Janssen Research & Development

Statistical Analysis Plan
(Week 48 Analysis)

A Phase 3, randomized, active-controlled, open-label study to evaluate switching to a darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) once-daily single-tablet regimen versus continuing the current regimen consisting of a boosted protease inhibitor (bPI) combined with emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) in virologically-suppressed, human immunodeficiency virus type 1 (HIV-1) infected subjects

Protocol TMC114IFD3013; Phase 3

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

Status: Final
Date: 05 April 2017
Prepared by: Janssen Research & Development, a division of Janssen Pharmaceutica NV
Document No.: EDMS-ERI-137287631

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

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ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ARV	antiretroviral
AST	aspartate aminotransferase
ATV	atazanavir
AUC_{24}	area under the plasma concentration-time curve over the 24h dosing interval
BIS	bone investigation substudy
BMD	bone mineral density
BMI	body mass index
bPI	boosted protease inhibitor
CI	confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{0h}	predose (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
TFV	tenofovir
TND	target not detected
VL	viral load
WHO	World Health Organization

1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the primary W48 analysis that will be performed after the last subject enrolled in the D/C/F/TAF arm completes the Week 48 visit, or prematurely discontinues from the study. The Week 96 analysis and the final analysis will each be described in separate SAPs.

1.1. Trial Objectives

The primary objective of this study is to demonstrate noninferiority in efficacy of a D/C/F/TAF once-daily single-tablet regimen relative to continuing the current bPI combined with FTC/TDF in virologically-suppressed (HIV-1 RNA <50 copies/mL) HIV-1 infected subjects, in regard to the proportion of virologic rebounders (defined as having confirmed HIV-1 RNA ≥50 copies/mL through Week 48, or in case of early discontinuation a last single viral load of HIV-1 RNA ≥50 copies/mL) with a maximum allowable difference of 4%.

The secondary objectives of this study are:

- To evaluate superiority of switching to a D/C/F/TAF once-daily single-tablet regimen versus continuing the current bPI combined with FTC/TDF in regard to the proportion of virologic rebounders through Week 48, in case noninferiority is established;
- To evaluate the proportion of rebounders through Week 48 in the 2 treatment arms;
- To evaluate efficacy as determined by continued suppression of HIV-1 RNA (<20, <50, and <200 HIV-1 RNA copies/mL as defined by the FDA snapshot analysis and time to loss of virologic response [TLOVR] algorithm) at Weeks 24 and 48 in the 2 treatment arms;
- To evaluate the safety and tolerability of the D/C/F/TAF regimen through 24 and 48 weeks of treatment;
- To evaluate the change from baseline in serum creatinine, eGFR for creatinine clearance (eGFRcr, by Cockcroft-Gault and by Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI]) and eGFR for cystatin C clearance (eGFRcyst, by CKD-EPI) in the 2 treatment arms at Weeks 24 and 48;
- To evaluate the change from baseline in renal biomarkers at Weeks 24 and 48;
- To evaluate immunologic changes (CD4+ cell count) through 24 and 48 weeks of treatment in the 2 treatment arms;
- To evaluate adherence through drug intake (as derived by drug accountability data), and explore correlation with primary efficacy outcome;
- To evaluate resistance in subjects who show virologic rebound through Weeks 24 and 48 in the 2 treatment arms;

- To evaluate long-term safety, resistance, and efficacy of the D/C/F/TAF regimen (until Week 96 and beyond);
- To evaluate the steady-state pharmacokinetics of DRV in the D/C/F/TAF arm.

Secondary objectives to be assessed in a bone investigation substudy performed at selected study sites:

- To evaluate the changes from baseline in bone biomarker levels at Weeks 24 and 48;
- To evaluate the safety of the 2 treatment arms as determined by the percent change from baseline in spine and hip bone mineral density (BMD) and changes in associated T-score at Weeks 24 and 48.

1.2. Trial Design

This is a randomized, active-controlled, open-label, multicenter, Phase 3 study to evaluate the efficacy, safety and tolerability of switching to a D/C/F/TAF once-daily single-tablet regimen compared to continuing the current regimen consisting of a bPI (limited to DRV once daily with rtv or COBI, ATV with rtv or COBI, or LPV with rtv) combined with FTC and TDF (FDC; hereafter referred to as FTC/TDF) in virologically-suppressed (HIV-1 RNA <50 copies/mL), HIV-1 infected adult subjects over a 48-week treatment period.

The aim was to include approximately 1100 subjects in this study. Eligible subjects were to be currently treated with a stable ARV regimen consisting of a bPI (limited to DRV once daily with rtv or COBI, ATV with rtv or COBI, or LPV with rtv) combined with FTC/TDF only, for at least 6 consecutive months preceding the screening visit, and virologically suppressed with at least 1 plasma HIV-1 RNA measurement <50 copies/mL (or HIV-1 RNA undetectable by a local HIV-1 RNA test) occurring between 12 and 2 months prior to screening while being on the stable ARV regimen and have HIV-1 RNA <50 copies/mL at the screening visit. A single viral load elevation of ≥50 copies/mL and <200 HIV-1 RNA copies/mL after previously reaching viral suppression ('blip') within 12 months prior to screening is allowed, provided a subsequent viral load measurement is <50 HIV-1 RNA copies/mL (or HIV-1 RNA undetectable by a local HIV-1 RNA test) prior to screening. A change in pharmacokinetic booster (i.e., rtv or COBI) was allowed provided such a switch occurred no less than 1 month prior to the screening visit. Subjects treated with the combination DRV + COBI + FTC/TDF and having completed the required visits in the Gilead Sciences Inc. (GSI)-sponsored study GS-US-216-0130, and who fulfilled the present protocol criteria, were also given the option to participate in this study.
Prior to or at the baseline visit (Day 1), subjects who met all eligibility criteria were to be randomized in a 2:1 ratio to one of the following 2 treatment arms:

- D/C/F/TAF Arm: Switch to regimen of a single FDC tablet containing DRV 800 mg/ COBI 150 mg/ FTC 200 mg/ TAF 10 mg (D/C/F/TAF tablet) once daily, (n = 734);
- Control Arm: Continue current regimen consisting of a bPI (limited to DRV once daily with rtv or COBI, ATV with rtv or COBI, or LPV with rtv) combined with FTC/TDF only, (n = 367).

