Statistical Analysis Plan for Clinical Study Report

Protocol Title:

Durability of Antiretroviral Suppression and the Real World Clinical Profile of the Novel 2-Drug Regimen Juluca, a Onepill-Regimen Consisting of Dolutegravir and Rilpivirine, in Routine Clinical Care in Germany

JUNGLE

eTrack ID: 208982

Version	Version 2.0
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Summary of Changes

Version Number	Version Date	Affected Section(s)	Summary of Revisions Made:
1.0	18.07.2023		Initial version
2.0	18.08.2023	Stratification variables; HIV TSQs	Specification of stratification variables and correction of HIV TSQs analysis

1 Approval – Signature page

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3 Abbreviations and Definitions

Abbreviation/Definition	Description
2DR	Two drug regime
3DR	Three drug regime
ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine Aminotransferase
ART	Antiretroviral therapy
AST	Aspartate Aminotransferase
BL	Baseline
BMI	Body mass index
CDC	United States Centers for Disease Control and Prevention (CDC); here: CDC Classification System for HIV Infection
CRF	Case Report Form
DA	Data analyses
DM	Data management

DMP	Data management plan
DOCX	Microsoft Word file
DTG	Dolutegravir
DVP	Data validation plan
EMF	Enhanced meta file
eGFR	Estimated glomerular filtration rate
FDA	U.S. Department of Health and Human Services, Food and Drug Administration
FPE	First participant enrolled
FU	Follow-up
GSK	GlaxoSmithKline
HIV	Human immunodeficiency virus
HIVTSQs	Treatment Satisfaction Questionnaire
HRQL	Health related quality of life
INSTI	Integrase inhibitor
LOCF	Last observation carried forward
LPE	Last participant enrolled
LPFV	Last participant first visit
MedDRA	Medical Dictionary for Regulatory Activities
MUC	MUC Research GmbH
NIS	Non-interventional study
NNRTI	Non-nucleosidic reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
PDF	Portable document format
PNG	Portable network graphics
RPV	Rilpivirine
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SDM	Symptoms Distress Module
ViiV	ViiV Healthcare

4 References

4.1 Internal

- SOP_Proc_StatAnalysis
- SOP_Guidance_for_Stata_Programming
- SOP_Stata_ProgVal

4.2 External

- 2.1_JUNGLE_protocol_final_14Mar2018
- a_208982_Protocol_Amendment 1_07Dec2018

5 Introduction

Introductory note:
Chapters 5 (*Introduction*), 6 (*Objectives*), 7.1, 7.2, and 7.3 (*Study design and participant enrollment*, *Sample size*, and *Participant enrollment: inclusion and exclusion criteria*) are extracted from the JUNGLE study protocol (Amendment 1; eTrack ID: 208982).

JUNGLE is a non-interventional single-arm study (NIS). This prospective, multicenter NIS will evaluate antiretroviral efficacy and tolerability of JULUCA, a novel two-drug combination of dolutegravir, an HIV-1 integrase strand transfer inhibitor (INSTI), and rilpivirine, an HIV-1 non-nucleoside reverse transcriptase inhibitor (NNRTI), in a real-world setting in Germany.

Recruitment target is a total of N=250 treatment-experienced and virologically suppressed patients, with a minimum of 180 participants. Inclusion into the study is independent from prescription of JULUCA. Eligible subjects will be followed up for approximately 3 years collecting information that can be obtained in routine clinical care.

The sample is deliberately non-stratified to reduce limitations on recruitment. The JUNGLE study is not hypothesis testing, but rather of descriptive nature; statistical analysis will be of descriptive nature only.

6 Objectives

Annotation: Timepoints for primary and secondary objectives are specified in section 11. *Planned Analyses*.

