programmatically identify such subjects. Upon further clinical evaluation additional comments or other specification reasons might need to be added, and these will be documented in the DPS. An identified subject will be classified to the Snapshot categories as follows:

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

Virologic response will then be categorized as follows: Yes (virologic success), or No (virologic failure and no viral load data in the Week 96 visit window).

The Snapshot approach will also be displayed over time by analysis time point, and will follow the same logic as defined above (please see Section 2.2.2 for visit intervals)

Imputations for missing values

The following imputation method is used to calculate **virologic response** at a given time point:

- observed case: subjects with a missing value are disregarded in the analysis for that time point.
- TLOVR: responders/non-responders are defined according to the FDA Time To Loss Of Virologic Response algorithm; a subject is considered a responder at a given time point if the applicable HIV-RNA criterion is fulfilled at that time point and at the subsequent time point; a subject is considered a confirmed non-responder at a time point in the following situations in order of precedence:
    - the subject shows a 'rebound' HIV-RNA value (>=threshold copies/mL) at that time point and the subsequent time point;
    - the subject shows a confirmed rebound at an earlier time point (irrespective of re-suppression of viral load)
    - the subject (permanently) discontinued at that time point or before
    - intermittently missing values are considered as response if the immediately preceding and following visits demonstrated response; in case the subject had not reached the next visit yet, no imputation is performed for the missing time points, unless the subject had discontinued the trial.
    - Remark: in case multiple virologic response observations are available within the same time window, all observations are used to determine TLOVR-imputed response for that time window. In case the subject has not reached the next visit yet, this subject is left out of the analysis for the missing time points.

4.2. Primary Efficacy Endpoint(s)

4.2.1. Definition

The primary efficacy endpoint of this study was the proportion of subjects who have HIV-1 RNA <50 copies/mL at Week 48 as defined by the FDA Snapshot analysis. Thus, the analysis of this endpoint is not described in the Week 96 SAP.

4.2.2. Analysis Methods

Not applicable.

4.3. Major Secondary Efficacy Endpoints

4.3.1. Definition

- The proportion of subjects with HIV-1 RNA <20, <50, and <200 copies/mL at Week 96 as defined by the FDA Snapshot analysis;
- The proportion of subjects with HIV-1 RNA <20, <50, and <200 copies/mL at Week 96 as defined by the time to loss of virologic response (TLOVR) algorithm;
- The change from reference in $\log_{10}$ HIV-1 RNA up to Week 96;
- The change from reference in CD4+ cell count up to Week 96;
- The development of viral resistance through Week 96;

4.3.2. Analysis Methods

4.3.2.1. Antiviral Efficacy

Tabulations (numbers and proportions) per time point will be provided for the Snapshot outcomes (success, failure, no data within window). Tabulations (numbers and proportions) will also be provided for Snapshot outcome at Week 96 based on observed data (i.e., subjects with a missing value are disregarded in the analysis for that time point), and TLOVR through Week 96. The exact 2-sided 95% CIs around in each treatment group will be calculated by the Clopper-Pearson method for Snapshot virologic success and virologic failure, and TLOVR response. Bar charts will be presented for Snapshot outcomes.

Cross-tabulations for protocol defined virologic failure (see Section 4.3.2.3) versus the FDA snapshot algorithm at Week 96 (HIV-1 RNA < 50 copies/mL) will be presented.

4.3.2.2. Immunologic Change

Change from reference is defined as: value at a given time point minus reference value.

Actual and changes from reference values in CD4+ cell count and $\log_{10}$ HIV-1 RNA at each time point will be summarized using descriptive statistics (n, mean (SE), median, min, and max).

The changes from reference in CD4+ cell count (NC=F) and $\log_{10}$ HIV-1 RNA (NC=F) at Week 96 will be constructed using analysis of covariance (ANCOVA), separately for each treatment group, including CD4+ cell count or $\log_{10}$ HIV-1 RNA at reference, respectively, as continuous covariate in the model.

Subjects who discontinue will have their CD4 or $\log_{10}$ HIV-1 RNA values after discontinuation imputed with their reference value, thus resulting in a 0 change (NC=F). Other (intermittent) missing values will be imputed using last observation carried forward (LOCF). Apart from imputed, observed data will also be presented. For cases where no observation is available at the baseline date, the last available screening value will be taken.

A supportive mixed model for repeated measures in change from reference in CD4+ cell count (observed) will also be performed separately for each treatment group. The model will include post-baseline change from reference as a response variable, terms for visit, and the corresponding reference value as a covariate An unstructured covariance matrix will be used to model the correlation among repeated measurements.

Cross-tabulations of Week 96 CD4 cell count versus reference will be provided using the categories: < 200, 200≤ x<350, 350≤x≤500, >500 cells/mm^3.

4.3.2.3. Resistance Determinations

Subjects who are on study medication and who experience a protocol defined confirmed virologic failure, i.e., virological non-response (NR), virologic rebound (RB), or viremic at final time point, 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.

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.

Virologic at Final Time Point:

- Any subject with on-treatment HIV-1 RNA ≥400 copies/mL at the study endpoint or study discontinuation after Week 8

For the management of subjects experiencing VF (and the resistance testing on samples from these subjects) see section 9.2.2.1 of the protocol.

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 at protocol defined VF and have HIV-1 RNA ≥400 copies/mL). Note: baseline genotype/phenotype may be available for subjects with confirmed VF if they showed evidence of reduced susceptibility after VF to any of the study drugs.

4.3.2.3.1. Genotype

At screening HIV-1 PR/RT genotype will be assessed by the GenoSureMG™ assay. Post-screening HIV-1 PR/RT genotype/phenotype will be assessed by the PhenoSenseGT™ assay.

Evaluation of screening and treatment-ermergent RAMs will be based on PI, N(t)RTI, and NNRTI mutation lists defined by IAS-USA. RAMs were considered treatment-emergent if they were detected post-baseline but not at screening/baseline. Individual listings will be generated. Genotypes will be shown per region (PR and RT), time point and treatment phase. Mutations will be marked by lists and if they emerged.

At screening, a tabulation per treatment group will present the number of patients with a specific mutation or number of patients with at least one PR or RT mutation belonging to a specific mutation list (see below). Percentages and the mean/median will be calculated based on the number of subjects with screening genotypes.

Post baseline, a tabulation of emerging mutations per treatment group will present the number of patients with a specific emerging mutation or number of patients with emerging mutations belonging to a specific mutation list (see below).

The analysis assumes a worst-case scenario in case of multiple post-screening sequencing results: if any of a patient's samples shows a mutation, the patient is assumed to have this mutation, even if other samples show wild-type virus. The percentage of patients with emerging mutations will be calculated on the number of patients with paired screening/baseline and post-baseline genotypes and on all ITT patients. The denominator should be shown.

All analyses will be conducted on the Efficacy ITT population, unless specified otherwise, and will be presented by “all patients with available post baseline genotypes” and by “protocol defined virologic failure with post baseline genotypes”, taking into account either “all genotypes” or only the “genotypes that are on-treatment”.

