Janssen Research & Development

Statistical Analysis Plan

A Phase II, open label, single arm trial to evaluate the pharmacokinetics, safety, tolerability, and antiviral activity of rilpivirine (TMC278) in antiretroviral naïve HIV-1 infected adolescents and children aged ≥ 6 to <18 years

Protocol TMC278-C213 (cohort 2, Final Analysis); Phase II

Edurant®/TMC278 (rilpivirine) oral

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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

NA

ABBREVIATIONS

17-OH	17-hydroxyprogesteron
3TC	lamivudine
ABC	abacavir
ACTH	adrenocorticotropic hormone
AE	Adverse Events
AESI	Adverse Events of Special Interest
ALT	alanine transaminase
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate transaminase
ATC	Anatomic and Therapeutic Chemical
AUC	area under the curve
AZT	zidovudine
BMI	Body Mass Index
CD4	cluster of differentiation 4
CI	Confidence Interval
CRF	Case Report Form
DAIDS	Division of AIDS
DHEAS	dehydroepiandrosterone-sulfate
DPS	Data Presentation Specifications
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
EOI	event of interest
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
FTC	Emtricitabine
FU	Follow Up
HIV-RNA	Human immunodeficiency virus Ribonucleic Acid
HR	Heart Rate
IDMC	Independent Data Monitoring Committee
ICH	International Conference on Harmonization
kg	Kilogram
LH	luteinizing hormone
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
mL	millilitre
NAP	Not Applicable
N(t)RTI	nucleoside/nucleotide reverse transcriptase inhibitors

nmol	nanomol
PBMC	peripheral blood mononuclear cell
PD	Pharmacodynamic
PK	Pharmacokinetic(s)
q.d.	quaque die (one a day)
QTc	corrected QT interval
QTcB	Bazett's square-root corrected QT
QTcF	Fridericia's square-root corrected QT
RPV	Rilpivirine
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
WHO-DD	World Health Organization-Drug Dictionary

1. INTRODUCTION

This statistical analysis plan (SAP) contains definitions of analysis sets, derived variables, and statistical methods for the final analysis of efficacy (antiviral activity), safety, tolerability and pharmacokinetics (PK) of the study TMC278-C213 Cohort 2 (children aged ≥6 to <12 years) for oral rilpivirine (RPV; TMC278). The SAP is to be interpreted in conjunction with the protocol amendment 10 dated 03 February 2020.

The final analysis will be performed when all participants of Cohort 2 have completed the Week 48 visit or discontinued earlier. It will also include the analysis of the post week 48 treatment extension period.

Analyses of TMC278-C213 Cohort 1 (adolescents aged ≥12 to <18 years) data at Week 24 (primary analysis), at Week 48 (interim analysis) and at Week 240 (final analysis) were described in the corresponding SAPs. These analyses have been completed. Therefore, this document focuses only on Cohort 2 (children aged ≥ 6 to < 12 years) analysis.

The Pediatric development of oral RPV is comprised of 2 studies: ie, TMC278-C213 (cohort 2) in HIV-1 infected ARV-naïve subjects aged ≥6 to <12 years and TMC278HTX2002 in HIV-1 infected virologically suppressed subjects aged ≥2 to <12 years. All Efficacy and Safety analyses described in this SAP will be performed separately for study TMC278HTX2002 (see the SAP for HTX2002 Week 24 and Week 48 Analysis), whereas PK analyses will be performed on pooled pharmacokinetic data from both TMC278HTX2002 and TMC278-C213 Cohort 2 studies.