6.1 Primary Objective

Evaluate sustainability of antiretroviral suppression in suppressed patients using JULUCA in routine clinical care in Germany to evaluate antiretroviral efficacy of the novel 2-Drug Regimen (2DR) of JULUCA

6.2 Secondary Objectives

- Gain an understanding of the major relevant patient populations for JULUCA in Germany, in terms of patient characteristics and history
- Describe real-life efficacy profile of JULUCA
- Describe real-life tolerability profile of JULUCA as measured by discontinuation rates due to adverse drug reactions (ADRs) and overall number of serious adverse events (SAEs)
- Analyze the development of viral resistance by evaluating available resistance data in case of virologic failure
- Describe impact on lipid metabolism
- Evaluate medical need for a substance and/or class sparing treatment regimen by assessing the reason for switching to JULUCA
- Describe participants' treatment satisfaction and symptom distress based on validated questionnaires
- Evaluate number of monitoring measures and referrals to other specialists

7 Study methods

7.1 Study design and participant enrollment

- Prospective, non-interventional, single-arm, multi-center study of participants with a clinical indication for HIV-1 therapy in routine clinical care with an observational period of 3 years.
- Investigators may enroll eligible subjects according to their availability and accessibility. The sample is deliberately nonstratified to reduce limitations on recruitment. This nonprobabilistic convenience sampling may not ensure for the sample group to be a true representative of the population without sampling error.
- Inclusion into the study is independent from prescription of JULUCA.
- Data collected during routine clinical care will be documented as study visits. This may include data from hospital records, clinical charts, electronic patient records or laboratory notes.
- Once a year and additionally at first follow-up visit, participants will be asked to complete the HIV Symptom Distress Module and the HIV treatment satisfaction questionnaire on a voluntary basis
- At each visit, participants will be prompted to give an estimate of their level of adherence in a single-item question

7.2 Sample size

Sample size was calculated based on the assumption of an antiviral efficacy of 90% (defined as VL <50 c/ml) and a max. study dropout rate of 30% over a period of 3 years. To reach a level of confidence of 95% with a target width of 0.1 (10%), a minimum of N=158 subjects are needed at the end of the study. When max. drop-out rate is included, a minimum number of N=226 subjects are needed. Therefore, the recruitment goal is N=250. If 250 participants cannot be recruited within 6 months, recruitment period may be extended until a minimum number of 180 participants is reached.

7.3 Study population: Inclusion and exclusion criteria

7.3.1 Inclusion criteria

- ≥ 18 years of age
- Documented HIV-1 infection
- Virologically suppressed (HIV RNA < 50 c/mL for at least 6 months)
- Prescription for JULUCA was issued independently from entering this study
- Ability to understand informed consent form and other relevant study documents

7.3.2 Exclusion criteria

- Any contraindication according to JULUCA SmPC
- Documented viral load > 50 c/ml at any timepoint within 6 months prior to inclusion into this study
- History of treatment failure
- Known or suspected substitutions associated with resistance to any NNRTI or INSTI
- Any antiretroviral therapy for the treatment of HIV-1 in addition to JULUCA
- HBV-coinfection
- Current participation in the ongoing non-interventional study
- TRIUMPH (study number: 202033) or any interventional clinical trial irrespective of indication
- Previous participation in clinical trials involving JULUCA

7.4 Flow chart

For details see 11.2 and 11.3.

Visit / Forms	Enrollment visit	Baseline visit (=last visit before start of therapy with DTG+RPV)	(Routine-based) Follow-up visits until end of study	Study discontinuation	Independent of visits, continuous reporting
Informed consent	X				
In-, exclusion criteria	X				
Date of start with JULUCA		X			
Demography		X			
HIV/ART history		X			
Anamnesis (drug adherence, pregnancy, vital signs incl. weight)		X	X	X	
Laboratory parameters (hematology, metabolic parameters and clinical chemistry, transaminases and lipids)		X	X	X	
Comedication		X	X	X	
Comorbidities		X	X	X	
Referrals to another medical specialist		X	X	X	
Resistance mutation testing		X	X	X	
HIV TSQ		X	X	X	
HIV SDM		X	X	X	
Date & reason of study discontinuation				X	
Post ART				X	
ADR/SAE					X
HIV-related characteristics (laboratory parameters)					X

7.5 Data management and analyses

The data management analyses will be performed by MUC Research GmbH after the finalization and approval of this SAP document by the sponsor and after data lock (following final reconciliation of data bases, Data Review Meeting) and database lock.