Protease mutations

- IAS-USA[3] Primary PI mutations (n=23)

  D30N, V32I, M46I/L, I47A/V, G48V, I50L/V, I54L/M, Q58E, T74P, L76V, V82A/F/L/S/T, N83D, I84V, N88S, L90M

- IAS-USA[3] Secondary PI mutations (n=52)

  L10C/F/I/R/V, V11I, G16E, K20I/M/R/T/V, L24I, L33I/F/V, E34Q, M36I/L/V, K43T, F53L/Y, I54A/S/T/V, D60E, I62V, L63P, I64L/M/V, H69K/R, A71I/L/T/V, G73A/C/S/T, V77I, V82I, I85V, N88D, L89I/M/V, I93L/M

- IAS-USA[3] DRV resistance-associated mutations (n=11)

  V11I, V32I, L33F, I47V, I50V, I54L/M, T74P, L76V, I84V, L89V

RT mutations

- IAS-USA[3] NRTI resistance-associated mutations (n=22)

  M41L, A62V, K65R/E/N, D67N, 69ins, K70E/R, L74V, V75I, F77L, Y115F, F116Y, Q151M, M184I/V, L210W, T215F/Y, K219E/Q

- IAS-USA[3] NNRTI resistance-associated mutations (n=34)
  V90I, A98G, L100I, K101E/H/P, K103N/S, V106A/I/M, V108I, E138A/G/K/Q/R, V179D/F/L/T, Y181C/I/V, Y188C/H/L, G190A/S, H221Y, P225H, F227C, M230I/L

- IAS-USA[3] Thymidine Analogue Mutations (TAMs) (n=8)
  M41L, D67N, K70R, L210W, T215Y/F, K219Q/E

- IAS-USA[3] TFV resistance-associated mutations

  K65R/E/N, K70E

- IAS-USA[3] FTC resistance-associated mutations
  K65R/E/N, M184I/V

4.3.2.3.2. Phenotype

Predicted phenotype based GenoSureMG™, in-vitro phenotype data, and the overall resistance assessments based on the PhenoSenseGT™ assay will be presented in individual patient listings per drug and time point, if available.

If available, fold change (FC) in 50% effective concentration (EC_{50}) of ARVs versus wild-type HIV-1 virus will be included in individual listings per drug and time point.

When one cut-off value is available, a drug is considered

- Sensitive if the FC is below or equal to the clinical cut-off (CCO) when available or below or equal to the biological cut-off (BCO) otherwise;
- Resistant if the FC is above the clinical or biological cut-off.

When two cut-off values are available, a drug is considered

- Sensitive if the FC is below or equal to the lower cut-off;
- Partially sensitive if the FC is above the lower cut-off and below or equal to the higher cut-off;
- Resistant if the FC is above the higher cut-off.

If paired genotype or phenotype data are available loss of genotypic or phenotypic ARV susceptibility will be analyzed. Loss of susceptibility is defined as being “sensitive” at baseline (for genotype and phenotype) to “partially sensitive” (phenotype) or “resistance possible” (genotype) or “resistant” at post-baseline (for genotype and phenotype). Loss of susceptibility will be tabulated (numbers and proportions) per class and individual ARV. All analyses will be conducted on the Efficacy ITT population, unless specified otherwise, and will be presented by “all patients with available post baseline genotype/phenotypes” and by “protocol defined virologic failure with post baseline genotype/phenotypes”, taking into account either “all genotypes/phenotypes” or only the “genotypes/phenotypes that are on-treatment”.

BCOs and CCOs for the PhenoSense® GT Phenotyping Assay

Class	Drug	Generic name	Cut-off PhenoSense GT™ (V7045/V7145)
NRTI	AZT	Zidovudine	1.9
	3TC	Lamivudine	**3.5**
	ddI	Didanosine	**1.3 – 2.2**
	d4T	Stavudine	**1.7**

	ABC	Abacavir	**4.5 – 6.5**
	FTC	Emtricitabine	3.5
	TDF	Tenofovir	**1.4 – 4.0**
NNRTI	NVP	Nevirapine	4.5
	DLV	Delavirdine	6.2
	EFV	Efavirenz	3.0
	ETR	Etravirine	**2.9 – 10.0**
	RLP	Rilpivirine	2.0
PI	ATV	Atazanavir	**2.2**
	ATV/rtv	Boosted Atazanavir	**5.2**
	DRV/rtv	Boosted Darunavir	**10.0 – 90.0**
	APV/rtv or fAPV/rtv	Boosted Amprenavir or fosamprenavir	**4.0 – 11.0**
	IDV/rtv	Boosted Indinavir	**10.0**
	LPV/rtv	Boosted Lopinavir (Kaletra)	**9.0 – 55.0**
	NFV	Nelfinavir	3.6
	RTV	Ritonavir	2.5
	SQV/rtv	Boosted Saquinavir	**2.3 – 12.0**
	TPV/rtv	Boosted Tipranavir	**2.0 – 8.0**

Clinical cut-offs are shown in bold; cutoffs are based on the PhenosenseGT algorithm version 13

5. SAFETY

For initial D/C/F/TAF, periods ”Baseline to Week 48”, “Week 48 to Week 96” and ”Baseline to Week 96” will be presented in the tables. For the late switchers, periods ”Baseline to Switch” and ”Switch to Week 96” will be presented.

5.1. Adverse Events

5.1.1. Definitions

Reported AE parameters and grades are based on the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events ("**DAIDS AE grading table**"). All AEs will be coded using MedDRA version 19.1.

Events of interest

The EOIs groups include a broad list of terms to identify potential cases. The list of all preferred terms belonging to each AEOI group is provided in Attachment 2. Upon further clinical evaluation additional EOIs might need to be added, and these will be documented in the DPS.

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

Adverse events of interest (AEOI) groups used for the safety analyses are the following:

- Renal AEOI (for PRT)

  Subgroups: laboratory related events,

  clinical events

- Bone AEOI (for fractures)

  Subgroups: Osteomalacia,

Bone Loss/atrophy,

Fracture, possibly osteoporotic,

Fracture other,

Other Bone Events

- Dyslipidaemia AEOI
- Liver AEOI
- Hyperglycemia AEOI
- Pancreas AEOI
- Severe skin AEOI
- Rash AEOI
- Immune reconstitution inflammatory AEOI
- Coronary artery AEOI
- Ocular AEOI (for posterior uveitis)
- Lipodystrophy AEOI
- Cardiac conduction AEOI

  Subgroups: Conduction defects,

  Torsade de pointes/QT prolongation

- Convulsion AEOI

Adverse Drug Reaction (ADR)

ADRs will be presented. A current list of all ADRs is in Attachment 3. In case multiple lists are available (US and EU definitions), ADRs will be tabulated separately per list.

5.1.2. Analysis Methods

A summary will be provided for the following treatment-emergent adverse events:

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

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

Additionally, where applicable, the exposure adjusted incidence rates (EAIR) will be provided. EAIR is calculated as follows:

EAIR=n/∑ti where n is the number of subjects with events, ti is subject's exposure time in patient-years

Summary of events and incidence tabulations for individual adverse events will be provided for AEOI and also for ADRs.

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

The number and percentage of subjects who experienced fracture events (subgroups Fracture, possibly osteoporotic and Fracture other of the Bone AEOI for fractures) will be summarized by treatment group.

Selected safety endpoints will be explored by subgroups defined in section 2.4.2. Details for subgroup analyses of safety endpoints will be provided in the DPS.

5.2. Clinical Laboratory Tests

5.2.1. Definitions

Laboratory parameters of the following lab subcategories will be investigated. The results will be displayed grouping the tests as follows:

- General biochemistry:
  - blood: creatine phosphokinase, alpha-1 acid glycoprotein
  - urine/dipstick: blood, nitrite, leukocyte esterase
- Hematology: hematocrit, hemoglobin, platelet count, red blood cell count (RBC), white blood cell count (WBC), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC).

  Hematology differential counts: basophils, eosinophils, lymphocytes, monocytes, neutrophils (counts and %).