1.1. Trial Objectives

The objectives are:

- to evaluate the steady-state pharmacokinetic (based on intensive PK analysis) of RPV 25 mg q.d. or adjusted dose of RPV (q.d.) in subjects aged ≥12 to <18 years and ≥6 to <12 years;
- to evaluate short-term safety, tolerability and antiviral activity/efficacy of RPV in these age groups;
- to evaluate safety, tolerability and efficacy of RPV over a 24-week (Cohort 1 only) and 48-week (Cohort 1 and 2) treatment period;
- to evaluate immunologic changes (as measured by $CD4^+$ cell parameters) over 24 weeks (Cohort 1 only) and 48 weeks (Cohort 1 and 2) of treatment with RPV;
- to assess the evolution of viral genotype and phenotype over 24 weeks (Cohort 1 only) and 48 weeks (Cohort 1 and 2) of treatment with RPV;
- to evaluate pharmacokinetics (by means of population pharmacokinetics) and pharmacokinetic-pharmacodynamic relationships for safety and efficacy of RPV;
- to evaluate treatment adherence as measured by the Study Adherence Questionnaire for Children and Teenagers/Caregivers (see Addendum 7 and 8 of the Clinical Trial Protocol respectively).
- to evaluate safety, tolerability and efficacy of RPV for up to 240 weeks of treatment (Cohort 1 only).
- to assess the palatability of the 2.5-mg tablet formulation of RPV, if applicable.

1.2. Trial Design

This is a Phase II, open label, single arm trial to evaluate the pharmacokinetics, safety, tolerability and efficacy of RPV 25 mg q.d. or adjusted dose of RPV (q.d.) in combination with an investigator-selected background regimen containing 2 nucleoside/nucleotide analogue reverse transcriptase inhibitors (N(t)RTIs [AZT, ABC, or TDF in combination with 3TC or FTC, age-appropriate formulations are to be used]), in antiretroviral (ARV) treatment-naïve adolescents and children aged ≥6 to <18 years. The study includes two cohorts:

- Cohort 1: adolescents aged ≥12 to <18 Years

- Cohort 2: children aged ≥6 to <12 Years

As Cohort 1 has been completed, this document focuses on Cohort 2.

In Cohort 2 of the trial, per the study protocol Amendment 10, ARV treatment-naïve HIV-1 infected participants aged ≥6 to <12 years with a plasma viral load ≥500 HIV-1 RNA copies/mL but ≤100,000 HIV-1 RNA copies/mL are included.

Up to study protocol Amendment 9, the study consisted of an initial treatment period of 48 weeks and a post Week 48 treatment extension period of 4 years (192 weeks). As of the study protocol Amendment 10, the post Week 48 treatment extension period of 4 years was removed for Cohort 2 participants. Participants who continue experiencing clinical benefit from RPV and their background regimen comprising 2 investigator-selected N(t)RTIs at the end of the initial 48-week treatment period, or ongoing participants who were already in the post Week 48 treatment extension period at the time of study protocol Amendment 10, continue treatment (ie, RPV + 2 N[t]RTIs) in the roll-over study TMC278IFD3004 or switch to locally available RPV (once commercially available AND reimbursed, OR accessible through another source [e.g. access program or government program]), or other locally available RPV-based regimens.

The analysis of the first 10 participants in Cohort 2, including PK modeling and simulation to further assess the RPV pediatric dose based on accumulating data, was discussed with and endorsed by the Independent Data Monitoring Committee (IDMC). With this, at the time of the study protocol Amendment 10, the following RPV dose recommendations were applied to newly enrolled subjects:

- RPV 25 mg q.d. for subjects with a body weight of ≥25 kg
- RPV 15 mg q.d. for subjects with a body weight of <25 kg

All ongoing participants in Cohort 2 (who are already in the post Week 48 treatment extension period at the time of the study protocol Amendment 10) remain on the RPV 25 mg q.d. dose + 2 N(t)RTIs (investigator-selected), until their roll-over to study TMC278IFD3004 has been completed. All newly recruited participants start treatment with the weight-appropriate RPV dose stated above + 2 N(t)RTIs (investigator-selected), until they reach a total treatment duration of 48 weeks or discontinue earlier. Newly recruited participants with a body weight of <25 kg and increase in weight such that they require a 25 mg RPV dose, can change to the 25 mg tablet formulation.