8 Analysis population, analyses sets

8.1 Modified Full Analysis Set

After closure of the database, all analyses will be based on the modified Full Analysis Set (mFAS) defined as follows:

- all participants of the FAS without
  - violation of in- or exclusion criteria (screening failures)major protocol violations (see 9)
- participants with protocol deviations may be excluded upon decision of the data review meeting.

The decision on the mFAS set will be made during the data review meeting prior to database lock.
A listing of all protocol violations and deviations will be produced, including the assessment major/minor and the procedure/consequence which followed.

8.2 Effectiveness Set

Following the primary endpoint, the effectiveness set comprises all participants of the mFAS except for
- participants lost to follow up (irrespective of last HIV-RNA level)
- participants on drug but without HIV-RNA in time window.

8.3 Safety Analysis Set

The safety analysis set includes all subjects who received at least one dose of DTG+RPV.

8.4 Subgroup Analysis

Specific study groups (see stratification Variable in 11.1.2) will be analyzed.

9 Protocol violations and deviations

Major protocol violations may include, but are not limited to:
- inclusion/exclusion criteria not met

Other protocol violations or deviations may include, but are not limited to:
- Prescription of JULUCA not according to its indication based on the latest SmPC at the time of prescription;

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10 Statistical Methods

10.1 Definition of analysis time window

10.2 Year 1, 2, and 3 follow-up windows

Year 1 follow-up window is defined as 9 to 15 months [275 days; 457 days] after the therapy start. This window applies to all variables incl. patient reported outcomes.

Rule for two or more assessments in the time window:
The closest available assessment to year 1 (365 days) after therapy start while the participant is on treatment and continued on study within the time window.

Year 2 follow-up window is defined as 21 to 27 months [640 days; 822 days] after the therapy start. This window applies to all variables incl. patient reported outcomes.

Rule for two or more assessments in the time window:
The closest available assessment to year 2 (730 days) after therapy start while the participant is on treatment and continued on study within the time window.

Year 3 follow-up window is defined as 33 to 39 months [1005 days; 1185 days] after the therapy start. This window applies to all variables incl. patient reported outcomes.

Rule for two or more assessments in the time window:
The closest available assessment to year 3 (1095 days) after therapy start while the participant is on treatment and continued on study within the time window.

10.2.1 Time period for incident (serious) adverse drug reactions and serious adverse events

For incident (S)ADRs/SAEs the following time window will be used:
Date of year 3 follow-up visit minus date of therapy start.

10.3 Statistical methods

- Missing data:

  For descriptive statistics, analyses will be based on valid (or observed) data per parameter (resulting in different sample sizes).

  The following data imputations will be performed:

  HIVTSQs (10 item version) score: If ≤3 items in one questionnaire are missing, mean of all other non-missing items of this participant at this visit will be imputed. If >3 items in one participant at a visit are missing, the whole score of this participant is set to missing

  For HIVTSQs individual item analysis no data will be imputed. However, the basis for this analysis will be the set of participants who completed the questionnaire at both time points

No further data imputation is performed.

- The frequency and proportions (based on the non-missing sample size) of observed levels will be reported for categorical measures.
- Continuous variables will be summarized using the following descriptive statistics: n (non-missing sample size), mean, standard deviation, median, selected quantiles (lower quartile (25%), upper quartile (75%)), minimum and maximum.
- All analyses will be performed respective analyses sets and the subgroups specified in 11.1.2

10.4 Participant disposition/analyses sets

Results based on the analyses according to the SAP will be provided in tables and listings and implemented in the study report where appropriate.

Subject disposition will include:

- number of subjects in the FAS, number of subjects in the mFAS
- number of study sites in the FAS, number of study sites in the mFAS
- number and listing of all subjects excluded from the mFAS (with reasons)
- listing of all protocol violations and deviations, including the assessment major/minor and the procedure/consequence which followed.