Laboratory Events of Interest

- Pancreatic Parameters: total amylase, lipase
- Hepatic parameters:
  - ALT, AST, alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), bilirubin (all types)
  - Urine/dipstick: bilirubin, urobilinogen
- Lipid parameters: cholesterol, HDL cholesterol (HDL-C) (all types), LDL cholesterol (LDL-C) (all types), TC/HDL, triglycerides; these will be analyzed overall irrespective of fasting status as well as restricted to results from fasting samples separately
- Glucose parameters will be analyzed overall irrespective of fasting status as well as restricted to results from fasting samples separately:
  - blood: glucose
  - urine/dipstick: glucose, ketones
- Renal parameters:

- blood: total protein, creatinine, blood urea nitrogen, uric acid, phosphorus, potassium, sodium, bicarbonate, chloride, albumin
- urine/chemistry: creatinine, sodium, phosphate, glucose, urine albumin, urine protein
- urine/dipstick: glucose, protein

Laboratory toxicities will be derived based on the DAIDS toxicity grading scale (see Protocol).

Note: Local lab results will not be used for the analyses.

5.2.2. Analysis Methods

Descriptive statistics for the actual values and changes from reference will be provided per time point.

Cross-tabulations of the worst toxicity grades through Week 96 versus reference, and cross-tabulations of the worst toxicity grades at Week 96 versus reference will also be provided if applicable. Subject listings of abnormal laboratory values will be provided.

Additionally, the following lipid-related abnormalities according to NCEP categories will be tabulated:

- Triglycerides abnormally high (≥150 mg/dL)
- Total cholesterol abnormally high (≥ 200 mg/dL)
- LDL abnormally high (≥ 100 mg/dL)
- HDL abnormally low (< 40 mg/dL)

Hy's Law Criteria

In addition, an analysis will be performed to identify all subjects meeting Hy's law criteria i.e. subjects showing 3-fold or greater elevations above the ULN of ALT or AST and a concomitant elevation of serum total bilirubin to >2xULN, without a concomitant elevated serum ALP (defined as serum alkaline phosphatase activity less than 2× the upper limit of normal).

5.2.3. Creatinine and Glomerular Filtration

5.2.3.1. Serum Creatinine and Cystatin C

Estimated glomerular filtration rate based on the creatinine clearance will be calculated according to the Cockcroft-Gault formula[1] ($eGFRcr_{CG}$) and the CKD-EPI formula ($eGFRcr_{CKD\text{-}EPI}$) and eGFR based on cystatin C clearance will be calculated according to the CKD-EPI formula ($eGFRcyst_{CKD\text{-}EPI}$).

- eGFRcr according to the Cockcroft-Gault formula (unit: mL/min):

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

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

- eGFRcr and eGFRcyst according to the CKD-EPI formula (unit: mL/min/1.73m^2):

$eGFRcr_{CKD\text{-}EPI}$

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

Scr >0.9 mg/dL	$141 \times (Scr/0.9)^{-1.209} \times 0.993^{age}$
$\underline{eGFRcyst_{CKD\text{-}EPI}}$	
Scyst ≤0.8 mg/L	$133 \times (Scyst/0,8)^{-0.499} \times 0.996^{age}$ [x 0.932 if female]
Scyst >0.8 mg/L	$133 \times (Scyst/0,8)^{-1.328} \times 0.996^{age}$ [x 0.932 if female]

Scr = serum creatinine (mg/dL), Scyst = serum cystatin C (mg/L)

The changes from reference in serum creatinine, $eGFRcr_{CG}$ and $eGFRcr_{CKD\text{-}EPI}$ and $eGFRcyst_{CKD\text{-}EPI}$ at Week 96 will be summarized by treatment arm and using descriptive statistics.

Within-treatment arm comparison versus reference at Week 96 will be assessed using Wilcoxon signed-rank test.

Stages of GFR at reference versus the minimum post-reference GFR value and the last available value will be summarized by count and percent of subjects. Kidney disease stages are defined as follows: 1 (Normal): GFR ≥ 90; 2 (Mild): GFR 60-89; 3 (Moderate): GFR 30-59; 4 (Severe): GFR 15-29; 5 (Renal Failure): GFR <15 mL/min).

In addition to the above, the number and proportion of subjects with a >25%, >50% and >75% decrease from reference will be tabulated.

5.2.3.2. Proximal Renal Tubular Function

Proteinuria by Quantitative Assessment

Total urine protein, total urine albumin, urine protein to creatinine ratio (UPCR) and urine albumin to creatinine ratio (UACR) will be summarized by treatment arm and visit using descriptive statistics.

The number and proportion of subjects with UACR and UPCR results in the following categories at Week 96 will be tabulated:

- UACR: < 30, ≥ 30 to 300, >300 mg/g
- UPCR: < 200 mg/g versus ≥ 200 mg/g

Median (Q1, Q3) percent change from reference over time will be plotted by treatment group.

The evolution over time of total urine protein and total urine albumin will also be presented.

Proteinuria by Urinalysis (Dipstick)

Treatment-emergent proteinuria by urinalysis (dipstick) through Week 96 will be summarized by treatment group. Cross-tabulation of grades at Week 96 versus reference will also be presented.

Other Renal Biomarkers

Selected renal biomarkers retinol binding protein (RBP) and beta-2-microglobulin, RBP to creatinine ratio and beta-2-microglobulin to creatinine ratio will be summarized by treatment arm and visit using descriptive statistics. The proportions of subjects with beta-2-microglobulin to creatinine ratio <=300 mg/g and >300 mg/g will be tabulated.

The number and proportion of subjects with retinal binding protein to creatinine ratio results in the following categories at Week 96 will be tabulated:

- < 50 years of age (at the time of lab assessment): < 130 mcg/g creatinine, ≥ 130 mcg/g creatinine

- ≥ 50 years of age (at the time of lab assessment): < 172 mcg/g creatinine, ≥ 172 mcg/g creatinine

Phosphate excretion

Other renal biomarkers include urine fractional excretion of phosphate (FEPO4) that will be summarized by treatment arm and visit using descriptive statistics.

Urine fractional excretion of Phosphate (FEPO4) will be calculated as follows:

- Based on unadjusted serum creatinine:

  FEPO4 (%) = (SCr × UPO4) / (SPO4 × UCr) × 100 (%)

The reference, post-reference, and change from reference in FEPO4 will be summarized by treatment arm and visit using descriptive statistics. Median (Q1, Q3) change from baseline in FEPO4 over time will be plotted by treatment group.

Subclinical renal proximal tubulopathy

Potential Markers of Renal Proximal Tubulopathy are:

1. Increase in serum creatinine ≥ 0.40 mg/dL from reference.
2. Confirmed ≥ 2 grade level increase from reference in graded proteinuria
3. Confirmed ≥ 1 grade level increase from reference in graded hypophosphatemia
4. Confirmed ≥ 1 grade level increase from reference in graded glycosuria concurrent with serum glucose <=100 mg/dL (normoglycemic glycosuria)

A confirmed laboratory abnormality is defined as an abnormality observed at 2 consecutive post-reference measurements or an abnormality observed at 1 measurement followed by study drug discontinuation

A subclinical renal proximal tubulopathy will be defined as confirmed abnormalities in any 2 out of the 4 renal parameters (serum creatinine and one or more of the 3 other markers of tubular dysfunction).