After the IDMC meeting on 16 October 2020, based on evaluation of all available PK (intensive and sparse), safety/tolerability and efficacy data, the RPV dose for newly recruited participants with body weight <20 kg in any pediatric trial for RPV, including study TMC278-C213, was confirmed as 12.5 mg once daily.

For more details refer section *6.1.1 Overview of Trial* of the Clinical Trial Protocol.

1.3. Statistical Hypotheses for Trial Objectives

No formal hypothesis will be tested.

1.4. Sample Size Justification

No formal sample size calculation was performed.

For more details refer *section 6.6.1.2. Cohort 2: Children Age ≥6 to <12 Years* of the Clinical Trial Protocol.

1.5. Randomization and Blinding

Randomization
As this is a single arm trial, no randomization procedures are applicable.

Blinding
Since this is an open label trial, blinding procedures are not applicable.

1.6. Changes to planned analyses

Not applicable

2. GENERAL ANALYSIS DEFINITIONS

2.1. Analysis Phases

Table 1 - Trial Phases

Trial phase	Start date	End date
Screening	Date of signing the informed consent	Start date of Treatment phase - 1 day
Treatment	Date of the first intake of RPV	If the participant *died during the study intervention phase*: minimum of • date of last RPV+ 7 days; • date of death If the participant *permanently stopped* the trial medication: minimum of: • date of last RPV intake + 7 days, if missing, maximum of (early withdrawal visit date; discontinuation date) + 7 days • date of last contact
Follow-up (not defined when derived End date is before Start date of this phase)	End date of the Treatment phase + 1 day	If the participant *died*: date of death Otherwise: date of last contact (or cut-off date for the analysis, if still in follow-up period)

If the date of first intake of the study medication is missing, this should be substituted by the baseline visit date.

2.2. Analysis Time Points

All visits/assessments will be allocated to the following time points as per the Table 2, based on the number of days in the respective phase, calculated as “assessment date – start date of phase + 1 day” for Treatment and Follow-up phase and “assessment date – start date of Treatment phase” for Screening phase.

If two visits fall within the same interval, the one closest to the target day is used for the analysis displays and graphics in order to have only one evaluation per participant per analysis time point. 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. All data are presented in the listings. If distances of both visits to the target day are equal, the visit latest in time is used.

Table 2 – Time intervals for reporting of efficacy and safety data

Phase	Visit	Target day	Analysis time point	Time interval (days)
Screening	1	-∞	Screening	<0
Treatment	2	1	Baseline*	[-∞, 1]
	3	8	Week 1	[2,11]
	4	15	Week 2	[12,21]
	5	29	Week 4	[22,42]
	6	57	Week 8	[43,70]
	7	85	Week 12	[71,98]
	8	113	Week 16	[99,140]
	9	169	Week 24	[141,196]
	10	225	Week 32	[197,252]
	11	281	Week 40	[253,308]
	12	337	Week 48	[309,350]
	13	421	Week 60	[351,462]
	14	505	Week 72	[463,546]
	15	589	Week 84	[547,630]
	16	673	Week 96	[631,714]
	17	757	Week 108	[715,798]
	18	841	Week 120	[799,882]
	19	925	Week 132	[883,966]
	20	1009	Week 144	[967,1050]
	21	1093	Week 156	[1051,1134]
	22	1177	Week 168	[1135,1218]
	23	1261	Week 180	[1219,1302]
	24	1345	Week 192	[1303,1386]
	25	1429	Week 204	[1387,1470]
	26	1513	Week 216	[1471,1554]
	27	1597	Week 228	[1555,1638]
	28	1681	Week 240	[1639,1722]
Follow-up	29	(3 x7) +1=22 after start FU phase	Post-treatment Follow-up week 4	[Start FU phase, ∞]

* Only the record prior to the first dose closest to target day 1 will be allocated to analysis time point 'Baseline'; all records prior to Day 1 that were not allocated to Baseline are assigned to 'Screening'.