The following dates will be displayed:

- date of first participant enrolled
- date of last participant enrolled
- date of first start with DTG+RPV
- date of last start with DTG+RPV
- date of last participant last visit

11 Planned Analyses

The CSR is planned to comprise the baseline characteristics, all primary and secondary endpoints (see chapters 11.3 and 11.3.2 respectively) as well as other relevant variables as described below.

11.1 Variables of interest

11.1.1 Variables identified for analysis

<u>Baseline characteristics</u>

- Demographics (see 11.2.1)
- Body weight and BMI (see 11.2.2)
- HIV-related characteristics (see)
- Previous ART regime and reason for switch to DTG+RPV (see 11.2.4)
- Laboratory parameters (renal parameters, transaminases, lipids and white and red blood counts) (see 11.2.5)

- Comorbidities and comedication at baseline (see 11.2.6)
- HIV Symptoms Distress Module (SDM) and treatment satisfaction questionnaire (HIVTSQs) (see 11.2.7)

Follow-up data

- Virologic response at years 1, 2 and 3* (including primary and secondary endpoints; for details see 11.3.1 and 11.3.2)
- Immunologic response (see 11.3.3)
- Participant self-assessment of adherence (see 11.3.4)
- Premature study discontinuation: yes/no, reason and date (see 11.3.5)
- Incident comorbidities (see 11.3.6)
- New comedications (see 11.3.6)
- Referrals to another medical specialist (see 11.3.7)
- Laboratory parameters (renal parameters, transaminases, lipids and blood count) (see 11.3.8)
- Body weight and BMI (see 11.3.9)
- (Serious) adverse drug reactions and serious adverse events (see 11.3.10)
- Pregnancies (see 11.3.11)
- HIV Symptoms Distress Module (SDM) and treatment satisfaction questionnaire (HIVTSQs) (see 11.3.12)

*(Variables identified with * refer to the primary endpoint)*

11.1.2 Stratification variables

Primary endpoint described under 11.3.1 is planned to be analyzed in respect to the total study population and in following subgroups:

- Age groups (<50 vs ≥50 years)

Secondary endpoints (HIV SDM, HIV TSQs, reason for switch to DTG+RPV, lipids, and safety parameters), described under 11.3.2 are planned to be analyzed in respect to the total study population and in following subgroups:

- Age groups (<50 vs ≥50 years)
- Relevant comorbities at baseline (yes/no)

11.2 Baseline (BL) characteristics

11.2.1 Demographics

- Age at baseline [years]
- Proportion of participants aged <50 vs ≥50 years (calculated)
- Sex/gender

11.2.2 BL body weight and BMI

- Weight [kg]
- BMI [kg/m²] (calculated)

11.2.3 HIV-related characteristics

- Proportion of participants with CDC stage A or B or C
- Proportion of participants with HIV-RNA <50 copies/mL
- Absolute CD4 cell count [cells/µL]
- Proportion of participants with absolute CD4 cell counts <200/µL; 200-349/µL; 350-499/µL; ≥ 500/µL (calculated)
- Relative CD4 cell count [%]
- Absolute CD8 cell count [cells/µL]
- Relative CD8 cell count [%]
- CD4/CD8 ratio (calculated)
- Proportion of participants with CD4/CD8 ratio <1 vs ≥1 (calculated)
- Detected resistance mutations prior to treatment with DTG+RPV (listing of mutations)

11.2.4 Previous ART regime and reason for switch to DTG+RPV

- Time since first HIV diagnosis [years]
- Time on antiretroviral treatment prior switch to DTG+RPV [years]
- Time on last ART regime prior switch to DTG+RPV [years]
- Number of treatment switches (categories), (N, %)
- Last ART regime prior switch to DTG+RPV (N, %)
- Primary and secondary reasons for therapy switch: Proportion of participants switched for the specific reasons; incl. listing of 'other' reason
- Proportion of participants with relevant adverse events of the previous ART treatment; incl. listing of the relevant adverse events