5.3. Vital Signs and Physical Examination Findings

5.3.1. Definitions

The following vital signs parameters will be analyzed:

– pulse (bpm)

– systolic blood pressure, SBP (mmHg)

– diastolic blood pressure, DBP (mmHg)

– weight (kg)

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

Abnormality code	Pulse (bpm)	DBP (mmHg)	SBP (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

Abnormality code	Pulse (bpm)	DBP (mmHg)	SBP (mmHg)
Abnormally high	≥ 120	-	-

In determining abnormalities, the following rules are applied:

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

Definition treatment-emergent:

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

5.3.2. Analysis methods

Descriptive statistics for the actual values and changes from reference per time point will be presented. For weight, comparative treatment phase and single arm treatment phase will be presented for Initial D/C/F/TAF group; data from baseline up to the switch, and from the switch up to Week 96 will be presented for the switch group.

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

Abnormal physical examination findings will be listed.

5.4. Bone Investigations

5.4.1. Definitions

The following bone formation markers will be analyzed:

– Serum total alkaline phosphatase (ALP)

– Serum type 1 procollagen N-terminal (P1NP)

Bone resorption markers:

– Urinary or serum collagen type 1 cross-linked C-telopeptide (CTX)

Other:

– parathyroid hormone (PTH)

– 25-hydroxy vitamin D (25-OH VitD)

DXA scan of spine and hip (data of other regions, e.g. femoral neck may also be analyzed if available):

– BMD values

– BMD T-scores

The BMD status will be derived based on T-scores using the following categories:

	Osteoporosis	Osteopenia	Normal
T-score	< -2.5	-2.5 to < -1	≥ -1

5.4.2. Analysis methods

Bone Biomarker:

Descriptive statistics for the actual values, change and percent changes from reference per time point will be presented for each bone biomarkers.

DXA scan:

Descriptive statistics for the actual values, change and percent changes from reference per time point will be presented for BMD parameters (including T- and Z-scores). Within-treatment arm comparison versus reference at Week 96 will be assessed using paired t-test.

The proportions of subjects with at least 3% change (decrease and increase separately) from reference in BMD will be presented at Week 96. Percent change from reference will also be tabulated based on thresholds; 5% and 7% (hip only).

BMD status will be tabulated (n, %) separately per time point, based on the T-score categories. Cross-tabulations for the BMD status at Week 96 versus reference will be produced.

REFERENCES

1. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16:31-41.
2. Guidance for Industry. Antiretroviral Drugs Using Plasma HIV RNA Measurements Clinical Considerations for Accelerated and Traditional Approval. October 2002.
3. Wensing AM, Calvez V, Günthard HF, et al. 2017 update of the drug resistance mutations in HIV-1. Top Antivir Med Dec2016/Jan2017; 24(4):132-141

ATTACHMENTS

ATTACHMENT 1

PREDEFINED MAJOR PROTOCOL DEVIATIONS-based on the current list

The predefined major protocol deviations of this study are described in the Protocol Deviation Criteria document. The deviations that are considered to have an (possible) impact on efficacy are a subset of the predefined major protocol deviations and are indicated with 'Yes' below (column 'Exclude from Per Protocol Analysis') and if such deviations are reported for a subject, the subject will be excluded from the PP analysis.

In addition to the below table, the following subjects will also be excluded from the per-protocol analysis set:

- Subjects with treatment adherence based on drug accountability derivation ii for the active ARVs (worst D/C/F/TAF adherence between baseline to switch and switch to Week 96 for the Initial D/C/F/TAF treatment group and worst adherence across DRV/COBI FTC/TDF, and D/C/F/TAF for the Late Switch to D/C/F/TAF treatment group) <65%. For the purpose of the per-protocol analysis set only, subjects with missing treatment adherence will be assumed to be above 65%.
- Subjects with no post-baseline viral load measurement (e.g., discontinued within 2 weeks).

Sequence No.	Description	Protocol Deviation coded term (DVDECOD)	Exclude from PP
1	Screening plasma HIV-1 RNA level < 1,000 copies/mL	Entered but did not satisfy criteria	Yes
2	The subject uses disallowed concomitant therapy specified in the protocol.	Entered but did not satisfy criteria	Yes
3	The subject has any known allergies to the excipients of the D/C/F/TAF, or DRV/COBI, or TDF/FTC tablets, but the subject was randomized	Entered but did not satisfy criteria	Yes
4	The dose of Investigational treatment arm (D/C/F/TAF tablet) or the active control arm was temporarily not according to protocol for more than 4 consecutive weeks.	Received wrong treatment or incorrect dose (missed dose or extra dose)	Based on >4 weeks period. In that case classified as major and excluded from PP
5	The intake of Investigational treatment arm (D/C/F/TAF tablet) or the active control arm was interrupted for toxicity reasons for more than 4 consecutive weeks.	Received wrong treatment or incorrect dose (missed dose or extra dose)	
6	The intake of Investigational treatment arm (D/C/F/TAF tablet) or the active control arm was interrupted for non - toxicity reasons for more than 4 consecutive weeks, or cumulatively for more than 8 weeks.	Received wrong treatment or incorrect dose (missed dose or extra dose	
7	The subject takes disallowed medication as defined per protocol.	Received a disallowed concomitant treatment	Yes (adjudication based on drug/class and duration).
8	Subjects not showing genotypic susceptibility to DRV, FTC, TFV	Entered but did not satisfy criteria	Yes
9	The subject missed two or more consecutive planned visits in the trial	Other	Yes

Sequence No.	Description	Protocol Deviation coded term (DVDECOD)	Exclude from PP
10	Misallocation of Medkits was observed during Dosage and administration of study drug and subject treated differently than what they were randomized to for more than 4 weeks	Other	Yes
11	After achieving confirmed (consecutive) HIV-1 RNA <50 copies/mL prior to Week 96 and scheduled Week 96 achieving HIV-1 RNA ≥ 50 copies/mL or >1$\log_{10}$ increase in HIV-1 RNA from the nadir at scheduled Week 96, but no retest in Week 96 window (90-102 weeks)	Other	Yes
12	Subject missed the Week 96 visit.	Other	Yes

ATTACHMENT 2

Adverse Events of Interest: List of Preferred Terms

AEOI	AEDECOD (MedDRA v19.1)
Rash AEOI	Acrodynia, Drug Eruption, Generalised erythema, Lupus miliaris disseminatus facei, Mucocutaneous rash, Rash, Rash erythematous, Rash generalised, Rash macular, Rash maculo-papular, Rash maculovesicular, Rash morbilliform, Rash papular, Rash pruritic, Rash rubelliform, Rash scarlatiniform, Red man syndrome, Rash vesicular, Rash follicular, Rash papulosquamous, Dermatitis, Dermatitis acneiform, Dermatitis allergic , Dermatitis herpetiformis , Skin necrosis, Skin reaction
Liver AEOI/Cholestasis and jaundice of hepatic origin	Bilirubin excretion disorder, Cholaemia, Cholestasis, Cholestatic liver injury, Cholestatic pruritus, Drug-induced liver injury, Hepatitis cholestatic, Hyperbilirubinaemia, Icterus index increased, Jaundice, Jaundice cholestatic, Jaundice hepatocellular, Mixed liver injury, Ocular icterus, Parenteral nutrition associated liver disease, Deficiency of bile secretion, Yellow skin