Randomization was stratified by the bPI used at screening.

Provided results from the Data Monitoring Committee (DMC) analyses or Week 24 interim analysis does not preclude (further) exposing subjects to D/C/F/TAF, subjects from the D/C/F/TAF arm will enter in the extension phase once they have completed their Week 48 visit. In addition, subjects in the control arm will receive the D/C/F/TAF tablet in the extension phase if, according to the investigator, they will benefit from it and if all conditions are fulfilled (which includes adequate viral load results). Subjects from the control arm will be required to attend a switch visit at Week 52 to receive D/C/F/TAF. All subjects in the extension phase will have to attend visits every 12 weeks up to Week 96. As from Week 96, all subjects are offered the possibility to continue D/C/F/TAF treatment, if they wish and if they continue to benefit from it, 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. After Week 96, subjects should attend visits every 6 months.

Subjects who prematurely discontinue or change study treatment during the treatment phase (from Day 1 to Week 48) or during the extension phase (only between Week 48 and 96) will be required to complete the early study treatment discontinuation (ESTD) visit assessments within 72 hours of stopping/changing study treatment.

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).

The study consists of a screening period of approximately 30 days starting from the signature of the informed consent form (ICF), a controlled treatment period of 48 weeks, an extension phase up to Week 96 and an optional extension beyond Week 96. A 30-day FU visit may take place as described above. A diagram of the study design is provided in Figure 1.

Figure 1: Schematic Overview of the Study

Baseline (Day 1)	**Week 24**	**Week 48** Primary analysis	**Week 96 or beyond**
Screening	**Treatment phase**	**Extension phase**	**Follow-up**
≤30 days prior to baseline	**Treatment arm 1 (Test)**: D/C/F/TAF once daily (n=734)	D/C/F/TAF	ESTD and/or 30-day FU visit
	Treatment arm 2 (Control): Continue current bPI combined with FTC/TDF only (n=367)		

A planned Week 24 interim analysis was performed after the last subject completed 24 weeks on study, or prematurely discontinued from the study. The analysis was done mainly to evaluate the safety and tolerability of D/C/F/TAF. However, efficacy of the 2 treatment arms was also assessed and the results were shared with the DMC. The primary Week 48 analysis will be performed after the last subject enrolled in the D/C/F/TAF arm reaches Week 48 or the last subject enrolled in the control arm completes the Week 52 visit (whichever comes last), or prematurely discontinues from the study. The Week 96 analysis will be performed after the last subject completes 96 weeks on study, or prematurely discontinues

from the study. The final analysis will be performed after all subjects have completed the extension phase (and the 30-day FU visit, if applicable).

The efficacy, as well as safety and tolerability, of the enrolled subjects and treatment regimens will be monitored by an external DMC.

1.3. Statistical Hypotheses for Trial Objectives

The null hypothesis in this study is that the proportion of virologic rebounders through Week 48 in the investigational treatment arm (D/C/F/TAF once-daily single-tablet regimen) is more than 4% higher than that in the control treatment arm (ongoing regimen consisting of a bPI combined with FTC/TDF)

The alternative hypothesis is that the rebounder rate in the D/C/F/TAF arm is at most 4% higher than that in the control arm.

1.4. Sample Size Justification

A sample size of 1100 subjects will yield 89% power if it is assumed that both treatment arms will have a rebound rate of 4% (confirmed HIV-1 RNA ≥50 copies/mL up to, and including the upper bound of the Week 48 window or have discontinued prematurely, irrespective of reason, having the last available HIV-1 RNA ≥50 copies/mL), that the noninferiority margin is 4%, and that the significance level of the test is at a 1-sided, 0.025 level.

For the bone investigation substudy, with 300 subjects (200 in the D/C/F/TAF treatment arm versus 100 in the control arm) and assuming an inter-subject variability of 4%, there is approximately 98% power to detect a 2% difference between the D/C/F/TAF treatment arm and the control arm in percent change from baseline in BMD at the lumbar spine. Other power calculations are presented below.

BMD at the Lumbar Spine, Power Calculations

	Mean % Change from Baseline	Common Standard Deviation (%)	Power
N=300	2	3.5	>99%
		4	98%
	3	3.5	>99%
		4	>99%

An interim DMC analysis was planned when approximately 50% of subjects had reached Week 12 (or discontinued earlier). At this DMC analysis a blinded sample size re-estimation (SSR) was planned. The sample size of 1100 subjects is based on the assumption that the overall Week 48 virologic rebound rate is 0.04, ensuring 90% power. However, the power is sensitive to this assumption; increase of the rebound rate to 0.07 would reduce the power to 70%.
The predicted Week 48 rebound rate was based on the observed Week 24 rebound. The following decision rule was proposed: a sample size increase to N=1400 would be considered if the observed Week 24 rebound rate was between 4% and 6%. This rule was justified in a simulation study.

The blinded SSR did not warrant an adjustment in study size.

1.5. Randomization and Blinding

Randomization

Central randomization was implemented in this study. Subjects were randomized in a 2:1 ratio to the investigational treatment arm (switch to D/C/F/TAF tablet), or the active control arm (maintain current regimen consisting of a bPI combined with FTC/TDF only). Randomization was stratified by the bPI used at screening (DRV with rtv or COBI, ATV with rtv or COBI, LPV with rtv). Randomization was based on a computer generated schedule, constructed via random permuted blocks to ensure balance across treatment arms in each stratum of the stratification factors, and prepared before the start of the study by or under the supervision of the sponsor.

