Janssen Scientific Affairs, LLC *

Statistical Analysis Plan

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

Protocol TMC114FD2HTX3002; Phase 3

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

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

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AMENDMENT HISTORY

The SAP is not amended for changes after database lock.

ABBREVIATIONS

ADA	anti-drug antibody
AE	adverse event
ALT/SGPT	alanine aminotransferase
ANCOVA	analysis of covariance
AST/SGOT	aspartate aminotransferase
ATC	anatomic and therapeutic Class
AUC	area under the curve
BMI	body mass index
BSA	body surface area
CI	confidence interval
CL	total systemic clearance
Cmax	maximum concentration
CRF	case report form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
D/C/F/TAF	DRV 800 mg + COBI 150 mg + FTC 200 mg + TAF 10 mg FDC
DMC	Data Monitoring Committee
DPS	Data Presentation Specifications
DRV	Darunavir
DSUR	Development of safety update report
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	Estimated glomerular filtration rate
ESTD	early study treatment discontinuation
F (%)	absolute SC bioavailability
FAS	full analysis set
FDA	Food and Drug Administration
FTC	emtricitabine
HRU	healthcare resource utilization
ICH	International Conference on Harmonization
IQ	interquartile
IVRS	interactive voice response system
LLOQ	lower limit of quantification
LOCF	last observation carried forward
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MRD	minimum required dilution
NAb	neutralizing antibodies
OI	Opportunistic infection
PD	pharmacodynamic
PI	principal investigator
PK	pharmacokinetic(s)
PP	per protocol
RPV	rilpivirine
RTV	ritonavir
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SMQs	standardised MedDRA queries
TAF	tenofovir alafenamide

TEAE	treatment-emergent adverse event
TDF	tenofovir disoproxil fumarate
TLOVR	time to loss of virologic response
Tmax	time to maximum concentration
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the interim analysis when last subject has been assessed for safety and resistance stopping rules and Week 48 primary 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. At the Interim analysis only selected endpoints will be analyzed, while at the week 48 Primary analysis, all endpoints will be analyzed. Data collected after primary analysis from subjects in the Extension treatment period will be analyzed separately. Details of each analysis contents will be described in DPS.

1.1. Trial Objectives

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

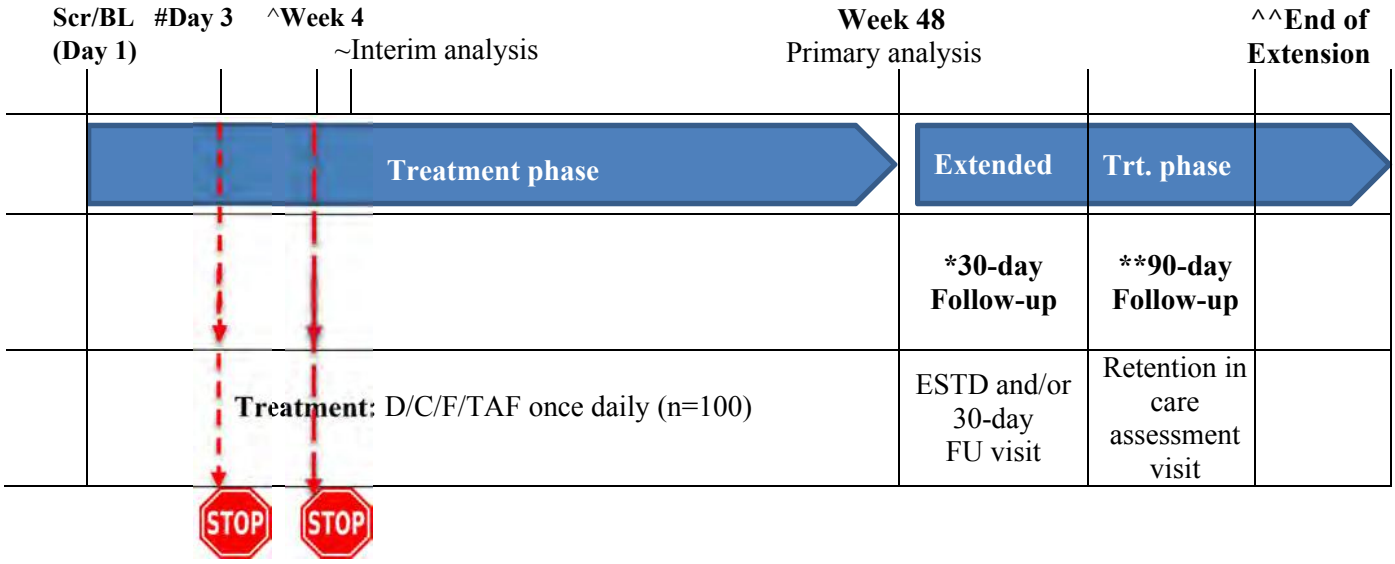
The secondary objectives of this study are:

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

- To evaluate healthcare resource utilization (HRU) and cost and their temporal trends in the study population through 48 weeks of treatment

1.2. Trial Design

Figure 1: Schematic Overview of the Study



#Assessment of safety labs stopping rule, day3+1 week.
^Assessment of drug resistance stopping rule, week4±1 week.
*Subjects with ongoing AEs/SAEs at the time of last study visit.
**Discontinued subjects from day 1 to week 48.
~analysis will be performed when last subject has been assessed for safety and resistance stopping rules
^^ subjects will continue D/C/F/TAF treatment during an extension period until the D/C/F/TAF FDC tablet becomes commercially available and is reimbursed, or can be accessed through another source or until the sponsor terminates clinical development.

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

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

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

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

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

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

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

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

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

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

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

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

Protocol defined virologic failure (PDVF) will be defined in this study as follows:

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

Subjects who meet the criteria for Virologic Nonresponse or Virologic Rebound will be managed according to the schema provided in Attachment 1 at the end of the document.

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

Subjects who prematurely discontinue study treatment during the treatment period (between Day 1 and Week 48) will be required to complete ESTD assessments as soon as possible but no later than 1 week of discontinuing study treatment.