AEOI	AEDECOD (MedDRA v19.1)
Liver AEOI/Hepatic failure, fibrosis and cirrhosis and other liver damage related conditions	Acute hepatic failure, Acute on chronic liver failure, Acute yellow liver atrophy, Ascites, Asterixis, Bacterascites, Biliary cirrhosis, Biliary cirrhosis primary, Biliary fibrosis, Cholestatic liver injury, Chronic hepatic failure, Coma hepatic, Cryptogenic cirrhosis, Diabetic hepatopathy, Drug-induced liver injury, Duodenal varices, Gallbladder varices, Gastric variceal injection, Gastric variceal ligation, Gastric varices, Gastric varices haemorrhage, Hepatectomy, Hepatic atrophy, Hepatic calcification, Hepatic cirrhosis, Hepatic encephalopathy, Hepatic encephalopathy prophylaxis, Hepatic failure, Hepatic fibrosis, Hepatic hydrothorax, Hepatic infiltration eosinophilic, Hepatic lesion, Hepatic necrosis, Hepatic steato-fibrosis, Hepatic steatosis, Hepatitis fulminant, Hepatobiliary disease, Hepatocellular foamy cell syndrome, Hepatocellular injury, Hepatopulmonary syndrome, Hepatorenal failure, Hepatorenal syndrome, Hepatotoxicity, Intestinal varices, Liver and small intestine transplant, Liver and small intestine transplant, Liver dialysis, Liver disorder, Liver injury, Liver operation, Liver transplant, Lupoid hepatic cirrhosis, Minimal hepatic encephalopathy, Mixed liver injury, Nodular regenerative hyperplasia, Non-alcoholic fatty liver, Non-alcoholic steatohepatitis, Non-cirrhotic portal hypertension, Oedema due to hepatic disease, Oesophageal varices haemorrhage, Peripancreatic varices, Portal fibrosis, Portal hypertensive enteropathy, Portal hypertensive gastropathy, Portal vein cavernous transformation, Portal vein dilatation, Portopulmonary hypertension, Renal and liver transplant, Retrograde portal vein flow, Reye's syndrome, Reynold's syndrome, Splenic varices, Splenic varices haemorrhage, Steatohepatitis, Subacute hepatic failure, Varices oesophageal, Varicose veins of abdominal wall, Anorectal varices, Anorectal varices haemorrhage, Intrahepatic portal hepatic venous fistula, Peritoneovenous shunt, Portal shunt, Portal shunt procedure, Small-for-size liver syndrome, Spider naevus, Splenorenal shunt, Splenorenal shunt procedure, Spontaneous intrahepatic portosystemic venous shunt, Stomal varices, Portal tract inflammation

Liver AEOI / Liver-related investigations, signs and symptoms	Alanine aminotransferase abnormal, Alanine aminotransferase increased, Ammonia abnormal, Ammonia increased, Ascites, Aspartate aminotransferase abnormal, Aspartate aminotransferase increased, Bacterascites, Bile output abnormal, Bile output decreased, Biliary ascites, Bilirubin conjugated abnormal, Bilirubin conjugated increased, Bilirubin urine present, Biopsy liver abnormal, Blood bilirubin abnormal, Blood bilirubin increased, Blood bilirubin unconjugated increased, Bromosulphthalein test abnormal, Child-Pugh-Turcotte score abnormal, Child-Pugh-Turcotte score increased, Computerised tomogram liver, Foetor hepaticus, Galactose elimination capacity test abnormal, Galactose elimination capacity test decreased, Gamma-glutamyltransferase abnormal, Gamma-glutamyltransferase increased, Guanase increased, Hepaplastin abnormal, Hepaplastin decreased, Hepatic artery flow decreased, Hepatic congestion, Hepatic enzyme abnormal, Hepatic enzyme decreased, Hepatic enzyme increased, Hepatic function abnormal, Hepatic hydrothorax, Hepatic hypertrophy, Hepatic mass, Hepatic pain, Hepatic sequestration, Hepatic vascular resistance increased, Hepatobiliary scan abnormal, Hepatomegaly, Hepatosplenomegaly, Hyperammonaemia, Hyperbilirubinaemia, Hypercholia, Hypertransaminasaemia, Kayser-Fleischer ring, Liver function test abnormal, Liver induration, Liver palpable, Liver scan abnormal, Liver tenderness, Mitochondrial aspartate aminotransferase increased, Molar ratio of total branched-chain amino acid to tyrosine, Oedema due to hepatic disease, Perihepatic discomfort, Retrograde portal vein flow, Total bile acids increased, Transaminases abnormal, Transaminases increased, Ultrasound liver abnormal, Urine bilirubin increased, X-ray hepatobiliary abnormal, 5'nucleotidase increased, Blood alkaline phosphatase abnormal, Blood alkaline phosphatase increased, Blood cholinesterase abnormal, Blood cholinesterase decreased, Deficiency of bile secretion, Glutamate dehydrogenase increased, Haemorrhagic ascites, Hepatic fibrosis marker abnormal, Hepatic fibrosis marker increased, Hypoalbuminaemia, Leucine aminopeptidase increased, Liver function test decreased, Liver function test increased, Liver iron concentration abnormal, Liver iron concentration increased, Model for end stage liver disease score abnormal, Model for end stage liver disease score increased, Periportal oedema, Peritoneal fluid protein abnormal, Peritoneal fluid protein decreased, Peritoneal fluid protein increased, Pneumobilia, Portal vein flow decreased, Portal vein pressure increased, Retinol binding protein decreased, Urobilinogen urine decreased, Urobilinogen urine increased

AEOI	AEDECOD (MedDRA v19.1)
Liver AEOI / Hepatitis, non infectious	Acute graft versus host disease in liver, Allergic hepatitis, Autoimmune hepatitis, Chronic graft versus host disease in liver, Chronic hepatitis, Graft versus host disease in liver, Hepatitis, Hepatitis acute, Hepatitis cholestatic, Hepatitis chronic active, Hepatitis chronic persistent, Hepatitis fulminant, Hepatitis toxic, Ischaemic hepatitis, Lupus hepatitis, Non-alcoholic steatohepatitis, Radiation hepatitis, Steatohepatitis, Granulomatous liver disease, Liver sarcoidosis, Portal tract inflammation
Hyperglycaemia AEOI	Acquired lipoatrophic diabetes, Blood 1,5-anhydroglucitol decreased, Blood glucose increased, Diabetes complicating pregnancy, Diabetes mellitus, Diabetes mellitus inadequate control, Diabetes with hyperosmolarity, Diabetic arteritis, Diabetic coma, Diabetic hepatopathy, Diabetic hyperglycaemic coma, Diabetic hyperosmolar coma, Diabetic ketoacidosis, Diabetic ketoacidotic hyperglycaemic coma, Diabetic metabolic decompensation, Fructosamine increased, Fulminant type 1 diabetes mellitus, Gestational diabetes, Glucose tolerance impaired, Glucose tolerance impaired in pregnancy, Glucose urine present, Glycosuria, Glycosuria during pregnancy, Glycosylated haemoglobin increased, Hyperglycaemia, Hyperglycaemic seizure, Hyperglycaemic unconsciousness, Impaired fasting glucose, Insulin resistance, Insulin resistance syndrome, Insulin resistant diabetes, Insulin-requiring type 2 diabetes mellitus, Ketoacidosis, Ketonuria, Ketosis, Latent autoimmune diabetes in adults, Metabolic syndrome, Monogenic diabetes, Neonatal diabetes mellitus, Pancreatogenous diabetes, Type 1 diabetes mellitus, Type 2 diabetes mellitus, Type 3 diabetes mellitus, Urine ketone body present, Hyperosmolar hyperglycaemic state