11.2.5 Laboratory parameters at BL

11.2.5.1 Renal parameters at BL

- Serum creatinine [mg/dL]
- eGFR [mL/min/1.73 m²] (calculated)

CKD-EPI Creatinine Equation (2021)

$eGFR_{cr} = 142 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.200} \times 0.9938^{Age} \times 1.012$ [if female]

(Scr = standardized serum creatinine in mg/dL; κ = 0.7 (females) or 0.9 (males); α = -0.241 (female) or -0.302 (male); min(Scr/κ, 1) is the minimum of Scr/κ or 1.0; max(Scr/κ, 1) is the maximum of Scr/κ or 1.0; Age (years))

- Blood nitrogen urea [mg/dL]

11.2.5.2 Liver parameters at BL

- ALT [U/L]
- AST [U/L]
- Gamma-GT [U/L]
- Total bilirubin [mg/dL]
- Bilirubin, direct [mg/dL]
- Alkaline phosphatase [U/L]

11.2.5.3 Lipids at BL

- Total cholesterol [mg/dL]
- LDL cholesterol [mg/dL]
- HDL cholesterol [mg/dL]
- Triglycerides [mg/dL]

11.2.5.4 Blood count at BL

- Hemoglobin [g/dL]
- Hematocrit [%]
- Red blood cells (RBC, erythrocytes) [$x10^6$/µL (T/L)]
- White blood cells (WBC, leukocytes) [$x10^3$/µL (G/L)]
- Lymphocytes [%]
- Platelets [G/L]

11.2.5.5 Serum chemistry at BL

- Amylase [U/L]
- Lipase [U/L]
- Lactate dehydrogenase (LDH) [U/L]
- Creatinine kinase (CK) [U/L]
- Serum glucose [mg/dL]
- Uric acid [mg/dL]
- Serum albumin [mg/dL]
- C reactive protein (CRP) [mg/dL]
- Quick [%]

11.2.5.6 Urine chemistry at BL

- Qualitative urine analysis (urine dipstick): leukocytes, pH value, proteins, bilirubin, urobilinogen, nitrite, glucose, ketones, and blood
- Quantitative urine parameters will be listed:
  - Total protein [mg/L]

- Albumin [mg/L]
- Creatinine [g/L]
- Phosphate [g/L]
- Glucose [mg/L]
- α-1-microglobuline [mg/L]

11.2.6 Comorbidities, concomitant medication

- Proportion of participants with a diagnosis of the relevant comorbidity-classes (prevalent at baseline)
- Proportion of participants treated with the relevant comedication-classes (prevalent at baseline)

11.2.7 HIV Symptoms Distress Module (SDM) and HIV Treatment Satisfaction Questionnaire (HIVTSQs) at BL

11.2.7.1 HIV Symptoms Distress Module (SDM) at BL

The HIV SDM is a 20-item self-reported measure that addresses the presence and perceived distress linked to symptoms commonly associated with HIV or its treatment. HIV SDM is a validated instrument to assess a total of 20 symptoms on a 5-point scale (0: CCI .'; 1: 'CCI .'; 2: 'CCI .'; 3: CCI '; 4: 'CCI .')
Total symptom distress will be calculated as the unweighted sum of the 20 items with scores ranging from 0 to 80. Higher scores indicate higher degrees of symptom distress.

Each of the following parameters of the SDM will be calculated as observed.

- SDM completed (yes/no)
- SDM total score

11.2.7.2 HIV Treatment Satisfaction Questionnaire (HIVTSQs) at BL

The HIVTSQs is a self-reported scale that measures overall satisfaction with treatment and by specific domains e.g., convenience, flexibility. HIVTSQs is a validated 10-item instrument with scores per item ranging from 0 CCI to 6 CCI with a recall period encompassing 'the past few weeks'; scores (per item) from 1 to 5 do not have specific descriptions defined on the questionnaire but represent intermediary responses between CCI (0) and CCI (6).
HIVTSQs Overall Treatment Satisfaction score:

- will be calculated as the unweighted sum of all 10 items of the HIVTSQs
- Total score range: 0–60 (with higher scores indicating greater treatment satisfaction)

The HIVTSQs total score will be calculated as described in section 10.3 and individual item scores will be calculated as observed.