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

to the site 30 days (±7 days) after completion of the last study-related visit (unless consent is withdrawn).

Subjects who have completed the Week 48 visit will be given the opportunity to continue D/C/F/TAF treatment during an extension period until the D/C/F/TAF FDC tablet becomes commercially available and is reimbursed, or can be accessed through another source, or until the sponsor terminates clinical development. During the extension period, subjects will return to the site once every 6 months.

Subjects who undergo ESTD will resume routine clinical care with their care provider who will determine the future care of that subject. For those subjects discontinuing therapy before Week 48, the investigator will be asked to monitor the subject's retention in care defined as having one documented clinic visit within 90 days of discontinuing the study treatment (unless consent is withdrawn).

The end of the study is defined as completion of the last data collection visit for the last subject participating in the study, which will be a maximum of 52 weeks after enrollment to allow for a 30-day follow-up visit as needed. A subject will be considered to have completed the study if data collection as required per protocol through the complete course of 48 weeks of ART has been completed.

An interim analysis is planned once all subjects have been assessed for safety and resistance stopping rules.

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

Extension treatment period data will be reported when all subjects discontinued study treatment or transition to commercial D/C/F/TAF.

1.1. Statistical Hypotheses for Trial Objectives

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

1.2. Sample Size Justification

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

100 subjects, the probability to observe an adverse event with a true incidence of 1% or 4% is 63% and 98% respectively.

1.3. Randomization and Blinding

Treatment Allocation

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

Blinding

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

2. GENERAL ANALYSIS DEFINITIONS

2.1. Visit Windows

As subjects, do not always adhere to the protocol visit schedule, the following rules are applied to assign actual visits to analysis visits. Listed below are the visit windows and the target days for each visit. The reference day is Study Day 1. If a subject has 2 or more actual visits in one visit window, the visit closest to the target day will be used as the protocol visit for that visit window. The other additional visit(s) will not be used in the summaries or analyses but they can be used for determination of clinically important endpoints. If 2 actual visits are equidistant from the target day within a visit window, the later visit is used.

All assignments will be made in chronological order. Once a visit date is assigned to a visit window, it will no longer be used for a later time point except for the endpoint. Listed below (Table1 are the visit windows and the target days for each visit defined in the protocol.

Table 1– Visit Windows

Parameter	Analysis Period	Scheduled Visit Number	Time Interval (label on output)	Time Interval (Day)*	Target Time Point (Day)
Efficacy and safety Assessments	1-2	1	Screening/ Baseline[a]	Day -3 - Day 1	1
	1-2	2	Week 2	Day 2 – Day 21	15
	1-2	3	Week 4	Day 22 – Day 42	29
	1-2	4	Week 8	Day 43 – Day 70	57
	1-2	5	Week 12	Day 71 – Day 126	85
	1-2	6	Week 24	Day 127 – Day 210	169
	2	7	Week 36	Day 211 – Day 294	253
	2	8	Week 48	Day 295 – Day 378	337
	3	9	Extension	Day 139- Day 222 of extension period	181
	3	10`	Extension	Day 319 of Day 403 extension period	361
	1-2	24	30 day Follow-up	Day 1 of FU onwards	31
	1-2	25	90 day Follow-up	Day 1 of FU onwards	91

*Relative to Study Day 1 , Analysis period 1: Interim Analysis, Analysis Period 2: Week 48 Primary Analysis, Analysis period 3: Only extension treatment period data after Primary analysis.
`if there are more extension visits, visit numbers will continue to label 11, 12…

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 or day 1 of treatment whichever the last visit before first dose.
Treatment Phase	Date of the first intake	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)
Extension Treatment phase	Week 48 visit date +1 day	Date of transition to commercial D/C/F/TAF or Trial Termination date.
^Follow-up	End of treatment phase +1 day	Trial termination date for all groups (date of last contact)
***90 day FU**	Date of premature study discontinuation + 1day	Date of retention in care assessment.

*90 day FU visit planned only discontinued subjects from day 1 to week 48 visit.

^30 day FU visit required for any subject who has ongoing AE or SAE at the time of his last study visit.

Data up to each subject's Week 48 visit are in scope for this primary analysis, and if applicable, any (confirmatory) viral load or genotype/phenotype results immediately subsequent to Week 48. Retention in care assessment is planned 90 days after discontinuation.

2.2. Analysis Sets

2.2.1. All Subjects

All subject analysis set population includes subjects who were screened.

2.2.2. All Enrolled Analysis Set

The all enrolled analysis set includes all subjects who were not screen failures and were dispensed treatment.

2.2.3. Efficacy Analysis Set(s)

The Intent to treat analysis set (ITT) includes all enrolled subjects who received at least 1 dose of study drug.

Efficacy analysis set (EAS) includes all ITT analysis set subjects who did not discontinue study due to safety or resistance stopping rules or did not discontinue study due to violation of inclusion criteria caused by un-confirmed HIV positive test.

The per protocol analysis set (PP) includes a subset of subjects in the intent to treat analysis set (ITT) who are in-compliance with the protocol. Compliance is defined as subjects who are not having major protocol deviation that is considered to have an impact on the safety or efficacy assessments.

2.2.3.1. Primary Efficacy Analysis Set

The ITT analysis set is the primary analysis set for efficacy analysis.

2.2.3.2. Secondary Efficacy Analysis Set

Secondary end points will be analyzed using ITT, EAS and PP. Details of analysis and study population will be described in the DPS.