2.3. Pooling Algorithm for Analysis Centers

Not applicable

2.4. Analysis Sets

2.4.1. All Enrolled Analysis Set

The 'All Enrolled' analysis set includes all participants who were not screen failures.

2.4.2. Full Analysis Set (FAS)

The FAS includes all participants who have taken at least 1 dose of RPV, regardless of their compliance with the protocol and adherence to the dosing regimen.

The FAS will be used as primary and only population for all analyses.

2.5. Definition of Subgroups

All results will be presented by dose and weight group:

- 12.5 mg q.d. <20kg
- 15 mg q.d. <20kg;
- 15 mg q.d. 20-<25kg;
- 25 mg q.d. <25kg;
- 25 mg q.d. ≥25kg;
- All RPV Recommended Dose;
- All Participants;

'All RPV Recommended Dose' group includes any patients with an initial administered weight-adjusted dose as per following dose scheme: 12.5 mg q.d. <20kg; 15 mg q.d. 20-<25kg; 25 mg q.d. >25kg.

In addition, the following subgroups are defined:

Efficacy:

- $CD4^+$ count at baseline (≤ 200, 200< - ≤ 400, > 400 cells/µL)
- Background regimen
    - ABACAVIR/LAMIVUDINE (ABC/3TC)
    - ZIDOVUDINE/LAMIVUDINE (AZT/3TC)
    - LAMIVUDINE/ TENOFOVIR DISOPROXIL FUMARATE (3TC/TDF)
- Adherence based on drug accountability (<80%, 80 - <95%, ≥95%) cumulative up to Week 48 for analysis up to Week 48

Safety:

- Baseline body weight: <15 kg; 15 kg - <20 kg; 20 - <25 kg; at least 25 kg
- RPV dose (12.5mg, 15mg, 25mg)
- $CD4^+$ count at baseline (≤ 200, 200< - ≤ 400, > 400 cells/µL)
- Background regimen
    - ABACAVIR/LAMIVUDINE (ABC/3TC)
    - ZIDOVUDINE/LAMIVUDINE (AZT/3TC)
    - LAMIVUDINE/ TENOFOVIR DISOPROXIL FUMARATE (3TC/TDF)

2.6. Study Day and Relative Day

Study Day 1 or Day 1 refers to the start of the first study agent administration (date of first intake). All efficacy and safety assessments at all visits will be assigned a day relative to this date.

Study day or relative day for a visit is defined as:

Study Day = visit date - date of Day 1 + 1; if visit date ≥ date of Day 1 (date of first study treatment (RPV) administration).

Study Day = visit date – date of Day 1; if visit date < date of Day 1 (date of first study treatment (RPV) administration).

There is no 'Day 0'.

2.7. Baseline

A baseline (or reference) value will be defined as the value of the last available assessment prior to the first study treatment (RPV) on Day 1.

If the baseline value is missing the last available screening value will be taken.

2.8. 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 agent start
  - The day of study agent start, if the month/year of the onset of AE is the same as month/year of the study agent start date and month/year of the AE resolution date is different
  - The day of study agent start or day of AE resolution date, whichever is earliest, if month/year of the onset of AE and month/year of the study agent 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 agent start date
  - Month and day of the study agent 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 agent 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.

AE onset/resolution dates with missing times will be imputed as follows:

- A missing time of onset of an adverse event will be set to the earlier of:
  - 00:01 as long as the onset date is after the study agent start date
  - The time of the study agent start if this is the same day the AE occurred.
- The missing time of resolution of an adverse event will be set to 23:59.

If a missing time is associated with a partial or missing date, the date will be imputed first prior to imputing the time.

3. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE REVIEW

An IDMC was installed to monitor pharmacokinetic, efficacy, and safety data of cohort 2, and to safeguard the participants in this trial.