- HIVTSQs completed (yes/no)
- HIVTSQs total score
- HIVTSQs individual item scores

11.3 Follow-up (FU) data

11.3.1 Primary Endpoint at year 3 follow-up

Primary endpoint is the proportion of participants with sustained virologic suppression, defined as HIV-RNA <50 copies/mL or if between 50-200 copies/mL with a subsequent next available measurement* (within 120 days) <50 copies/mL at year 3 follow-up.

*(*Any subsequent measurement will be accepted as a consecutive measurement as long as measured no later than 120 days after the initial measurement. If no subsequent HIV-RNA measurement is performed within 120 days this is scored as a confirmed HIV-RNA ≥200 copies/mL)*

Listing for participants excluded for primary endpoint analyses for the following reason:

- Lost to follow-up

11.3.2 Secondary Endpoints (EPs) (analyzed at years 1, 2 and 3 follow-up, unless otherwise stated)

- Primary endpoint is the proportion of participants with sustained virologic suppression, defined as HIV-RNA <50 copies/mL or if between 50-200 copies/mL with a subsequent next available measurement* (within 120 days) <50 copies/mL at years 1 and 2 follow-up
- Proportion of participants with HIV-RNA <50 copies/mL at years 1, 2 and 3 follow-up
- Proportion of participants with low level viremia, defined as a HIV-RNA measurement ≥50 copies/mL and <200 copies/mL at years 1, 2 and 3 follow-up
- Proportion of participants with virologic rebound, defined as two consecutive HIV-RNA measurements ≥200 copies/mL from baseline until year 3 follow-up
- Proportion of participants with two consecutive measurements of ≥200 copies/mL, or treatment switch due to virologic failure or due to intolerability as determined at the discretion of the physician from baseline until year 3 follow-up
- Number of HIV monitoring measures (HIV-RNA measurements) [normalized to participant years] from baseline until year 3 follow-up
- Number and frequency of serious adverse events (SAEs) from baseline until year 3 follow-up [normalized to participant years] (see 11.3.10)
- Number and frequency of adverse drug reactions (ADRs) from baseline until year 3 follow-up [normalized to participant years] (see 11.3.10)
- Adherence to therapy [refers to missed monthly doses] at years 1, 2 and 3 follow-up (see 11.3.4)
- Change in lipid laboratory values at years 1, 2 and 3 follow-up (see 11.3.8.3)
- Change in treatment satisfaction [HIV Treatment Satisfaction questionnaire] at years 1, 2 and 3 follow-up (see 11.3.12.2)
- Change in symptom distress [HIV Symptom Distress Module questionnaire] at years 1, 2 and 3 follow-up (see 11.3.12.1)
- Reason for switch to DTG+RPV (see 11.3.5)
- Referral to other medical specialist from baseline until year 3 follow-up (see 11.3.7)
- Proportion of participants with resistance testing from baseline until year 3 follow-up
- Listing of detected resistance-associated mutations from baseline until year 3 follow-up
    - Listing of new (emerging) resistance-associated mutations, incl. resistance-associated mutations detected prior to treatment with DTG+RPV and last HIV-RNA

11.3.3 Immunologic response at years 1, 2 and 3 follow-up

- Absolute CD4 cell count [cells/µL]
- Change in absolute CD4 cell count [cells/µL] from baseline; comparison of levels within groups (paired observations, Wilcoxon signed rank test)
- Proportion of participants with absolute CD4 cell counts <200/µL; 200-349/µL; 350-499/µL; ≥ 500/µL (calculated)
- Absolute CD8 cell count [cells/µL]
- Change in absolute CD8 cell count [cells/µL] from baseline; comparison of levels within groups (paired observations, Wilcoxon signed rank test)
- CD4/CD8 ratio (calculated)
- Change in CD4/CD8 ratio (calculated) from baseline
- Proportion of participants with CD4/CD8 ratio <1 vs ≥1 (calculated)
- Change in proportion of participants with CD4/CD8 ratio <1 vs ≥1 (calculated) from baseline