2.2.4. Safety Analysis Set

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

2.3. Definition of Subgroups

Subgroup	**Version**	**Definition**	**Applied Analysis**
Race		• White • Black of African American • Asian • American Indian or Alaska Native • Native Hawaiian or Pacific Islander • Other	Efficacy Safety
Gender		• Female • Male	Efficacy Safety
Time from initial HIV diagnosis to Enrolment		• [0-1[day • [1-2[days • [2-3[days • [3-7[days • [7-14[days	Efficacy
Baseline Viral Load categories		• >100K • ≤100K	Efficacy MRU
Baseline Viral Load categories2		• ≤100K • 100K-500K • >500K	Efficacy
Baseline CD4+ categories		• >200 • ≤ 200	Efficacy MRU
Baseline CD4+ categories2		• <50 • 50-200	Efficacy

Subgroup	Version	Definition	Applied Analysis
		• >200	
Adherence based on pill count		• > 95% • ≤ 95%	Efficacy
Age Group	1(Adult)	**Adults** • 18-25 • 26-50 • 51-64 • ≥65	Efficacy Safety
Age Group2	1(Adult)	**Adults** • 18-30 • ≥30	MRU
BMI	1	• underweight <18.5 kg/m^2 • normal 18.5-<25 kg/m^2 • overweight 25-<30 kg/m^2 • obese ≥30 kg/m^2	Efficacy Safety
HIV-1 subtype		• B • non-B	Efficacy
Any PI RAMs (primary + secondary		• 0-3 • 4-6 • 7-9 • ≥10	Efficacy
Presence of one or more primary and/or DRV RAMs,		• Yes/No	Efficacy
Presence of one or more NRTI RAMs		• Yes/No	Efficacy
Presence of one or more NNRTI RAMs		• Yes/No	Efficacy
Presence of one or more M184I/V		• Yes/No	Efficacy
Presence of one or more Primary INI RAMs		• Yes/No	Efficacy
Presence of one or more Secondary INI RAMs		• Yes/No	Efficacy
HIV Acquisition Risk Factor		• Heterosexual contact • Intravenously injectable drug use • MSM • Multiple • Other	Efficacy Safety

2.4. Study Day and Relative Day

Study Day 1 or Day 1 refers to the start of the first study drug administration. If subjects start medication a day after baseline/screening visit, actual treatment administration date will be used as Day 1 instead of screening/baseline visit date.

All efficacy and safety assessments at all visits will be assigned a day relative to this date.

2.5. Baseline and Endpoint

Baseline is defined as the last observation prior to start of study drug.

Endpoint is defined as the last available postbaseline result within the analysis period. Unscheduled visit results are included in this definition and will be considered as the endpoint value if the unscheduled visit result is the last postbaseline result available within the analysis period.

2.6. Imputation Rules for Missing AE Date/Time of Onset/Resolution

Partial AE onset dates will be imputed as follows:

- If the onset date of an adverse event is missing day only, it will be set to:
  - First day of the month that the AE occurred, if month/year of the onset of AE is different than the month/year of the study treatment start
  - The day of study treatment start, if the month/year of the onset of AE is the same as month/year of the study treatment start date and month/year of the AE resolution date is different
  - The day of study treatment start or day of AE resolution date, whichever is earliest, if month/year of the onset of AE and month/year of the study treatment start date and month/year of the AE resolution date are same
- If the onset date of an adverse event is missing both day and month, it will be set to the earliest of:
  - January 1 of the year of onset, as long as this date is on or after the study treatment start date
  - Month and day of the study treatment start date, if this date is the same year that the AE occurred
  - Last day of the year if the year of the AE onset is prior to the year of the study treatment start date,
  - The AE resolution date.
- Completely missing onset dates will not be imputed.

Partial AE resolution dates not marked as ongoing will be imputed as follows:

- If the resolution date of an adverse event is missing day only, it will be set to the earliest of the last day of the month of occurrence of resolution or the day of the date of death, if the death occurred in that month.
- If the resolution date of an adverse event is missing both day and month, it will be set to the earliest of December 31 of the year or the day and month of the date of death, if the death occurred in that year.
- Completely missing resolution dates will not be imputed.

3. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE REVIEW

An interim analysis is planned once all subjects have been assessed for safety and resistance stopping rules. There will be no DMC analysis planned.

Interim analysis contents will be defined in DPS.

4. SUBJECT INFORMATION

The number of subjects in each analysis set will be summarized. In addition, the distribution of subjects by site ID will be presented unless otherwise noted.

4.1. Demographics and Baseline Characteristics

Table 2 presents a list of the demographic variables that will be summarized, for the ITT, EAS and PP analysis set(s). Demographics will also be summarized by study subgroups using the ITT analysis set. Additionally, all demographics and baseline disease characteristics data will be listed Substance use (alcohol consumption and nicotine use) data will be listed only.

Table 02: Demographic Variables

Continuous Variables:	**Summary Type**
Age (years)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum]).
Weight (kg)	
Height (cm)	
Body Mass Index (BMI) (kg/m^2)	
Categorical Variables:	Frequency distribution with the number and percentage of subjects in each category.
Age ([18-25 years, 26-50 years, 51-64 years, and >65 years])	
Gender (male, female, undifferentiated)	
Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Other, Unknown, Multiple)	
Ethnicity (Hispanic or Latino, not Hispanic or Latino)	
BMI ([underweight <18.5 kg/m2, normal 18.5-<25 kg/m2, overweight 25-<30 kg/m2, obese ≥30 kg/m2])	
Woman of childbearing potential (Of childbearing potential/Permanently Sterilized/ Postmenopausal/ NA)	
Nicotine use (Never used, current user, former user)	
Alcohol consumption (Never used, current user, former user)	
Highest education level (Less than high school, …)	
Marital status (Single- newer married, married, …)	
Employment status (Employed full time for wages, …)	
State belongs to (Alabama, …)	
Have insurance (Yes/no)	
Social support of the subject (Friend, Family member, …)	
Current housing situation	

[a]If multiple race categories are indicated, the Race is recorded as 'Multiple'

Table 03: Baseline HIV disease characteristics

Continuous Variables:	**Summary Type**
Baseline CD4+ (absolute count and %)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum]).
Time since diagnosis of HIV infection to study enrolment (days)	
Baseline-screening eGFR	
Baseline HIV-1 Viral load (absolute count)	
% of subjects receving PrEP prior to baseline	