Blinding

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

2. GENERAL ANALYSIS DEFINITIONS

2.1. Treatment Arms

Following notations for the treatment arms will be used:

- **D/C/F/TAF Arm**: subjects who switch to D/C/F/TAF treatment at baseline (initial switchers)
- **Control Arm**: subjects who continue on their bPI treatment and who switch to D/C/F/TAF treatment in the extension (late switchers)
- **All**: All subjects (only for Subject Information)

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) In case of withdrawal use: – Minimum(last intake date of study drug, study withdrawal date)

Trial phase	Start date	End date
Follow-up	End of last treatment phase +1 day	Trial termination date for all groups (date of last contact)

Data up to each subject's Week 48 visit are in scope for this analysis, and if applicable, any (confirmatory) viral load or genotype/phenotype results immediately subsequent to Week 48 (up to 6 weeks).

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 respective phase, calculated as "assessment date – start date of phase + 1 day" for (Non-) Comparative Treatment/Extension 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
Follow-up	14	31	Follow-up	Day 1 onwards

[a] 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'.

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. Intent-to-Treat Analysis Set

The intent-to-treat (ITT) analysis set will include all the subjects who were randomized and received at least 1 dose of treatment subsequent to randomization in the study. Subjects will be grouped according to the treatment arm (D/C/F/TAF 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 at the 30-day FU visit) is also performed on this analysis set.

2.3.2. 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.

The PP analysis set is the secondary analysis set for efficacy analysis.

The per protocol (PP) set is defined as the ITT analysis set minus subjects with major protocol violations as listed in Attachment 1. The PP analysis set is the secondary analysis set for efficacy analysis.

2.3.3. Pharmacokinetic Analysis Set

The pharmacokinetic analysis set (PK) will include all subjects who were randomized to the D/C/F/TAF arm (and the control arm, if applicable), have received at least 1 dose of investigational treatment (or control treatment, if applicable) in the study, and having at least one pop PK parameter of any analytes of interest available.

2.3.4. Bone Investigation Substudy Analysis Set

The bone investigation substudy (BIS) analysis set will include all subjects in the ITT set and having at least one post-baseline value either in biomarker or in BMD data. The bone investigation analysis will be performed on this analysis set. 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 drug accountability (>95%: adherent, ≤95%: non-adherent, missing/unknown)
- Screening and baseline viral load
  - <50; if all screening and baseline viral load values are below 50 copies/mL
  - ≥50; if at least one viral load value during screening or baseline ≥50 copies/mL)
- CD4+ count at baseline (<200, ≥200 [200≤x<350, 350≤x≤500, >500] 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, non-Hispanic or Latino)
- Gender (Female, Male)
- Age group (≤50, >50 years)
- Region (Europe, North America)

- Re-classified bPI at screening (see section 2.5):
  - DRV once daily with rtv or COBI; ATV with rtv or COBI; LPV with rtv
  - ATV with rtv or COBI, or LPV with rtv
  - DRV with rtv; DRV with COBI
- Booster at screening (ritonavir or cobicistat)
- Number of previous ARVs used (3, 4, 5, 6, 7, >7) and previous PI, N(t)RTI or NNRTI used (0, 1, 2, 3, 4, >4)
- Number of previous ARVs used excluding screening ARVs (0, 1, 2, 3, 4, >4) and previous PI, N(t)RTI or NNRTI used excluding screening (0, 1, 2, 3, 4, >4)
- Previous ARV failure and previous PI, N(t)RTI or NNRTI failure (0, ≥1)
- WHO Clinical Staging of HIV/AIDS

2.4.2. Subgroups for Safety 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)
- Ethnicity (Hispanic or Latino, non-Hispanic or Latino)
- Gender (Female, Male)
- Age group (≤50, >50 years)
- Region (Europe, North America)
- Re-classified bPI at screening:
  - DRV once daily with rtv or COBI; ATV with rtv or COBI; LPV with rtv
  - ATV with rtv or COBI, or LPV with rtv
  - DRV with rtv; DRV with COBI
- Booster at screening (ritonavir or cobicistat)
- $eGFR_{CG}$ (<70, ≥70 mL/min)
- WHO Clinical Staging of HIV/AIDS

Subgroups for Bone Investigation Analyses:

- bPI at screening
- Race (American Indian or Alaska Native, Asian, Black or African American, White, Native Hawaiian or other Pacific Islander, Other, Non Black)
- Gender
- Baseline BMI ((underweight (<18.5 kg/m^2), normal range (18.5 to <25.0 kg/m^2), overweight (≥25.0 kg/m^2) and obese (≥30.0 kg/m^2))
- Age group (≤50, >50 years)
- Current smoking status (yes/no)

2.4.3. Subgroups for Pharmacokinetic Analyses

- Age group (≤65, >65 years; 65 <= x <= 74, 75 <= x < 85, >=85 years)
- $eGFR_{CrCG}$ and $eGFR_{CystCKD-EPI}$

a. Stage 1 (Normal or High GFR): ≥ 90 mL/min,
b. Stage 2 (Mild CKD): 60-89 mL/min,
c. Stage 3 (Moderate CKD): 30-59 mL/min,
d. Stage 4 (Severe CKD): 15-29 mL/min,
e. Stage 5 (End Stage of CKD): <15 mL/min

- Hepatitis B/C coinfection status (Yes/No)
- Treatment adherence ≤95%, >95%

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

For the purpose of analysis the stratification factor (bPI) will be re-classified based on the value from the history of ARV therapy data at screening.
The re-classified stratification factor will be used for analysis. Listings showing the discrepancies between the strata entered at randomization (IVRS/IWRS) and actual screening bPI data will be presented.

3. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE REVIEW

An external DMC was 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 are provided in a separate DMC charter.

A formal futility analysis for lack of (non-inferior) efficacy of the D/C/F/TAF regimen was performed, using a conditional power approach, ie, probability of claiming non-inferiority at the completion of the study based on the available interim data. The analysis occurred when 1149 subjects were enrolled, of which at least 58% had reached Week 24 and 0.1% week 48. To this end, available interim data regarding virologic rebound were used. Further details regarding the derivation of the conditional power and the choice of threshold for the conditional power to stop for futility were provided in the DMC charter and DMC statistical analysis plan. The futility analysis was guided by the DMC, and the sponsor and study team remained blinded. It was not the intention to stop the study early in case of noninferiority/superiority of the D/C/F/TAF regimen versus the control group.

In addition, a blinded sample size re-estimation procedure was applied to allow for an adjustment in sample size to maintain adequate power in case the overall rate of rebound was anticipated to be different than assumed. Details were provided in the DMC charter.

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

4. SUBJECT INFORMATION

4.1. Demographics and Baseline Characteristics

For all ITT subjects, the following demographic and baseline disease parameters will be presented, using descriptive statistics and/or frequency tabulations:

Continuous demographic parameters:

- age at screening (years)
- height at baseline (cm)
- weight at baseline (kg)
- body mass index (BMI) at baseline = weight (kg) / (height (m))²

Categorical demographic parameters

- age at screening (categories in years: x≤ 65, x > 65, x≤ 50, x > 50)
- sex (categories: female, male)
- race (categories: American Indian or Alaska Native, Asian, Black or African American, White, Native Hawaiian or other Pacific Islander, Other)
- ethnicity (Hispanic or Latino/Not Hispanic or Latino)
- woman of childbearing potential (Of childbearing potential/Permanently Sterilized/ Postmenopausal/ NA)
- country
- region (North America, Europe)

Continuous baseline HIV disease characteristics:

- Baseline CD4+ (absolute count and %)
- Time since diagnosis of HIV infection (years)
- Time since first ARV therapy (years)

Categorical baseline HIV disease characteristics:

- Screening and Baseline viral load (<20 [<20 target detected, <20 target not detected], <50, ≥ 50 HIV-1 RNA copies/mL)
- Baseline CD4 cell count (<200, ≥200 [200≤x<350, 350≤ x≤500, >500] cells/mm^3)
- Mode of HIV-infection
- WHO clinical stage of HIV infection
- Previous ARVs used (overall and per class: PI, N(t)RTI, and NNRTI)
- Previous ARVs (overall and per class) excluding ARV regimen at screening (bPI plus FTC/TDF)
- Previous ARV failure (overall and per class: PI, NRTI, and NNRTI)

General baseline characteristics:

- $eGFRcr_{CG,}$ $eGFRcr_{CKD-EPI}$, $eGFRcyst_{CKD-EPI}$ (Continuous)
- $eGFRcr_{CG}$ (<50, 50≤x<70, x≥70 mL/min)
- $eGFRcr_{CG}$, $eGFRcr_{CKD-EPI}$ and $eGFRcyst_{CKD-EPI}$ (Kidney Disease Stages) (Stage 1 (Normal or High GFR): ≥ 90 mL/min, Stage 2 (Mild CKD): 60-89 mL/min, Stage 3 (Moderate CKD): 30-59 mL/min, Stage 4 (Severe CKD): 15-29 mL/min, Stage 5 (End Stage of CKD): <15 mL/min)
- Subclinical renal proximal tubulopathy (yes/no)
- Nicotine use (yes/no (but former user)/no (never used))
- Alcohol consumption (yes/no (but former user)/no (never used))
- Drug use (yes/no (but former user)/no (never used))
- Family history of hypertension (yes/no)
- Family history of diabetes (yes/no)
- Phosphaturia (Urine fractional excretion of Phosphate (FEPO4)
    - Continuous and categorical (>10%)
- Proteinuria by urinalysis (by DAIDS toxicity grade)
- Proteinuria (urine albumin-to-creatinine ratio (UACR) ≤ 30 mg/g (normal), 30 to 300 mg/g) (microalbuminuria) and > 300 mg/g (macroalbuminuria)
- Proteinuria (urine protein- to-creatinine ratio (UPCR), < 200 mg/g versus ≥ 200 mg/g)
- Normoglycemic glycosuria (subjects with normal glucose levels [DAIDs grade] and with positive glycosuria [DAIDs grade])
- Hepatitis B positive serology (HBsAg)
- Hepatitis C positive (for serology or HCV RNA)
- Personal medical history of:
    - hypertension (yes/no)
    - diabetes/hyperglycemia (yes/no)
    - dyslipidemia (yes/no)
    - overweight/obesity
    - cardiovascular disease (yes/no)
    - chronic renal disorder (yes/no)
    - osteopenia/osteoporosis (yes/no)
- History of drug allergy/hypersensitivity
    - ARV allergy (yes)
    - other (yes)

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

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

4.3. Treatment Adherence

Treatment adherence based on drug accountability will be summarized by means of descriptive statistics and frequency tabulations. Cumulative treatment adherence through Week 48 will be determined (derivation i).

The following parameters are derived:

Amount to be taken through Week 48 = (number of days since start of treatment × number of tablets to be taken per day).

Number of days since start of treatment 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.
- Week 48 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 Week 48, 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.

4.4. Extent of Exposure

Descriptive statistics will be tabulated for the duration of treatment of both D/C/F/TAF and control, in weeks, during the respective active treatment phases, up to the Week 48 visit, or in case of early

discontinuation, last study medication intake. In addition, subject-years of exposure will be shown, derived as mean of treatment duration ((in weeks) x N) x 7 / 365.25.
Treatment duration (in weeks) is derived as follows for each of the three therapies:

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

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

4.5. 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 (Attachment 1) will also be tabulated.