11.3.4 Participant self-assessment of adherence at years 1, 2 and 3 follow-up

- Participant self-assessment of adherence of last months (i.e. missed doses) (N, %)

11.3.5 Study discontinuation prior to year 3 follow-up

- Proportion of participants discontinued the JUNGLE study prior to year 3 follow-up visit
- Reasons for study discontinuation (N, %) - incl. listing of 'other' reason
- Participants discontinued due to virologic reasons: LOCF HIV-RNA copies/mL (listing)
- ART regimes after discontinuation of the JUNGLE study (N, %)

11.3.6 Incident comorbidities and new comedications

- Proportion of participants with a new (incident) diagnosis of the relevant comorbidity-classes (all observations from baseline until year 3 follow-up)

- Proportion of participants treated with a new (incident) relevant comedication-classes (all observations from baseline until year 3 follow-up)

11.3.7 Referrals to another medical specialists

- Percentage of participants referred to another medical specialists (all referrals from baseline until year 3 follow-up)

11.3.8 Laboratory parameters at years 1, 2 and 3 follow-up

11.3.8.1 Renal parameters at years 1, 2 and 3 follow-up

- Serum creatinine [mg/dL]
- Change in serum creatinine [mg/dL] from baseline
- eGFR [mL/min/1.73 m^2] (calculated)

CKD-EPI Creatinine Equation (2021)
$eGFR_{cr} = 142 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.200} \times 0.9938^{Age} \times 1.012$ [if female]

(Scr = standardized serum creatinine in mg/dL; κ = 0.7 (females) or 0.9 (males); α = -0.241 (female) or -0.302 (male); min(Scr/κ, 1) is the minimum of Scr/κ or 1.0; max(Scr/κ, 1) is the maximum of Scr/κ or 1.0; Age (years))

- Change in eGFR [mL/min/1.73 m²] from baseline
- Blood nitrogen urea [mg/dL]
- Change in blood nitrogen urea [mg/dL] from baseline

11.3.8.2 Liver parameters at years 1, 2 and 3 follow-up

- ALT [U/L]
- Change in ALT [U/L] from baseline
- AST [U/I]
- Change in AST [U/I] from baseline
- Gamma-GT [U/L]
- Change in gamma-GT [U/L] from baseline
- Total bilirubin [mg/dL]
- Change in total bilirubin [mg/dL] from baseline
- Bilirubin, direct [mg/dL]
- Change in bilirubin, direct [mg/dL] from baseline
- Alkaline phosphatase [U/L]
- Change in alkaline phosphatase [U/L] from baseline

11.3.8.3 Lipids at years 1, 2 and 3 follow-up

- Total cholesterol [mg/dL]
- Change in total cholesterol [mg/dL] from baseline
- LDL cholesterol [mg/dL]
- Change in LDL cholesterol [mg/dL] from baseline
- HDL cholesterol [mg/dL]
- Change in HDL cholesterol [mg/dL] from baseline
- Triglycerides [mg/dL]
- Change in triglycerides [mg/dL] from baseline

11.3.8.4 Blood count at years 1, 2 and 3 follow-up

- Hemoglobin [g/dL]
- Change in hemoglobin [g/dL] from baseline
- Hematocrit [%]
- Change in hematocrit [%] from baseline
- Red blood cells (RBC, erythrocytes) [$x10^6$/µL (T/L)]
- Change in red blood cells (RBC, erythrocytes) [$x10^6$/µL (T/L)] from baseline
- White blood cells (WBC, leukocytes) [$x10^3$/µL (G/L)]
- Change in white blood cells (WBC, leukocytes) [$x10^3$/µL (G/L)] from baseline
- Lymphocytes [%]
- Change in lymphocytes [%] from baseline
- Platelets [G/L]