Categorical Variables:	Frequency distribution with the number and percentage of subjects in each category.
All assays used to determine initial HIV diagnosis (HIV-1 Rapid Antibody Assay (4th generation), …)	
HIV confirmatory test results (Yes/No)	
CDC Disease Classification (Stage A,…)	
Worst clinical stage of HIV-infection according to WHO (Clinical stage 1 (asymptomatic), …)	
HIV Acquisition Risk Factor (MSM, …)	
Screening and Baseline viral load (<100K , ≥ 100K HIV-1 RNA copies/mL)	
Baseline CD4 cell count (<200, ≥200 [200≤x<350, 350≤ x≤500, >500] cells/mm3)	
HCV/HBV coinfection status	
Time from HIV diagnosis to enrolment (0-1) days, [1-2),days, [2-3) days, [3-7) days, [7 -14) days	
HIV-1 subtype (B, Non-B)	
Any PI RAMs (primary + secondary) (0-3,4-6,7-9, ≥10)	
Presence (Yes/No) of one or more • primary and/or DRV RAMs, • NRTI RAMs, • NNRTI RAMs, • M184I/V, • Primary INI RAMs, • Secondary INI RAMs	

If multiple race categories are indicated, the Race is recorded as 'Multiple'

4.2. Disposition Information

Screened subjects and reason for screen failures will be listed only.

The number of subjects in the following disposition categories will be summarized throughout the study:

- Subjects receiving study drug
- Subjects completing the study
- Subjects who discontinued study drug
- Reasons for discontinuation of study drug
- Subjects who terminated study prematurely
- Reasons for termination of study

The above categories will include summaries.

Additionally, discontinued subject due to stopping rules (safety or resistance) will be tabulated by stopping rule type and reason of stopping.

A listing of subjects will be provided for the following categories:

- Subjects who discontinued study drug

- Subjects who terminated study prematurely
- Subjects who discontinued study treatment due to safety stopping rule
- Subjects who discontinued study treatment due to resistance stopping rule

4.3. Treatment Compliance (Adherence)

Treatment adherence defined based on pill count.

Study drug compliance will be summarized descriptively and frequency tabulations. Cumulative treatment adherence through Week 48 will be determined.

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, 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.

"If medication kit was not returned, did subject take all the tablets?" question in CRF answered 'Yes', number of tables returned will be set to zero.

Study drug compliance (%) (**Level of adherence)** = (actual amount taken / amount to be taken) × 100%

Treatment adherence is defined as:

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

- sub-optimal-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%

The number and percentage of subjects who have at least 95% study drug compliance through the study timepoints and overall will be summarized.

Predictors of suboptimal adherence will be assessed among below intrinsic and extrinsic factors.

Intrinsic / Extrinsic factors: Gender, age category, race, ethnicity, BMI category, current tobacco use, current alcohol consumption, highest education level, employment status, social support of the subject, marital status, current housing situation, have an insurance, clinical stage of HIV infection and time to start of the study treatment.

Logistic regression model will be used to assess predictors of suboptimal adherence (<95% adherence by pill count) in the study population at week 24 and week 48 analysis timepoints.

Univariate logistic regression models will be used to assess the effect of the covariates to the adherence over specified timepoints.

A Final multivariate logistic regression model will be fitted to any covariate with significant affect (at 15% level) based on the univariate modeling. If any of the selected covariates is no longer significant at (10% significance level) in the multivariate model, it will be excluded again. Exclusion of covariates is performed stepwise with backward elimination procedure, starting with the covariate that is least significant. Covariates in the model with 10% significant level will be concluded as predictors of suboptimal adherence.

4.4. Extent of Exposure

The number and percentage of subjects who receive study drug will be summarized.

Descriptive statistics of study drug duration, in weeks, (N, mean, SD, median, and range (minimum, maximum)) will be presented for the ITT analysis set.

Subject-weeks of exposure are calculated as (days of exposure)/7. Subject-weeks will be presented.

Study drug duration is defined as (date of last dose of study drug – date of first dose of study drug) +1. Duration will be tabulated in weeks with dividing duration of exposure by 7.

Total dose days of exposure is defined as the total number of days that study drug was administered to the subject (excluding days of known study drug interruption). If dates of study drug interruptions are not fully known, in terms of start and end date of interruption, these interruptions will not be excluded from total days of exposure.

4.5. Protocol Deviations

In general, the following list of major protocol deviations may have the potential to impact subjects' rights, safety or well-being, or the integrity and/or result of the clinical study. Subjects with major protocol deviations will be identified prior to database lock and the subjects with major protocol deviations will be summarized by category.

- Developed withdrawal criteria but not withdrawn
- Entered but did not satisfy inclusion/exclusion criteria
- Received a disallowed concomitant treatment

- Received incorrect dose
- Other

4.6. Prior and Concomitant Medications

Prior and Concomitant medications will be coded using the [World Health Organization Drug Dictionary (WHO-DD)]. Prior medications are defined as any therapy used up to 30 days before the day of first dose (partial or complete) of study drug. Concomitant medications are defined as any therapy used on or after the same day as the first dose of study drug, including those that started before and continue on after the first dose of study drug.

Prior and concomitant therapies will be also grouped as follows for specific drugs, using a list of dictionary derived terms provided as metadata. These groups will be tabulated (n, %) per analysis phase:

- lipid lowering drugs
- antidiabetic drugs
- antihypertensive drugs
- drugs for cardiovascular disease
- antiosteoporotic drugs
- antidepressants
- opportunistic infection (OI) /prophylaxis drugs

Summaries of concomitant medications will be presented by ATC term. The proportion of subjects who receive each concomitant medication will be summarized as well as the proportion of subjects who receive at least one concomitant medication.

Prior medications will be summarized by ATC term.

4.7. Medical History

Subjects past and/or concomitant diseases will be tabulated by medical history categories general medical history and family history separately. Tabulation (n, %) will be done by body system and medical term. Additionally, all medical history will be listed by medical history category.