4.6. Prior and Concomitant Medications

Prior medications are defined as any therapy used before the day of first dose (partial or complete) of study agent. 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. When counting the number of ARVs at a specific time point or during a specific time period, the separate compounds of these combination drugs are counted

Prior and 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

4.7. Medical History

Medical conditions in medical history will be grouped using a list of medical history terms provided as metadata. These medical conditions, along with baseline values of certain laboratory, vital signs and DXA parameters will be used to determine medical history groups of interest:

- Hypertension
- Diabetes/Hyperglycemia
- Dyslipidemia
- Overweight/Obesity
- Cardiovascular disease
- Chronic renal disorder
- Osteopenia/Osteoporosis

These groups and their subgroups will be tabulated (n, %). For each of these groups, listings of the subjects meeting each of these (sub)categories and listings of relevant comedications will be provided.

5. EFFICACY

5.1. Analysis Specifications

5.1.1. Level of Significance

All statistical tests will be interpreted at the one-sided 2.5% significance level or equivalently at the 5% two-sided significance level. Despite the SSR exercise applied for this study, no adjustment of the Type-I error will be accounted for; p-values for the key efficacy results will be provided in order to facilitate interpretation.

5.1.2. Data Handling Rules

Plasma viral load levels will be measured using the ROCHE COBAS® AmpliPrep/COBAS® Taqman® HIV-1 Test, v2.0 assay, 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.

5.2. Primary Efficacy Endpoint

5.2.1. Definition

The primary efficacy endpoint of this analysis is the proportion of subjects with virologic rebound cumulatively through 48 weeks.

The rebounders are defined as:

- subjects who show confirmed HIV-1 RNA ≥50 copies/mL up to, and including Week 48,
- subjects who discontinued prematurely (irrespective of reason) for which the last available (single) HIV-1 RNA value on treatment was ≥50 copies/mL.

All other situations are considered non-rebounders.

5.2.2. Analysis Methods

A 2-sided 95% CI of the difference in cumulative virologic rebound rate between the treatment groups (D/C/F/TAF minus control arm), will be constructed using a Mantel-Haenszel test controlling for stratification factor, i.e., bPI at screening. Exact 2-sided 95% CIs around the rebound rate in each treatment group will be calculated by the Clopper-Pearson method.

It will be concluded that the D/C/F/TAF single-tablet regimen is noninferior to the control regimen if the upper bound of the 2-sided 95% confidence interval (CI) of the difference between treatment arms (D/C/F/TAF arm - control arm) in rebounder rate is less than 4% (ie, a margin of 4% is applied to noninferiority assessment).

Homogeneity of treatment effect across the strata will be tested. The weighted least squares chi-squared statistic [Fleiss, 1981] will be used to test for one-way homogeneity. Following Lui and Kelly [Lui, 2000]

method will be applied. Any heterogeneity found to be statistically significant will be explored and if necessary results will be reported. Tests of homogeneity will be assessed at the one-sided 10% level of significance.

If noninferiority of the D/C/F/TAF arm to control arm is established, the upper bound of the 95% CI will be compared to 0; if the upper bound of the 95% CI is less than 0, then superiority of D/C/F/TAF over the control arm will be established. The bPI stratum-adjusted 2-sided CMH test will also be used to assess superiority as a secondary assessment. P-values for these tests will be provided as well.

5.3. Major Secondary Efficacy Endpoints

- The proportion of subjects with virologic rebound based on the HIV-1 RNA ≥20 and ≥200 copies/mL threshold through 48 weeks;
- The proportion of subjects with virologic response and failure based on the 20, 50 and 200 copies/mL threshold at Week 48, as defined by the FDA snapshot approach (5.3.1);
- The proportion of subjects with virologic response and failure based on the 20, 50 and 200 copies/mL at Week 48, as defined by the TLOVR algorithm (5.3.1);
- Time to virologic rebound up to Week 48
- The change from baseline in CD4+ cell count

5.3.1. Definitions

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

- Virologic success:
  - HIV RNA <20/50/200 copies/mL in the Week 48 visit window (Week 42-54)
- Virologic failure:
  - HIV RNA ≥20/50/200 copies/mL in the Week 48 visit window (Week 42-54)
  - Virologic failure leading to discontinuation
  - Discontinued due to other reason (i.e. other than AE/death or virologic failure) and last available HIV-RNA ≥20/50/200 copies/mL
- No viral load data in the Week 48 visit window
  - Discontinued due to AE/death (subjects will be classified in this category if discontinued prior to Week 48 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 48 visit window but on study

The following threshold criteria are considered:

- <20: HIV RNA below 20 copies/mL (target not detected or target detected)
- <50: HIV RNA below 50 copies/mL
- <200: HIV-RNA below 200 copies/mL

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 (permanently) discontinued at that time point or before
    - 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)
    - 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.

  In addition, TLOVR outcome table at Week 48 will be presented.

Time to rebound: The time (in weeks) calculated from baseline until the first rebound time point (time point before confirmation of rebound) up to Week 48 visit. Subjects never losing the response up to Week 48 visit will be censored at the end of the (non-) comparative treatment phase.

Immunologic response: The change from baseline in CD4+ count and CD4% at a given time point is defined as: (CD4+/CD4% at a given time point - baseline CD4+/CD4%).
Subjects who discontinue will have their CD4 values after discontinuation imputed with their baseline 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.