The following analyses are shared and discussed by the IDMC:

- The first analysis (mini-cohort of 5 participants) is not discussed, only shared with the IDMC; can be discussed if requested by the IDMC.
- The analysis when at least 12 participants with body weight <25 kg from TMC278-C213 Cohort 2 and TMC278HTX2002 combined have been treated for at least 4 weeks with the original and/or adjusted RPV dose will be shared and discussed.
- The analyses when all participants have reached 12, 24, and 48 (final analysis) weeks of treatment will be shared and discussed.

Further details are described in the IDMC charter.

4. SUBJECT INFORMATION

The number of participants in FAS will be summarized and listed by dose and weight group and overall.

4.1. Demographics and Baseline Characteristics

Table 3 presents a list of the demographic variables that will be summarized.

Table 3 - 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/m2)	
Categorical Variables	Frequency distribution with the number and percentage of participants in each category.
Age (≥6 - < 9years; ≥9 - < 12years)	
Weight (<20kg; 20 - <25kg, ≥25kg)	
Sex (male, female)	
Childbearing Potential (Yes, No)	
Race[a] (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Not allowed to ask per local regulations, Multiple)	
Ethnicity (Hispanic or Latino, not Hispanic or Latino, Not allowed to ask per local regulations)	
Country[b]	
Tanner Stage	

[a] If multiple race categories are indicated, Race is recorded as 'Multiple'
[b] Summary will be detailed for sites in each country

Table 4 presents a list of the baseline disease characteristic variables that will be summarized.

Table 4 - Baseline Disease Characteristic Variables

Continuous Variables:	**Summary Type**
CD4+ count (cells/μL) at Baseline	Descriptive statistics (N, mean, SD, median, and range [minimum and maximum]).
CD4+ count (%) at Baseline	
HIV-1 viral load (copies/ml / $\log_{10}$ copies/ml) at Baseline	
Duration of known HIV Infection (years): [screening date – date of first confirmed positive HIV test + 1]/365.25 *Note*: provide duration in years; in case of incomplete date of first confirmed positive HIV test, impute with the 1st day of the month and/or 1st month of the year in order to derive the duration.	
Categorical Variables	Frequency distribution with the number and percentage of participants in each category.
ARV Prevention mother to child transmission (Yes, No)	
HIV – 1 subtype	

Hepatitis B/C co-infection status (Yes, No, NAV)	
Mode of HIV infection (Blood transfusion, Hemophilia-associated injections, Heterosexual contact, Intravenously injectable drug use, Mother to Child transmission, MSM, Occupational exposure, Other)	
Clinical stage of HIV infection at screening according to the CDC classification system for HIV infection and AIDS (N, A, B, C)	
CD4+ count at Baseline (≤ 350, 350 - < 500, 500 - <750, ≥750 cells/µL)	
HIV-1 viral load at Baseline (≤100,000 copies/mL; >100,000 copies/mL)	

4.2. Disposition Information

Screened participants and reason for screen failures will be summarized overall.

The number of participants in the following disposition categories will be summarized throughout the study by dose and weight group and overall.

For the All Enrolled Analysis Set:

- Participants enrolled
- Participants enrolled but not treated
- Participants treated with study treatment (FAS)

and for FAS:

- Participants completing the 48-week initial treatment period
- Participants who terminated the 48-week initial treatment period prematurelyReasons for termination the 48-week initial treatment period

- Participants completing the post week 48 treatment extension (up to Week 240)
- Participants who terminated the post week 48 treatment extension prematurely
- Reasons for termination of the post week 48 treatment extension

4.3. Treatment Adherence

Treatment adherence is defined based on drug accountability and based on the Study Adherence Questionnaire for Children and Teenagers / the Study Adherence Questionnaire for Caregivers (see *Addendum 7: Study Adherence Questionnaire for Children and Teenagers* and *Addendum 8: Study Adherence Questionnaire for Caregivers* of the Clinical Trial Protocol).