AEOI	AEDECOD (MedDRA v19.1)
Dyslipidaemia AEOI	Acquired lipoatrophic diabetes, Acquired mixed hyperlipidaemia, Apolipoprotein B/Apolipoprotein A-1 ratio increased, Autoimmune hyperlipidaemia, Blood cholesterol abnormal, Blood cholesterol decreased, Blood cholesterol esterase increased, Blood cholesterol increased, Blood triglycerides abnormal, Blood triglycerides decreased, Blood triglycerides increased, Diabetic dyslipidaemia, Dyslipidaemia, Familial hypertriglyceridaemia, Fat overload syndrome, High density lipoprotein abnormal, High density lipoprotein decreased, High density lipoprotein increased, Hypercholesterolaemia, Hyperlipidaemia, Hypertriglyceridaemia, Hypo HDL cholesterolaemia, Hypotriglyceridaemia, Intermediate density lipoprotein decreased, Intermediate density lipoprotein increased, LDL/HDL ratio decreased, LDL/HDL ratio increased, Lecithin-cholesterol acyltransferase deficiency, Lipid metabolism disorder, Lipids abnormal, Lipids decreased, Lipids increased, Lipoprotein (a) abnormal, Lipoprotein (a) decreased, Lipoprotein (a) increased, Low density lipoprotein abnormal, Low density lipoprotein decreased, Low density lipoprotein increased, Non-high-density lipoprotein cholesterol decreased, Non-high-density lipoprotein cholesterol increased, Primary hypercholesterolaemia, Remnant hyperlipidaemia, Remnant-like lipoprotein particles increased, Total cholesterol/HDL ratio abnormal, Total cholesterol/HDL ratio decreased, Total cholesterol/HDL ratio increased, Type I hyperlipidaemia, Type II hyperlipidaemia, Type IIa hyperlipidaemia, Type IIb hyperlipidaemia, Type III hyperlipidaemia, Type IV hyperlipidaemia, Type V hyperlipidaemia, Very low density lipoprotein abnormal, Very low density lipoprotein decreased, Very low density lipoprotein increased
Lipodystrophy AEOI	Body fat disorder, Facial wasting, Fat redistribution, Fat tissue decreased, HIV lipodystrophy, Lipoatrophy, Lipodystrophy acquired, Lipohypertrophy, Partial lipodystrophy

AEOI	AEDECOD (MedDRA v19.1)
Immune reconstitution inflammatory AEOI	Immune reconstitution inflammatory syndrome, Mycobacterium avium complex immune restoration disease, Immune Reconstitution Inflammatory Syndrome associated tuberculosis, Immune Reconstitution Inflammatory Syndrome associated Kaposi's sarcoma,

Coronary artery AEOI	Acute coronary syndrome, Acute myocardial infarction, Angina unstable, Blood creatine phosphokinase MB abnormal, Blood creatine phosphokinase MB increased, Coronary artery embolism, Coronary artery occlusion, Coronary artery reocclusion, Coronary artery thrombosis, Coronary bypass thrombosis, Coronary vascular graft occlusion, Kounis syndrome, Myocardial infarction, Myocardial necrosis, Myocardial reperfusion injury, Myocardial stunning, Papillary muscle infarction, Post procedural myocardial infarction, Postinfarction angina, Silent myocardial infarction, Troponin I increased, Troponin increased, Troponin T increased, Blood creatine phosphokinase abnormal, Blood creatine phosphokinase increased, Cardiac ventricular scarring, ECG electrically inactive area, ECG signs of myocardial infarction, Electrocardiogram Q wave abnormal, Electrocardiogram ST segment abnormal, Electrocardiogram ST segment elevation, Electrocardiogram ST-T segment elevation, Infarction, Myocardial necrosis marker increased, Scan myocardial perfusion abnormal, Vascular graft occlusion, Vascular stent occlusion, Vascular stent thrombosis, Angina pectoris, Angina unstable, Anginal equivalent, Arteriosclerosis coronary artery, Arteriospasm coronary, Coronary angioplasty, Coronary arterial stent insertion, Coronary artery bypass, Coronary artery disease, Coronary artery dissection, Coronary artery insufficiency, Coronary artery restenosis, Coronary artery stenosis, Coronary brachytherapy, Coronary bypass stenosis, Coronary endarterectomy, Coronary no-reflow phenomenon, Coronary ostial stenosis, Coronary revascularisation, Coronary vascular graft stenosis, Dissecting coronary artery aneurysm, ECG signs of myocardial ischaemia, External counterpulsation, Haemorrhage coronary artery, Ischaemic cardiomyopathy, Ischaemic mitral regurgitation, Microvascular coronary artery disease, Myocardial ischaemia, Percutaneous coronary intervention, Prinzmetal angina, Stress cardiomyopathy, Subclavian coronary steal syndrome, Subendocardial ischaemia, Arteriogram coronary abnormal, Cardiac stress test abnormal, Computerised tomogram coronary artery abnormal, Computerised tomogram coronary artery abnormal, Electrocardiogram ST segment depression, Electrocardiogram ST-T segment abnormal, Electrocardiogram ST-T segment depression, Electrocardiogram T wave abnormal, Electrocardiogram T wave inversion, Exercise electrocardiogram abnormal, Exercise test abnormal, Post angioplasty restenosis, Stress echocardiogram abnormal, Vascular stent restenosis, Vascular stent stenosis

AEOI	AEDECOD (MedDRA v19.1)
Severe skin AEOI	Acute generalised exanthematous pustulosis, Cutaneous vasculitis, Dermatitis bullous, Dermatitis exfoliative, Dermatitis exfoliative generalised, Drug rash with eosinophilia and systemic symptoms, Epidermal necrosis, Erythema multiforme, Exfoliative rash, Oculomucocutaneous syndrome, Skin necrosis, Stevens-Johnson syndrome, Toxic epidermal necrolysis, Toxic skin eruption, Acquired epidermolysis bullosa, Blister, Blister rupture, Bullous impetigo, Conjunctivitis, Corneal exfoliation, Drug eruption, Epidermolysis, Epidermolysis bullosa, Fixed drug eruption, Genital ulceration, HLA-B*1502 assay positive, HLA-B*5801 assay positive, Hypopharyngeal synechiae, Lip exfoliation, Mouth ulceration, Mucocutaneous ulceration, Mucosa vesicle, Mucosal erosion, Mucosal exfoliation, Mucosal necrosis, Mucosal ulceration, Nikolsky's sign, Noninfective conjunctivitis, Oral mucosal blistering, Oral mucosal exfoliation, Oral papule, Oropharyngeal blistering, Pemphigoid, Pemphigus, Penile exfoliation, Skin erosion, Skin exfoliation, Staphylococcal scalded skin syndrome, Stomatitis, Tongue exfoliation, Vaginal exfoliation, Vaginal ulceration, Vulval ulceration, Vulvovaginal rash, Vulvovaginal ulceration
Cardiac conduction AEOI/Conduction defects	Accessory cardiac pathway, Adams-Stokes syndrome, Agonal rhythm, Atrial conduction time prolongation, Atrioventricular block, Atrioventricular block complete, Atrioventricular block first degree, Atrioventricular block second degree, Atrioventricular conduction time shortened, Atrioventricular dissociation, Bifascicular block, Brugada syndrome, Bundle branch block, Bundle branch block bilateral, Bundle branch block left, Bundle branch block right, Conduction disorder, Defect conduction intraventricular, Electrocardiogram delta waves abnormal, Electrocardiogram PQ interval prolonged, Electrocardiogram PQ interval prolonged, Electrocardiogram PR prolongation, Electrocardiogram PR shortened, Electrocardiogram QRS complex prolonged, Electrocardiogram QT prolonged, Electrocardiogram repolarisation abnormality, Lenegre's disease, Long QT syndrome, Paroxysmal atrioventricular block, Sinoatrial block, Trifascicular block, Ventricular dyssynchrony, Wolff-Parkinson-White syndrome