- Change in platelets [G/L] from baseline

11.3.8.5 Serum chemistry at years 1, 2 and 3 follow-up

- Amylase [U/L]
- Change in amylase [U/L] from baseline
- Lipase [U/L]
- Change in lipase [U/L] from baseline
- Lactate dehydrogenase (LDH) [U/L]
- Change in lactate dehydrogenase (LDH) [U/L] from baseline
- Creatinine kinase (CK) [U/L]
- Change in creatinine kinase (CK) [U/L]
- Serum glucose [mg/dL]
- Change in serum glucose [mg/dL] from baseline
- Uric acid [mg/dL]
- Change in uric acid [mg/dL]
- Serum albumin [mg/dL]
- Change in serum albumin [mg/dL] from baseline
- C reactive protein (CRP) [mg/dL]
- Quick [%]

11.3.8.6 Urine chemistry at years 1, 2 and 3 follow-up

- Qualitative urine analysis (urine dipstick): leukocytes, pH value, proteins, bilirubin, urobilinogen, nitrite, glucose, ketones, and blood
- Quantitative urine analysis, displayed as listing:
  - Total protein [mg/L]
  - Albumin [mg/L]
  - Creatinine [g/L]
  - Phosphate [g/L]
  - Glucose [mg/L]
  - α-1-microglobuline [mg/L]

11.3.9 Body weight and BMI at years 1, 2 and 3 follow-up

- Weight [kg]
- Change in weight [kg] from baseline;
- BMI [kg/m²] (calculated)
- Change in BMI [kg/m²] (calculated) from baseline

11.3.10 (Serious) adverse drug reactions and serious adverse events from baseline until year 3 follow-up

Incident (serious) adverse drug reactions [(S)ADRs] and severe adverse events [SAEs] of each participant will be presented in listings and as

- Number and frequency of SAEs [normalized to patient years]
- Number and frequency of (S)ADRs [normalized to patient years]

For definition of periods see 10.2.1.

In detail the following parameters will be evaluated:

Include nature of the (S)ADR/SAE (MedDRA System Organ Class and MedDRA Preferred Term), date and time of onset and resolution, intensity, causal relationship with DTG+RPV, seriousness, interruption or withdrawal of DTG+RPV, countermeasure and outcome.

Handling of repeated events in the summary statistics:

- 'per participant': Each subject will only be counted once and any repetitions of (S)ADR/SAE will be ignored; the denominator will be the total population size.
- 'per MedDRA term': All MedDRA terms will be counted and the repetitions of (S)ADR/SAE will be not ignored; the denominator will be the total MedDRA term number.

11.3.11 Pregnancies from baseline until year 3 follow-up

- Listing of incident pregnancies

11.3.12 HIV Symptoms Distress Module (SDM) and HIV Treatment Satisfaction Questionnaire (HIVTSQs) at years 1, 2 and 3 follow-up

11.3.12.1 HIV Symptoms Distress Module (SDM)

Each of the following parameters of the SDM will be calculated as observed.

- SDM completed (yes/no)
- SDM total score
- Change in SDM total score from baseline

11.3.12.2 HIV Treatment Satisfaction Questionnaire (HIVTSQs) at years 1, 2 and 3 follow-up

The HIVTSQs total score will be calculated as described in section 10.3 and individual item scores will be calculated as observed.

- HIVTSQs completed (yes/no)
- HIVTSQs total score
- Change in HIVTSQs total score from baseline
- HIVTSQs individual item scores
- Change in HIVTSQs individual item scores from baseline

12 Software

Data merge and statistical analyses will be carried out using the STATA® package (version Stata/SE 17).

13 Output Format

Tables and listings will be provided as Portable Document Format (PDF) or Microsoft Word (DOCX) file. Figures will be provided as Enhanced Meta File (EMF) and/or Portable Network Graphics (PNG) file.