The following parameters are derived cumulatively up to week 48 or post Week 48 periods/ last intake for discontinued participants. Treatment adherence will be summarized descriptively by dose and weight group and overall.

Drug Accountability:

Drug accountability (DA) can only be calculated at time points when all kits that have been dispensed before that time point have been returned – if DA cannot be derived (eg. cumulative up to week 48):

- impute with value based on next available time point for which a DA calculation can be done, eg. if cumulative DA up to week 48 cannot be derived, derive DA up to week 60; if not calculable, derive DA up to week 72 etc.
- otherwise, use value based on closest preceding time point

Total Amount to be taken (in mg) =

$\sum_{across\ RPV\ doses}$(number of days on same RPV dose x strength in mg of RPV dose).

Number of days on same RPV dose is based on:

- first and last RPV study medication intake date (if available) of the prescribed RPV dose or, in case participant discontinued and last RPV study medication intake date is missing, discontinuation date

Actual Total amount taken (in mg) =
$\sum_{across\ RPV\ doses}$((number of tablets dispensed – number of tablets returned) x strength in mg of RPV dose)

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

Treatment adherence is defined as:
- adherent: the level of adherence is > 95%
- non-adherent: the level of adherence is ≤ 95%

Additionally, following categories of level of adherence will be defined:
- > 95%
-]80%; 95%]
-]65%; 80%]
-]50%; 65%]
- ≤ 50%

The numbers and percentages of participants by adherence category will be tabulated and descriptive statistics of adherence (%) will be shown.

Interruptions (for adverse events [AEs]) are not to be considered for the calculation of adherence: ie, they will not be subtracted from the amount to be taken.

PENTA Questionnaires:
Source for this adherence measure is the Study Adherence Questionnaire for Children and Teenagers (or, when completed by the caregiver, the Study Adherence Questionnaire for Caregivers), more specifically the following 2 questions:
i. Report of missed doses in last 3 days (Question 10).
ii. Report of missed doses over the last 2 weeks (Question 11).

If both child and a caregiver completed the questionnaire, the Child Questionnaire will be given precedence.

Results will be summarized for RPV and for the background regimen separately, and further as follows:

i. Missed doses in last 3 days (Q10):
- on a by visit basis (0, 1, 2, or 3 doses missed)
- cumulatively, with the following categories and subcategories:
  1. never missed a dose
  2. missed not more than 1 dose
     a. at most once
     b. more than once
  3. missed 2 or more doses
     a. at most once
     b. more than once

ii. Missed doses (Y/N) in the last 2 weeks (Q11):
- on a by visit basis (Y/N)
- cumulatively, with the following categories and subcategories:
  1. never missed doses
  2. missed doses,
     a. at most once
     b. more than once

Treatment adherence, for both RPV and background regimen, is defined as:
- adherent: cumulatively, did not miss (2 or more) doses more than once (i.1., i.2.(a&b), i.3.a, ii.1, and ii.2.a)
- non-adherent: cumulatively, missed (2 or more) doses more than once (i.3.b or ii.2.b)

4.4. Extent of Exposure

The number and percentage of participants who receive RPV will be summarized by dose and weight group and overall.

Exposure is defined as the duration of RPV treatment. The duration is calculated as follows:

(date of last dose of RPV – date of first dose of RPV) + 1.

Note that this definition implies that drug interruptions are ignored in calculating exposure.

Descriptive statistics for RPV duration in weeks: ie, duration in days / 7; (N, mean, SD, median, and range [min, max]) will be presented by dose and weight group and overall for the initial treatment period, and the initial treatment and post Week 48 periods combined.

In addition, duration of exposure will be summarized by dose and weight group and overall in the following duration categories: <1 week, 1-<2 weeks, 2-<4 weeks, 4-<8 weeks, 8-<12 weeks, 12-<16 weeks, 16-<24 weeks, 24-<32 weeks, 32-<40 weeks, 40-48 weeks and then every 24 weeks until week 240.