4.8. Retention in Care Analyses

Number of subjects with early study treatment discontinuation and number of subjects with a documented clinic visit within 90 days of discontinuing study drug (providing consent is not withdrawn) who attend to retention of care assessment will be tabulated.

5. EFFICACY

5.1. Analysis Specifications

5.1.1. Level of Significance

There will be no formal statistical testing.

5.1.2. Data Handling Rules

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

Imputation of left censored HIV-1 RNA values: viral load results recorded as "< 20cp/mL HIV RNA detected" "< 20cp/mL HIV RNA copies/mL Not Detected" and "NO HIV-1 RNA DETECTED
" will be scored at 19.

If there are retesting, repeating the same analyze from same collected sample, last or retested results will be used in analysis.

5.1.3. Virologic Response Definitions

The following imputation methods will be used to calculate **virologic response** at a given time point addition with applying 50/200 copies/mL as threshold.

Five imputation mechanisms are considered:

1. Observed
2. NC=F
3. M=F
4. TLOVR
5. FDA Snapshot

The first mechanism, **Observed**, does not require an imputation procedure. subjects with a missing value are disregarded in the analysis for that time point.

In the second mechanism, **NC=F**, non-completers (NC) get imputed values of failure after the moment of study treatment discontinuation. For intermediate missing values, response is imputed when the previous and next observed data are response. If a subject is still ongoing or has completed study treatment and no next observed assessment is available, missing values will be imputed via LOCF. Otherwise, intermediate missing values are imputed with failure.

In the third mechanism, **M=F**, all missing values are imputed as failure.

In the fourth mechanism TLOVR, responders/non-responders are defined according to the FDA Time To Loss Of Virologic Response algorithm; a subject is considered a responder at a given time point if the applicable HIV-RNA criterion is fulfilled at that time point and at the subsequent time point; a subject is considered a confirmed non-responder at a time point in the following situations in order of precedence:

- the subject shows a 'rebound' HIV-RNA value (≥threshold copies/mL) at that time point and the subsequent time point;
- the subject shows a confirmed rebound at an earlier time point (irrespective of re-suppression of viral load)
- the subject (permanently) discontinued at that time point or before
- intermittently missing values are considered as response if the immediately preceding and following visits demonstrated response; in case the subject had not reached the next visit yet, no imputation is performed for the missing time points, unless the subject had discontinued the trial.
- Remark: in case multiple virologic response observations are available within the same time window, all observations are used to determine TLOVR-imputed response for that time window. In case the subject has not reached the next visit yet, this subject is left out of the analysis for the missing time points.

The fifth mechanism FDA snapshot approach**:** The snapshot mechanism is based on the last available plasma HIV-1 RNA level within the window of an analysis time point. This does not necessarily coincide with the HIV-1 RNA assessment with USE = 'Y'.

The snapshot approach will classify subjects into 3 outcome categories: "virologic success", "virologic failure", or "no viral load data in the Week 48 visit window". Several subcategories of the outcome will also be presented in the analysis and are shown below. The categories below are mutually exclusive such that a subject will be included in one 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 <50/200 copies/mL in the Week 48 visit window (Week 42-54)
- Virologic failure:
  - HIV RNA ≥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 ≥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 <50/200 copies/mL (or missing)
  - Missing data during the Week 48 visit window but on study

An identified subject will be classified to the snapshot categories as follows:

Virologic response will then be categorized as follows: Yes (virologic success), or No (virologic failure and no viral load data in the Week 48 visit window).

The snapshot approach will also be displayed over time by analysis time points, and will follow the same logic as defined above week 48 time point. (please see Section Visit Windows for visit intervals)

5.2. Primary Efficacy Endpoint(s)

5.2.1. Definition

The primary efficacy endpoint is the proportion of subjects who have HIV-1 RNA <50 copies/mL at Week 48 as defined by the FDA snapshot analysis (see section 5.1.3).

5.2.2. Estimand

Population: Type 1 (HIV-1) Infected treatment naïve subjects using the ITT population.

Endpoint: Proportion of subjects who have HIV-RNA<50 copies/mL at Week 48 as defined by the FDA snapshot analysis

Measure of Intervention: Effect of the initial treatment. Missing data and discontinued subjects are included to the primary estimation as defined by the FDA snapshot algorithm.

5.2.3. Analysis Methods

The proportion of subjects who have HIV-1 RNA<50 copies/mL will be calculated along with the 95% CIs. The Wilson (Score) method for the CI will be used.

Similar analysis will be performed for the per protocol (PP) population and EAS population as sensitivity analysis.

Subgroup analysis of primary endpoint will be performed for subgroups of baseline VL categories, baseline CD4+ categories, adherence rate categories, race, age, gender, time to initial diagnosis of HIV to start of study and presence of the M184/V mutation at baseline.

5.3. Major Secondary Endpoints

5.3.1. Definition

- Proportion of subjects who have HIV-1 RNA <50 copies/mL at Week 24 as defined by the FDA snapshot analysis in ITT, EAS and PP populations.
- Proportion of subjects who have HIV-1 RNA <50 copies/mL at Week 24 and week 48 as defined by the TLOVR algorithm in ITT, EAS and PP populations.
- Proportion of subjects experiencing protocol defined virologic failure at Week 24 and Week 48 and during the extension phase in ITT population.
- Proportion of subjects lost to follow-up through 24 and 48 weeks of treatment in ITT populations.

- Mean log_{10} change in HIV-1 viral load from baseline through Week 24 and Week 48 analysis timepoints in ITT populations.

- Changes from baseline in $CD4^+$ cell count at Weeks 12, 24, and 48 in ITT population.

5.3.2. Analysis Methods

As secondary analyses, the proportion of subjects with HIV-1 RNA <50 copies/mL at each time point as defined by the FDA snapshot analysis will be analyzed using the same method as for the primary efficacy endpoint.

In addition, confirmed virologic response defined as HIV-1 RNA <50 copies/mL at Week48 determined by the TLOVR algorithm will be analyzed. TLOVR algorithm is defined at section 5.1.3.