5.3.2. Analysis Methods

Binary Outcomes (virologic rebound, snapshot and TLOVR approach)

Tabulations (numbers and proportions) per time point will be provided for the snapshot outcomes. Tabulations (numbers and proportions) will also be provided for the categorical parameters (virologic rebounders and TLOVR), through Week 48. The treatment arms will be compared by the risk difference and the 95% CIs constructed using the stratum adjusted Mantel-Haenszel difference in proportions, where the stratification factor (bPI at screening) determines the strata. Graphs will be presented for virologic rebounders and snapshot outcomes. Viral load profile plots will be provided for subjects with virologic rebound and/or virologic failure per snapshot algorithm.

The difference in proportion of virologic rebound between the treatment groups will be explored by subgroups defined in section 2.4.1. Exact (unconditional) CI of at least 95% confidence will be used[1].

Time to virologic rebound

Time to virologic rebound will be graphically presented by means of Kaplan-Meier curves and the treatment groups will be compared by means of the Cox proportional hazards model including terms for treatment, bPI at screening, and any predose (screening phase) viral load ≥50 copies/mL (Yes/No).

Immunologic Change

Descriptive statistics (n, mean (se), median, and ranges) per time point will be provided for the continuous parameters, CD4 cell count actual values and change from baseline. CIs for the means and mean changes will be calculated. The difference in changes from baseline between the two treatment arms and the 95% CIs at Week 24 and Week 48 will be constructed using ANCOVA, including term for bPI at screening and baseline CD4+ value as a covariate. A sensitivity analysis using Mixed-effects model for repeated measures (MMRM) approach will also be performed to obtain an estimate of the between-treatment difference along with its 95% CI. The model will include post-baseline change from baseline as a response variable, terms for treatment, bPI at screening, visit, the interaction of visit and treatment and the corresponding baseline value as a covariate. An unstructured covariance matrix will be used to model the correlation among repeated measurements.

Cross-tabulations of Week 48 CD4 cell count versus baseline will be provided using the categories: < 200, 200≤ x<350, 350≤x≤500, >500 cells/mm^3

Per Protocol Analysis

The primary and key secondary endpoints will also be analyzed on the per protocol (PP) population. Details on which outputs are included for the PP population will be provided in the Data Presentation Specifications (DPS) document.

5.4. Resistance Determinations

Inclusion of subjects for resistance analysis will be based on the availability of post-baseline genotypic/phenotypic data also described below (see 5.2.1).

5.4.1. Genotype

HIV-1 PR/RT genotype will be assessed by the GenoSureMG™ assay. Genotypes were requested on eligible samples with a viral load ≥ 400 copies/mL. Results will be shown per PR and RT and time point and will be generated in individual listings. Name and date of mutation lists will be indicated.

The analysis aims to characterize the frequency of post-baseline PR and RT resistance mutations in all subjects with genotype data and in subjects with virologic rebound having genotype data.

If applicable, 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). The analysis assumes a worst case scenario in case of multiple post-baseline 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.

All analyses will be conducted on the Efficacy ITT population, unless specified otherwise.

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

5.4.2. Phenotype

Predicted phenotype based GenoSureMG™ and in-vitro phenotype data, if applicable, based on PhenoSense™ HIV assay, will be presented in individual patient listings per drug and time point.Fold change (FC) in 50% effective concentration (EC50) of ARVs versus wild-type HIV-1 virus will be included in individual listings per drug and time point.

PhenoSense™ was additionally requested to determine the drug susceptibility of the virus if genotypic markers were observed. Using the fold change (FC), each drug will be categorized into sensitive/partially sensitive/resistant based on cut-off values.

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.

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

6. SAFETY

6.1. Adverse Events

6.1.1. 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.

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
- Lipid-related 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 the Attachment 3 and upon further clinical evaluation, additional (grouped) terms might need to be added. The medical assessment of the safety data will be performed according to a pre-specified algorithm (attached to the DPS) and will lead to the final list of ADRs. In case multiple lists are available (US and EU definitions), ADRs will be tabulated separately per list.

6.1.2. 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.

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. Statistical comparisons of the subject incidence rates between the 2 treatment groups will be performed using Fisher's exact test.
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.

6.2. Clinical Laboratory Tests

6.2.1. 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
- Liver related 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.

6.2.2. Analysis Methods

Descriptive statistics for the actual values and changes from baseline will be provided per time point.
For laboratory parameters of interest, P-values for the difference between the 2 treatment groups in baseline values and the change from baseline will be estimated from Van Elteren test stratified for bPI used at screening. Within-treatment comparison will be assessed at Week 48 using Wilcoxon signed-rank test.

Cross-tabulations of the worst toxicity grades through Week 48 versus reference, and cross-tabulations of the worst toxicity grades at Week 48 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 also 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).

6.2.3. Creatinine and glomerular filtration

6.2.3.1. Serum Creatinine and Cystatin C

Estimated glomerular filtration rate based on the creatinine clearance will be calculated according to the Cockcroft-Gault formula[4] ($eGFRcr_{CG}$) 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):

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

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

- eGFRcr and eGFRcyst according to the CKD-EPI formula (unit: mL/min/1.73m²):

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

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	$141 \times (Scr/0.9)^{-1.209} \times 0.993^{age}$

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

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 baseline in serum creatinine, $eGFRcr_{CG}$ and $eGFRcr_{CKD\text{-}EPI}$ and $eGFRcyst_{CKD\text{-}EPI}$ at Week 48 will be summarized by treatment arm and using descriptive statistics. The difference between the 2 treatment arms in change from baseline in serum creatinine and various estimates of eGFR will be

tested using ANCOVA at Week 48, including corresponding baseline value and other clinically relevant factors in the model. A supportive repeated measures analysis will be performed to obtain an estimate of the between-treatment difference along with its 95% CI. The model will include post-baseline change from baseline as a response variable, terms for treatment, visit, the interaction of visit and treatment and the corresponding baseline 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.