Total subject years of exposure is calculated as [sum of (days of exposure)/365.25]. Total subject years of exposure will be presented by dose and weight group and overall for the initial treatment period, and the initial treatment and post Week 48 periods combined.

4.4.1. Diaries

A listing will be created for all participants who underwent intensive PK sampling, comprising of the date and time of RPV intake from the start of study treatment (or start of an adjusted RPV-dose, if applicable) until the day of intensive PK sampling, based on the information entered in the participant diary.

4.5. Protocol Deviations

The major protocol deviations may have the potential to impact participants' rights, safety or well-being, or the integrity and/or result of the clinical study. Participants with major protocol deviations will be identified prior to database lock and major protocol deviations (including a category for COVID-19 related protocol deviations) will be summarized by category.

4.6. Prior and Concomitant Medications

Prior medications are defined as any therapy used before the day of first dose (partial or complete) of RPV. Concomitant medications are defined as any therapy used on or after the same day as the first dose of RPV, including those that started before and continue after the first dose of study agent. Follow-up medications are defined as any therapy that started after the date of the last dose of RPV.

For non-ARV therapies, summaries of concomitant medications will be presented by Anatomic and Therapeutic Chemical (ATC) class level using the World Health Organization-Drug Dictionary (WHO-DD), and by dose and weight group and overall. The proportion of participants who receive each concomitant medication will be summarized as well as the proportion of participants who receive at least 1 concomitant medication.

For ARV therapies, summaries of prior and concomitant (ie, background regimen) medications will be presented by individual ARVs and combination ARVs as collected in the electronic Case Report Form (eCRF) by dose and weight group and overall. The proportion of participants for each category of medication will be summarized.

Participants who switched ARV therapy during treatment will be listed.

5. EFFICACY

5.1. Analysis Specifications

5.1.1. Level of Significance

No statistical testing will be done as this is a single arm trial.

5.1.2. Data Handling Rules

Viral Load:

Viral load testing will be measured at a central laboratory using standardized HIV-1 viral load assays as the concentration of HIV-1 RNA in plasma. Reanalyzed samples will not be used in any of the calculations or summary statistics.

Imputation of left-censored values: values below the detection limit (ie, 20 copies/mL) will be scored as 1 less than the detection limit in the analysis (ie, 20-1=19 copies/mL), unless explicitly specified differently.

Imputation of right-censored values: in case viral loads were above the upper limit of quantitation (ie, 10,000,000 HIV-1 RNA copies/mL), the viral load will be scored as 1 more than the detection limit in the analysis, unless explicitly specified differently.

Regardless of which assay was used to define response (undetectable)/loss of response (detectable) in the analysis, a cut-off of 50 copies/mL will be applied.

If no observation is available at baseline the last available screening value will be taken.

Immunology:

For cases where no observation is available at the baseline date, the last available screening value will be taken.

In case multiple observations (different sampling dates) are available within a single visit window, only the one closest to the target day will be selected for the displays to select unique observations per time point (visit window).

Rounding:
For point estimates (means or percentages), the following rounding rules are applied:
- CD4 count: 1 decimal
- all log-transformed parameters (including change in log10 viral load): 2 decimals
- all other parameters (including viral load in case not log-transformed, and Fold Change (FC)): 1 decimal

For confidence intervals (CIs), median, interquartile range, min and max: number of decimals for according point estimate.

For SDs and SEs: number of decimals for according point estimate + 1 decimal.

5.2. Efficacy Endpoints

The following efficacy parameters will be analyzed:

Virology
- The change in plasma viral load in $\log_{10}$ from baseline up to Week 48 (the initial treatment period only).
  The viral load change from baseline at a given time point is defined as:
  viral load at a given time point - baseline viral load
  Observed data are used to calculate the change in viral load. No imputation will be done for missing values;
- Proportion of participants with a viral load <50 and <400 HIV-1 RNA copies/mL (virologic response) at all time points up to Week 48 and post Week 48 (observed case);
- Virologic outcome < 50 and <400 HIV-1 RNA copies/mL using the FDA Snapshot approach analysis algorithm for the 48-week treatment period ;
- Proportion of participants with virologic failure (see definitions below) for the 48-week treatment period and till end of study: ie, 48-week treatment and post Week 48 periods combined.