Actual and changes from baseline values in CD4+ cell count and log_{10} HIV-1 RNA at each time point will be summarized using descriptive statistics (n, mean (SE), median, min, and max). Mean actual and change from baseline over time data will be presented box plot.

For the change from baseline following imputation methods will be used.

Two imputation mechanisms will be considered:
1. Change (observed)
2. Change (NC=F)

"Change (observed)" means: No imputation is done.

"Change (NC=F)" means:
For subjects who discontinued study treatment, all time points after discontinuation are imputed with the baseline value and thus a change of 0 (NC=F). Intermittent missing results are imputed with the last post-baseline observation carried forward (LOCF).

5.4. Resistance Analysis

5.4.1. Definition

- The number of PR, RT, IN mutations will be tabulated based on resistance tests performed at the screening/baseline visit.

- The number of treatment-emergent PR, and RT as well as specific mutations associated with resistance to DRV, FTC, and TAF based on the observed virologic failures through the study period.

- The proportion of subjects meeting resistance stopping rules, requiring discontinuation of study drug, based on the findings of screening/baseline resistance testing will be reported at week 24 and week 48 analysis.

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

5.4.2. Analysis Methods

5.4.2.1.1. Genotype

At screening HIV-1 PR/RT/IN genotype will be assessed by the GenoSure Prime® assay. Post-screening HIV-1 PR/RT genotype will be assessed by the PhenoSenseGT™ assay

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

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

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

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

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

PR, RT and IN mutations specified below.

Protease mutations

- IAS-USA[2] Primary PI RAMs (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[2] Secondary PI RAMs s (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[2] DRV RAMs (n=11)

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

RT mutations

- IAS-USA[2] NRTI RAMs (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[2] NNRTI RAMs (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[2] Thymidine Analogue Mutations (TAMs) (n=8)
  M41L, D67N, K70R, L210W, T215Y/F, K219Q/E

- IAS-USA[2] TFV RAMs

  K65R/E/N, K70E

- IAS-USA[2] FTC RAMs
  K65R/E/N, M184I/V

IN mutations

- IAS-USA[2] primary INI RAMs (n=11)

  T66I, E92Q, F121Y, Y143C/H/R, S147G, Q148H/K/R, N155H

- IAS-USA[2] secondary INI RAMs (n=10)

  T66A/K, L74M, E92G, T97A, E138A/K, G140A/S, R263K

5.4.2.1.2. Phenotype

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

If available, fold change (FC) in 50% effective concentration (EC_{50}) of ARVs will be tabulated. Loss of phenotypic susceptibility may be analyzed depending on the number of PDVF with post baseline genotype/phenotype data.

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	2.5
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 or higher version.

Adverse Drug Reaction (ADR)

ADRs will be presented. A current list of all ADRs is in 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 definition), ADRs will be tabulated separately per list.

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

- Dyslipidaemia AEOI

- Liver AEOI

  Subgroups: Cholestasis and jaundice of hepatic origin

  Hepatic failure, fibrosis and cirrhosis and other liver damage related conditions

  Liver-related investigations, signs and symptoms

  Hepatitis, non infectious

- 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

Incidence of treatment-emergent adverse events of interest will be summarized as AE summary tables.

A listing of subjects who died will be provided.

6.2. Analysis Methods

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Any AE occurring at or after the initial administration of study drug through the day of last dose plus 1 day is considered to be treatment emergent. If the event occurs on the day of the initial administration of study drug, then the event will be assumed to be treatment emergent. If the event date is recorded as partial or completely missing, then the event will be considered to be treatment emergent unless it is known to be prior to the first administration of study drug based on partial onset date or resolution date. All reported treatment-emergent adverse events will be included in the analysis. For each adverse event, the number and percentage of subjects who experience at least 1 occurrence of the given event will be summarized. 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.

AE listings will be provided for subjects who:

- Had SAEs
- Had AEs leading to discontinuation of study drug.
- Had grade 3 or 4 AE
- Who had each AEoI category

Selected safety endpoints will be explored by subgroups defined in Section 2.3. Details for subgroup analyses of safety endpoints will be provided in the DPS.

6.3. Clinical Laboratory Tests

All clinical laboratory tests will be displayed for the subjects included in the ITT analysis set.

Descriptive statistics will be presented for all chemistry, hematology, and urinalysis laboratory tests at scheduled time points. If there are retesting, repeating the same analyze from same collected sample, last or retested results will be used in analysis.

Change from baseline to each scheduled time points will be summarized for chemistry, hematology, and urinalysis (pH, and specific gravity) tests. A box plot of change from baseline to analysis timepoints will be provided for the following laboratory tests: eGFR, ALT and AST

Descriptive statistics by DAIDS toxicity grade over time will be presented. Shift summaries from baseline DAIDS toxicity grade to the worst on-treatment toxicity grade will also be presented.

If the DAIDS grading is not available, shift tables will be provided summarizing the shift in laboratory values from baseline to week 48 analysis time points with respect to abnormality criteria (low, normal, high).

6.4. Vital Signs and Physical Examination Findings

Continuous vital sign parameters including height, weight, pulse, blood pressure (systolic and diastolic), will be summarized at each assessment time point.

Changes from Baseline will be summarized for the each scheduled time points. Descriptive statistics (mean, standard deviation, median, minimum and maximum) will be presented.

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.

A listing of subjects with treatment-emergent clinically important vital signs will be presented, along with a listing of all vital sign measurements.

Vital Signs

Abnormality Code	Pulse (bpm)	DBP[a] (mmHg)	SBP[a] (mmHg)
Abnormally low	≤50	≤50	≤90
Grade 1 or mild	-	>90 - <100	>140 - <160
Grade 2 or moderate	-	≥100 - <110	≥ 160 - <180
Grade 3 or severe	-	≥110	≥180
Abnormally high	≥120	-	-

[a] Classification of adverse events related to hypotension/hypertension should be done according to the DAIDS grading table (Attachment 2 at protocol).

In determining abnormalities, the following rules are applied:

- worst grades/abnormalities are determined over the whole observational period for each trial period 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 period if it is worse than the reference corresponding to this period. 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.