Stages of GFR at baseline versus the minimum post-baseline 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 baseline will be tabulated.

6.2.3.2. 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 comparison between the 2 treatment arms will be performed using Van Elteren test at Week 48, stratified for bPI used at screening. The within-treatment comparison will be performed at Week 48 using Wilcoxon signed-rank test.

The number and proportion of subjects with UACR and UPCR results in the following categories at Week 48 will be tabulates:

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

Median (Q1, Q3) percent change from baseline 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 48 will be summarized by treatment group. Cross-tabulation of grades at Week 48 versus baseline 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 comparison of the percent changes from baseline between the 2 treatment arms at Week 48 will be performed using the Van Elteren test stratified for bPI used at screening. Within-treatment comparison will be assessed at Week 48 using Wilcoxon signed-rank test.

The proportions of subjects with beta-2-microglobulin to creatinine ratio ≤343.5 µg/g and >343.5 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 48 will be tabulated:

- < 50 years of age: < 130 mcg/g creatinine, ≥ 130 mcg/g creatinine
- ≥ 50 years of age: < 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. Percent change from baseline will be compared between the 2 treatment groups at Week 48 using Van Elteren test controlling for bPI used at screening. Within group comparison will be done at Week 48 using Wilcoxon rank sum test.

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

- Based on unadjusted serum creatinine:
  FEPO4 (%) = (SCr × UPO4) / (SPO4 × UCr) × 100 (%)

The baseline, post-baseline, and change from baseline 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 baseline.
2. Confirmed ≥ 2 grade level increase from baseline in graded proteinuria
3. Confirmed ≥ 1 grade level increase from baseline in graded hypophosphatemia
4. Confirmed ≥ 1 grade level increase from baseline 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-baseline 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).

6.3. Vital Signs and Physical Examination Findings

6.3.1. Definitions

The following vital signs parameters will be analyzed:

– pulse (bpm)

– systolic blood pressure, SBP (mmHg)

– diastolic blood pressure, DBP (mmHg)

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

	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
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.

6.3.2. Analysis methods

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

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

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

6.4. Electrocardiogram

ECG assessments were done locally, only at screening and thus not suitable to be analyzed.

6.5. Bone Investigations

6.5.1. 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

6.5.2. Analysis methods

Bone Biomarkers:

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

For each bone biomarker; ALP, CTX, P1NP, PTH, and 25-OH VitD, the within-treatment comparison will be done using Wilcoxon signed-rank test at Week 24 and 48, versus subject's own baseline measurement. The comparison of the percent change from baseline between the 2 treatment arms will be performed at Week 24 and 48 using the Van Elteren test stratified for bPI used at screening.

DXA scan:

Descriptive statistics for the actual values, change and percent changes from baseline per time point will be presented for BMD parameters (including T- and Z-scores).

The between-treatment differences of the percent change in BMD at Weeks 24 and 48 will be estimated using ANCOVA model, including baseline BMD value, bPI at screening, race, gender, baseline BMI and age at study entry, current smoking status (Y/N). The within-treatment comparison will be done using 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 Weeks 24 and 48. This model will include post-baseline percent change from baseline as a response variable, terms for treatment, time point, the interaction of treatment and time point, the corresponding baseline BMD value, bPI at screening, race, gender, baseline BMI and age at study entry, current smoking status (Y/N), as a covariates. An unstructured covariance matrix will be used to model the correlation among repeated measurements.

The proportions of subjects with at least 3% change (decrease and increase separately) from baseline in BMD will be presented at Week 24 and Week 48. Percent change from baseline 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 24 and Week 48 versus reference will be produced.

7. PHARMACOKINETICS/PHARMACODYNAMICS

7.1. Pharmacokinetics

Pharmacokinetic assessments (sparse sampling) was performed for all subjects randomized to the D/C/F/TAF arm to evaluate the pharmacokinetics of DRV and COBI. The pharmacokinetic samples may also be used for evaluation of the pharmacokinetics of FTC, TAF, and/or TFV, if deemed necessary, upon request of the study pharmacologist.

Descriptive statistics will be calculated for the plasma concentrations of DRV and COBI. For this, only plasma concentrations from PK samples taken between 20 and 28 hours after the prior D/C/F/TAF dose (Cpredose) will be taken into account. Plasma concentrations will be summarized per analyte (DRV, COBI) and by visit. In addition, for each subject an average value across visits will be calculated, for DRV and COBI.

Based on the individual plasma concentration-time data (sparse samples), using the actual dose taken and the actual intake and sampling times, individual pharmacokinetic parameters (AUC_{24h} and C_{0h}) of DRV will be derived using population pharmacokinetic modeling and Bayesian feedback. Model specifications will be described in a separate report. Population pharmacokinetic modeling for other ARVs may be performed, if plasma concentrations are determined, and appropriate population pharmacokinetic models are available.

Descriptive statistics will be calculated for the derived pharmacokinetic parameters of DRV. Summary statistics will include n, mean, SD, coefficient of variation (CV), geometric mean, median, minimum and maximum.

Summary of PK parameters (DRV) and $C_{predose}$ (DRV and COBI) will also be presented by subgroups defined in section2.4.3. Similar analyses may be performed for the plasma concentration and/or derived PK parameters of other ARVs upon the sponsor's request, as applicable.

7.2. Pharmacokinetic/Pharmacodynamic Relationships

7.2.1. Relation to Efficacy Endpoints

Vertical bar charts of the proportion of subjects with virologic rebound will be generated for each PK parameters exposure quartiles (≤ Q1, > Q1 - ≤ median, > median - ≤ Q3, > Q3). A logistic regression model will be performed. The dependent variable will be the virologic rebound through Week 48 and the factor will be DRV exposure category (≤ Q1, > Q1 - ≤ median, > median - ≤ Q3, > Q3). The predicted % rebound and all pairwise comparisons among the exposure categories will be presented. For the modeling, the lowest exposure group should be the reference category.