AEOI	AEDECOD (MedDRA v19.1)
Cardiac conduction AEOI / Torsade de pointes/QT prolongation	Electrocardiogram QT interval abnormal, Electrocardiogram QT prolonged, Long QT syndrome, Long QT syndrome congenital, Torsade de pointes, Ventricular tachycardia
Pancreas AEOI	Amylase abnormal, Hyperlipasaemia, Pancreatic enzymes abnormality, Amylase increased, Lipase abnormal, Pancreatic enzymes abnormal, Blood trypsin increased, Lipase increased, Pancreatic enzymes increased, Hyperamylasaemia, Lipase urine increased, Cullen's sign, Grey Turner's sign, Haemorrhagic necrotic pancreatitis, Hereditary pancreatitis, Ischaemic pancreatitis, Oedematous pancreatitis, Pancreatic abscess, Pancreatic haemorrhage, Pancreatic necrosis, Pancreatic phlegmon, Pancreatic pseudocyst, Pancreatic pseudocyst drainage, Pancreatitis, Pancreatitis acute, Pancreatitis haemorrhagic, Pancreatitis necrotising, Pancreatitis relapsing, Pancreatorenal syndrome

AEOI	AEDECOD (MedDRA v19.1)
Convulsions AEOI	Acquired epileptic aphasia, Acute encephalitis with refractory, repetitive partial seizures, Alcoholic seizure, Atonic seizures, Atypical benign partial epilepsy, Automatism epileptic, Autonomic seizure, Baltic myoclonic epilepsy, Benign familial neonatal convulsions, Benign rolandic epilepsy, Biotinidase deficiency, Change in seizure presentation, Clonic convulsion, Complex partial seizures, Convulsion in childhood, Convulsion neonatal, Convulsions local, Convulsive threshold lowered, Deja vu, Double cortex syndrome, Dreamy state, Drug withdrawal convulsions, Early infantile epileptic encephalopathy with burst-suppression, Eclampsia, Epilepsy, Epileptic aura, Epileptic psychosis, Febrile convulsion, Frontal lobe epilepsy, Generalised non-convulsive epilepsy, Generalised tonic-clonic seizure, Glucose transporter type 1 deficiency syndrome, Hemimegalencephaly, Hyperglycaemic seizure, Hypocalcaemic seizure, Hypoglycaemic seizure, Hyponatraemic seizure, Idiopathic generalised epilepsy, Infantile spasms, Juvenile myoclonic epilepsy, Lafora's myoclonic epilepsy, Lennox-Gastaut syndrome, Migraine-triggered seizure, Molybdenum cofactor deficiency, Myoclonic epilepsy, Myoclonic epilepsy and ragged-red fibres, Partial seizures, Partial seizures with secondary generalisation, Petit mal epilepsy, Polymicrogyria, Post stroke epilepsy, Post stroke seizure, Postictal headache, Postictal paralysis, Postictal psychosis, Postictal state, Post-traumatic epilepsy, Psychomotor seizures, Focal dyscognitive seizures, Schizencephaly, Seizure, Seizure anoxic, Seizure cluster, Seizure like phenomena, Severe myoclonic epilepsy of infancy, Simple partial seizures, Status epilepticus, Sudden unexplained death in epilepsy, Temporal lobe epilepsy, Tonic clonic movements, Tonic convulsion, Tonic posturing, Topectomy, Uncinate fits

AEOI	AEDECOD (MedDRA v19.1)
Ocular AEOI (for Posterior Uveitis)	Acute zonal occult outer retinopathy, Anterior chamber cell, Anterior chamber fibrin, Anterior chamber flare, Anterior chamber inflammation, Aqueous fibrin, Autoimmune retinopathy, Autoimmune uveitis, Behcet's syndrome, Birdshot chorioretinopathy, Blau syndrome, Blindness, Blindness transient, Blindness unilateral, Chemical iritis, Chorioretinitis, Chorioretinopathy, Choroiditis, Ciliary hyperaemia, Cystoid macular oedema, Cytomegalovirus chorioretinitis, Eales' disease, Endophthalmitis, Exudative retinopathy, Eye inflammation, Fuchs' syndrome, Glaucomatocyclitic crises, Iridocyclitis, Iritis, Macular oedema, Non-infectious endophthalmitis, Noninfective chorioretinitis, Noninfective retinitis, Ocular toxicity, Ocular vasculitis, Optic discs blurred, Panophthalmitis, Photophobia, Photopsia, Retinal exudates, Retinal oedema, Retinal pigment epitheliopathy, Retinal toxicity, Retinal perivascular sheathing, Retinal vasculitis, Retinitis, Subretinal fluid, Sudden visual loss, Susac's syndrome, Sympathetic ophthalmia, Traumatic iritis, Tubulointerstitial nephritis and uveitis syndrome, Uveitis, Uveitis-glaucoma-hyphaema syndrome, Vision blurred, Visual acuity reduced, Visual field defect, Visual impairment, Vitreal cells, Vitreous floaters, Vitreous opacities, Vitritis, Vogt-Koyanagi-Harada syndrome
Renal AEOI (for PRT) / laboratory related events	Aminoaciduria, Beta-N-acetyl D glucosaminidase increased, Hyperphosphaturia, Renal glycosuria, Acquired aminoaciduria, Hyperchloraemia , Protein urine, Protein urine present, Proteinuria, Urine phosphorus abnormal, Beta-N-acetyl D glucosaminidase abnormal, Blood chloride increased, Blood phosphorus decreased, Blood potassium decreased, Blood uric acid abnormal, Blood uric acid decreased, Glucose urine present, Glycosuria, Hyperuricosuria, Hypokalaemia, Hypophosphataemia, Amino acid level abnormal, Amino acid level increased, Urine phosphorus increased, Urine uric acid abnormal, Urine uric acid increased
Renal AEOI (for PRT) / clinical events	Polydipsia, Polyuria, Nephropathy toxic, Renal tubular disorder, Chronic kidney disease, Fanconi syndrome, Fanconi syndrome acquired, Renal tubular acidosis

AEOI	AEDECOD (MedDRA v19.1)
Bone AEOI (for fractures) / Osteomalacia	Hypophosphataemic rickets, Osteomalacia, Chronic kidney disease-mineral and bone disorder, Renal rickets, Rickets
Bone AEOI (for fractures) / Bone Loss/atrophy	Bone atrophy, Bone decalcification, Bone density decreased, Bone formation decreased, Bone loss, Craniotabes, High turnover osteopathy, Hungry bone syndrome, Osteodystrophy, Osteolysis, Osteoporosis circumscripta cranii, Osteopenia, Senile osteoporosis , Osteoporosis, Cementoplasty
Bone AEOI (for fractures) / Fracture, possibly osteoporotic	Femoral neck fracture, Hip fracture, Lumbar vertebral fracture, Osteoporotic fracture, Spinal compression fracture, Spinal fracture, Thoracic vertebral fracture
Bone AEOI (for fractures) / Fracture other	Acetabulum fracture, Ankle fracture, Atypical femur fracture, Atypical fracture, Avulsion fracture, Cervical vertebral fracture, Chance fracture, Clavicle fracture, Closed fracture manipulation, Comminuted fracture, Complicated fracture, Compression fracture, Elevation skull fracture, Epiphyseal fracture, External fixation of fracture, Femur fracture, Fibula fracture, Foot fracture, Forearm fracture, Fracture, Fracture delayed union, Fracture displacement, Fracture malunion, Fracture nonunion, Fracture pain, Fracture reduction, Fracture treatment, Fractured ischium, Fractured sacrum, Fractured coccyx, Greenstick fracture, Hand fracture, Humerus fracture, Ilium fracture, Internal fixation of fracture, Limb fracture, Lower limb fracture, Multiple fractures, Open reduction of fracture, Open reduction of spinal fracture, Osteochondral fracture, Osteosynthesis, Patella fracture, Pathological fracture, Pelvic fracture, Periprosthetic fracture, Pubis fracture, Radius fracture, Rib fracture, Sacroiliac fracture, Scapula fracture, Skull fracture, Skull fractured base, Spinal fusion fracture, Sternal fracture, Stress fracture, Tibia fracture, Torus fracture, Traumatic fracture, Ulna fracture, Upper limb fracture, Wrist fracture