7. PATIENT REPORTED OUTCOME

7.1. HIV-Treatment Satisfaction Questionnaire (HIVTSQs)

HIVTSQs will be scored as below.
Each test question (idem) will be scored a scale from 6 to 0.

Treatment satisfaction:
All the items are summed up to produce Treatment satisfaction score (range 0 to 60). The higher the score, the greater the satisfaction with treatment.

General satisfaction/Clinical subscale: Items 1,2, 3, 9 and 10.
All the items are summed to produce a score (range:0-30). The higher the score, the greater the satisfaction within this subscale.

Lifestyle/Ease subscale: items 4, 5, 6, 7 and 8
All the items are summed to produce a score (range:0-30). The higher the score, the greater the satisfaction within this subscale.

In case of missing item score, overall score of a subject will be calculated as below, providing the number of missing values does not exceed the number tolerable without unacceptable loss of reliability:

1.Sum, the existing idem scores,
2.Divide this sum by the number of existing item scores
3. Then multiply by 10.

Descriptive statistics for absolutes values and changes in HIVTSQs scores will be calculated for each question, for each subscale and overall at each timepoint, where applicable. Overall mean HIVTSQs scores and mean changes over time will be demonstrated graphically.

7.2. 4-Day Self Report

Patient self-reported adherence to study medication will be measured by 4-day recall self-report as collected Drug Adherence page of eCRF.

Patient-reported adherence rates to study treatment will be presented descriptively per analysis time point. Additionally, all self-reported adherence will be listed.

8. PHARMACOKINETICS/PHARMACODYNAMICS

8.1. Pharmacokinetics

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

Plasma concentration will be listed only.

9. HEALTH ECONOMICS

9.1. Medical Resource Utilization and Health Economics

The number of medical resource utilization will be tabulated by the type of resource (e.g., overnight hospitalization, Emergency Room visit, Outpatient visit, General practitioner visit, Specialist visit, etc.) and by classification of MRU (HIV-related, All-cause HRU). For each overnight hospitalization, further classification will be by intensive care unit use (yes, no).

Descriptive statistics of overall length of hospital stay and overall length of intensive care unit use will be tabulated throughout the study.

Costs of care will be calculated by assigning costs based on Centers for Medicare & Medicaid Services (CMS) fee schedule or MEPS as appropriate, to assessed MRU on a per subject per month basis. Descriptive statistics will be calculated to compare the costs of care from baseline

to Weeks 12, 24, and 48. Exploratory analysis might be performed examining relationship between HRU and HIVTSQs scores.

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

Direct medical costs will be calculated in United States (USA) dollars based on HRU noted above

Additionally, all MRU data will be listed.