7.2.2. Relation with Safety Endpoints

Boxplots of the DRV AUC_{24h} will be generated for subjects with an event of interest (see Section 6.1.1) versus subjects without the event.

Additionally, boxplots of DRV AUC_{24h} will also be generated for subjects with any treatment-emergent laboratory abnormality (based on the DAIDS toxicity grading scale) versus subjects without an abnormality. The boxplots will be created for the following specific laboratory parameters:

Biochemistry	Lipids	Glucose metabolism
ALT	HDL	Glucose
AST	LDL	
Total bilirubin	Triglycerides	
Alkaline phosphatase	Total cholesterol	
Total amylase	Total cholesterol / HDL	
Creatinine		
eGFR ($eGFRcr_{CG}$ and $eGFRcr_{CKD-EPI}$)		
$eGFRcyst_{CKD-EPI}$		
UACR[#]		
UPCR[#]		

[#] UACR and UPCR will be presented using categories < 30 vs. ≥30 mg/g for UACR, and < 200 mg/g vs. ≥ 200 mg/g for UPCR

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1. Agresti, A. and Min, Y. (2001), On Small-Sample Confidence Intervals for Parameters in Discrete Distributions, Biometrics, 57, 963–971
2. Guidance for Industry. Antiretroviral Drugs Using Plasma HIV RNA Measurements Clinical Considerations for Accelerated and Traditional Approval. October 2002.
3. Wensing AM, et al. 2015 Update of the Drug Resistance Mutations in HIV-1: October/November 2015. IAS-USA Topics in Antiviral Medicine. 2015;23 (4):132-141.
4. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16:31-41.

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 table below, subjects with a baseline HIV-1 RNA value ≥50 copies/mL and subjects with treatment adherence <65% per derivation ii will also be excluded from the per-protocol analysis set.

Sequence No.	Description	Protocol Deviation coded term (DVDECOD)	Exclude from PP
1	The subject has not been treated with a stable ARV regimen consisting of a bPI (limited to DRV or ATV with rtv or COBI, or LPV with rtv) combined with FTC/TDF only for at least 6 consecutive months preceding the screening visit.	Entered but did not satisfy criteria	Yes
2	• During the 12 months preceding screening while on stable ART: - The subject **did not** have at least 1 plasma HIV-1 RNA measurement <50 copies/mL (or HIV-1 RNA undetectable by a local HIV-1 RNA test) occurring between 12 and 2 months prior to the screening visit while on the stable ARV regimen or - The subject has a documented plasma HIV-1 RNA concentrations ≥200 copies/mL. or - The subject has documented **more than 1** plasma HIV-1 RNA concentrations ≥50 copies/mL (or HIV-1 RNA detectable by a local HIV-1 RNA test)	Entered but did not satisfy criteria	Yes

	or - The subject has at least 1 single documented plasma HIV-1 RNA concentrations ≥50 copies/mL and <200 copies/mL **but** had no subsequent VL measurement <50 HIV-1 RNA copies/mL at the latest 2 months prior to screening or • At the screening visit has HIV-1 RNA ≥50 copies/mL.		
3	The subject has a history of failure on DRV treatment or any of DRV RAMs (V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V, L89V) (if historical genotypes are available)	Entered but did not satisfy criteria	Yes
4	The subject uses disallowed concomitant therapy specified in the protocol	Entered but did not satisfy criteria	Yes
5	The subject has any known allergies to the excipients of the D/C/F/TAF tablet, but the subject was randomized.	Entered but did not satisfy criteria	Yes

6	The dose of Investigational treatment arm (D/C/F/TAF tablet) or the active control arm (maintain current regimen consisting of a bPI with FTC/TDF) 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
7	The intake of Investigational treatment arm (D/C/F/TAF tablet) or the active control arm (maintain current regimen consisting of a bPI with FTC/TDF) was interrupted for toxicity reasons for more than 4 consecutive weeks.	Received wrong treatment or incorrect dose (missed dose or extra dose)	
8	The intake of Investigational treatment arm (D/C/F/TAF tablet) or the active control arm (maintain current regimen consisting of a bPI with FTC/TDF) 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	
9	The subject takes disallowed medication as defined per protocol.	Received a disallowed concomitant treatment	Yes (adjudication based on drug/class and duration).
10	The subject missed two or more consecutive planned visits in the trial	Other	Yes
11	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
12	The HIV-1 RNA value was ≥50 copies/mL but a retest was not collected or was collected >6 weeks after availability of the results (except for screening and baseline results).	Other	Yes
13	Subject missed the Week 48 visit.	Other	

*Some sites assumed that protocol language “abnormal lab values that would lead to exclusion could be repeated once” applied also to viral load >50c/mL at screening.

** Including subjects whose HIV-1 RNA was ≥50 copies/mL at screening, but had a HIV-1 RNA <50 copies/mL at a not per protocol defined retest during the

screening period and who were randomized based on the latter HIV-1 RNA.

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 morbiliform, 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

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 hypertension, 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 triaditis

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, Liver palpable subcostal

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, Hyperosmolar hyperglycaemic state, 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, Hyperglycaemic hyperosmolar nonketotic syndrome

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
Immune reconstitution inflammatory AEOI	Immune reconstitution 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, Cardiac enzymes increased

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, Genital 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
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 trypsine 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
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, 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, Convulsion, Grand mal convulsion

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, Urine amino acid level abnormal, Urine 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
Bone AEOI (for fractures) / Osteomalacia	Hypophosphataemic rickets, Osteomalacia, Renal osteodystrophy , 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, Fracture treatments (excl skull and spine), 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
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

ADR grouped Terms

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

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

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

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