AEOI	AEDECOD (MedDRA v19.1)
Bone AEOI (for fractures) / Other Bone Events	Bone density abnormal, Bone disorder, Bone erosion, Bone lesion, Bone formation test abnormal, Bone fragmentation, Bone metabolism disorder, Bone pain, Bone resorption test abnormal, Bone scan abnormal, Bone development abnormal, Bone swelling, Epiphysiolysis, Nuclear magnetic resonance imaging spinal abnormal, Osteonecrosis, Osteonecrosis of jaw, Secondary sequestrum, Skeletal injury, Skeletal survey abnormal, Skull X-ray abnormal, Spinal X-ray abnormal, Vertebral lesion, Vertebral wedging, X-ray limb abnormal, X-ray of pelvis and hip abnormal, Bone densitometry

ATTACHMENT 3

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

Adverse Drug Reaction System Organ Class	Adverse Drug Reaction	Adverse Event Preferred Term
GASTROINTESTINAL DISORDERS	ABDOMINAL DISTENSION	ABDOMINAL DISTENSION
	ABDOMINAL PAIN	ABDOMINAL PAIN
		ABDOMINAL PAIN LOWER
		ABDOMINAL PAIN UPPER
	DIARRHOEA	DIARRHOEA
		FREQUENT BOWEL MOVEMENTS
	DYSPEPSIA	DYSPEPSIA
	FLATULENCE	FLATULENCE
	NAUSEA	NAUSEA
	PANCREATITIS ACUTE	PANCREATITIS
		PANCREATITIS ACUTE
	VOMITING	VOMITING
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	ASTHENIA	ASTHENIA
	FATIGUE	FATIGUE
HEPATOBILIARY DISORDERS	ACUTE HEPATITIS	HEPATITIS
		HEPATITIS ACUTE
		HEPATOTOXICITY
IMMUNE SYSTEM DISORDERS	(DRUG) HYPERSENSITIVITY	DRUG HYPERSENSITIVITY
		HYPERSENSITIVITY

Adverse Drug Reaction System Organ Class	Adverse Drug Reaction	Adverse Event Preferred Term
	IMMUNE RECONSTITUTION SYNDROME	IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME
		IMMUNE RECONSTITUTION SYNDROME
METABOLISM AND NUTRITION DISORDERS	ANOREXIA	DECREASED APPETITE
	DIABETES MELLITUS	DIABETES MELLITUS
		DIABETES MELLITUS INADEQUATE CONTROL
		TYPE 2 DIABETES MELLITUS
		GLUCOSE TOLERANCE IMPAIRED
	LIPODYSTROPHY	FACIAL WASTING
		FAT REDISTRIBUTION
		FAT TISSUE INCREASED
		LIPOATROPHY
		LIPODYSTROPHY ACQUIRED
		LIPOHYPERTROPHY
		PARTIAL LIPODYSTROPHY
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	MYALGIA	MYALGIA
	OSTEONECROSIS	OSTEONECROSIS
NERVOUS SYSTEM DISORDERS	HEADACHE	HEADACHE
PSYCHIATRIC DISORDERS	ABNORMAL DREAMS	ABNORMAL DREAMS
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	GYNAECOMASTIA	GYNAECOMASTIA
		HYPERTROPHY BREAST
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	ANGIOEDEMA	ALLERGIC OEDEMA
		ANGIOEDEMA

Adverse Drug Reaction System Organ Class	Adverse Drug Reaction	Adverse Event Preferred Term
		CIRCUMORAL OEDEMA
		CONJUNCTIVAL OEDEMA
		CORNEAL OEDEMA
		EPIGLOTTIC OEDEMA
		EYE OEDEMA
		EYE SWELLING
		EYELID OEDEMA
		FACE OEDEMA
		GINGIVAL OEDEMA
		GINGIVAL SWELLING
		GLEICH'S SYNDROME
		HEREDITARY ANGIOEDEMA
		LARYNGEAL OEDEMA
		LARYNGOTRACHEAL OEDEMA
		LIP OEDEMA
		LIP SWELLING
		OCULORESPIRATORY SYNDROME
		OEDEMA MOUTH
		OROPHARYNGEAL SWELLING
		PALATAL OEDEMA
		PERIORBITAL OEDEMA
		PHARYNGEAL OEDEMA
		SCLERAL OEDEMA
		SMALL BOWEL ANGIOEDEMA
		SWELLING FACE
		SWOLLEN TONGUE

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

ATTACHMENT 4

List of AE Preferred Terms (MedDRAv 19.1) for Vital Signs Blood Pressure and Heart Rate

- Blood pressure abnormal
- Blood pressure decreased
- Blood pressure abnormal
- Blood pressure diastolic abnormal
- Blood pressure diastolic decreased
- Blood pressure diastolic increased
- Blood pressure increased
- Blood pressure systolic abnormal
- Blood pressure systolic decreased
- Blood pressure systolic increased
- Blood pressure abnormal
- Labile blood pressure
- Accelerated hypertension
- Diastolic hypertension
- Essential hypertension
- Labile hypertension
- Malignant hypertension
- Systolic hypertension
- Diastolic hypotension
- Hypotension
- Heart rate abnormal
- Heart rate decreased
- Heart rate increased
- Heart rate irregular
- Bradycardia
- Tachycardia

ATTACHMENT 5

Comment fields and other reason for discontinuation specification identified as efficacy related.

Comment (COVAL)	Other Reason for Discontinuation Specification (DSTERM)
SUBJECT HAS FAILED TO REACH VL <40 BY WEEK 36 OF STUDY. PI & SUB PI WANT HIM TO BE UNDETECTABLE BY NOW. DISCUSSED AT MDT - DECISION MADE TO CHANGE ARV THERAPY - THIS MEANS WE MUST WITHDRAW SUBJECT	VIROLOGICAL FAILURE AND DEVELOPMENT OF RESISTANCE TO STUDY DRUG. PER PI DISCRETION, SUBJECT WITHDRAWN FROM STUDY.
WE AGREE THE SUBJECT DID NOT MEET PROTOCOL-DEFINED CRITERIA FOR VIROLOGICAL FAILURE; I WAS NOT CONVINCED THE REGIMEN HE WAS TAKING WAS THE OPTIMAL FIRST-LINE REGIMEN IN HIS PARTICULAR CASE.	
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CONSIDERED PATIENT WITHDRAWN DUE TO LACK OF EFFICACY - THE PATIENT WAS COMPLIANT	