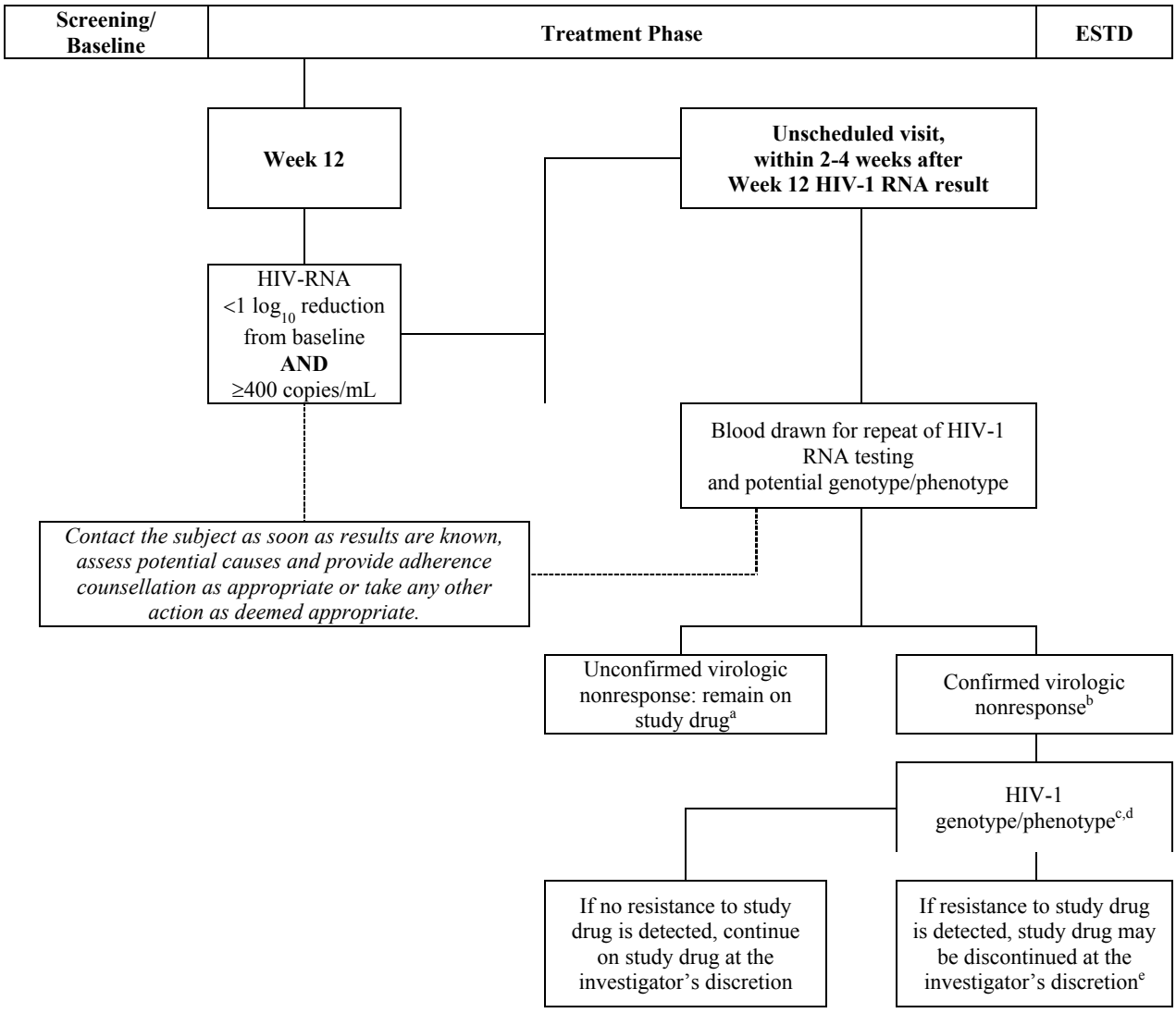
REFERENCES

1. HIV-Treatment Satisfaction Questionnaire. Available at http://www.healthpsychologyresearch.com/sites/default/files/guidelines/HIVTSQ%20Summary_rev.11.8.15.pdf . Accessed 3 March 2017
2. Wensing AM, Calvez V, Günthard HF, et al. 2017 update of the drug resistance mutations in HIV-1. Top Antivir Med Dec2016/Jan2017; 24(4):132-141 https://www.iasusa.org/sites/default/files/tam/24-4-132.pdf

ATTACHMENTS

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

Virologic Nonresponse Schema



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

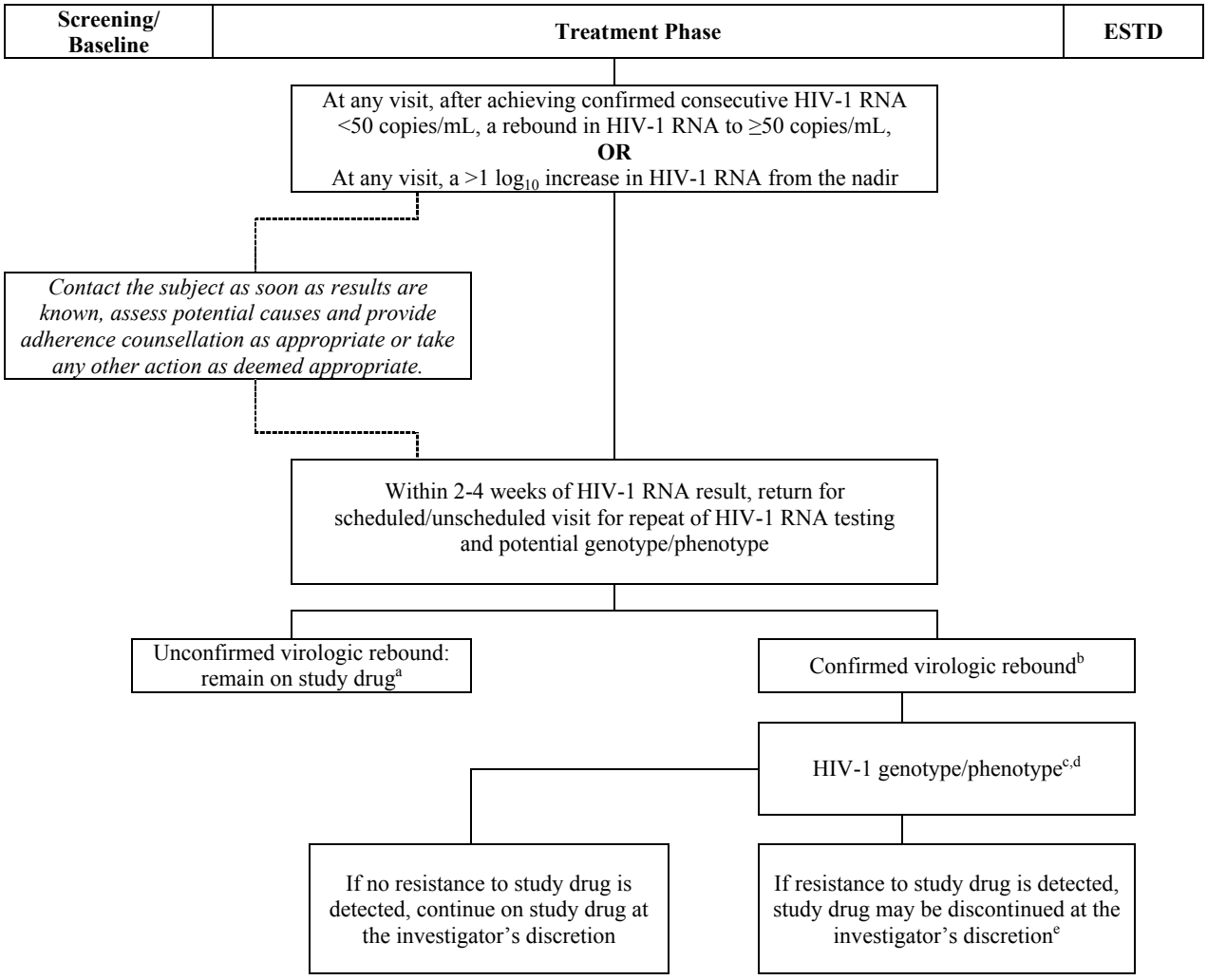
[b] Upon confirmation of virologic nonresponse potential causes should be documented. Assessment should include lack of adherence, concomitant medication, and comorbidities (eg, active substance abuse, depression, or other intercurrent illnesses).

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

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

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

Virologic Rebound Schema



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

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

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

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

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

ATTACHMENT 2: Adverse Events of Special Interest

Adverse events of special interest are defined as follows:

Adverse Events of Interest: List of Preferred Terms

AEOI	AEDECOD (MedDRA v20)
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

AEOI	AEDECOD (MedDRA v20)
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

AEOI	AEDECOD (MedDRA v20)
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

AEOI	AEDECOD (MedDRA v20)
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

AEOI	AEDECOD (MedDRA v20)
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

AEOI	AEDECOD (MedDRA v20)
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

AEOI	AEDECOD (MedDRA v20)
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

AEOI	AEDECOD (MedDRA v20)
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

AEOI	AEDECOD (MedDRA v20)
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