Immunology
- The change in $CD4^+$ cell count (absolute and %) from baseline up to Week 48 and post Week 48.

5.2.1. Definitions

Virologic response
Virologic response is defined as follows:
0 = non-responder: the viral load test result is above some threshold value
1 = responder: the viral load test result is below some threshold value

The following threshold criteria are considered:
- <50: viral load below 50 copies/mL
- <400: viral load below 400 copies/mL

Observed case: a participant is considered a responder, respectively non-responder, if the viral load test result is below, respectively above, the threshold defining response (<50 or <400); with a missing value are disregarded in the analysis for that time point

Virologic failure

Lack of response: confirmed decrease in plasma viral load of <1.0 $\log_{10}$ at Week 12 from the baseline viral load.

Loss of response: two consecutive measurements of ≥400 HIV-1 RNA copies/mL after having been confirmed virologic responder (confirmed responder is defined as two consecutive measurements of <50 copies/mL).

Suspected Virologic Failure: HIV-1 RNA ≥200 copies/mL after confirmed HIV-1 RNA of <50 copies/mL.

FDA Snapshot approach:

The following outcome subcategories are defined (giving priority in the order as presented below, such that each participant is categorized into a single subcategory)

1) Participant's background N(t)RTI regimen was switched as not permitted by the protocol; participants who experienced a switch in their background regimen composition that lasted more than one week and not permitted by the protocol (identify these from protocol deviations [ADDV]) and that occurred before the earliest onset of AEs leading to permanent stop, and, if the participant is ongoing, that occurred up to and including the end day of the 48 week window, are assigned outcome subcategory = 'Virologic failure – switch in background N(t)RTIs not permitted by the protocol'.
2) Participant discontinued trial for virologic failure during treatment phase – if reason for discontinuation is 'SUBJECT REACHED A VIROLOGIC ENDPOINT' and HIV-1 RNA is missing at Week 48 then outcome subcategory = ' Virologic failure - leading to discontinuation';
3) Viral load data in the Week 48 window
   - if last available HIV RNA in the time window is <50/400 copies/mL then outcome='Virologic success: HIV RNA < 50/400 copies/mL at Week 48';
   - if last available HIV RNA in the time window is ≥50/400 copies/mL then outcome='Virologic failure: HIV RNA ≥50/400 copies/mL at Week 48;
4) No HIV RNA data in Week 48 window;
   - if the participant completed Week 48 but HIV RNA data at Week 48 is missing then outcome='Missing data during window but on study';
   - if the reason for discontinuation='ADVERSE EVENT/HIV RELATED EVENT' and the earliest AE leading to permanent stop was not preceded by a switch in the background regimen that was not permitted by the protocol (see point 1) above), then outcome='Discontinued due to AE/death';
   - if the reason for discontinuation is 'OTHER', 'SPONSORS DECISION', 'SUBJECT DID NOT FULFILL ALL INCLUSION/EXCLUSION CRITERIA', 'SUBJECT INELIGIBLE TO CONTINUE THE TRIAL', 'SUBJECT LOST TO FOLLOW-UP', 'SUBJECT NONCOMPLIANT' or 'SUBJECT WITHDREW CONSENT': if the last available HIV RNA is <50/400 copies/mL (or no post baseline HIV RNA data available), outcome subcategory = 'Discontinued due to other reason and the last available HIV RNA < 50/400 copies/mL (or missing)', and (ii) if the last available HIV RNA ≥50/400 copies/mL, outcome subcategory = 'Virologic failure - discontinued due to other reason and last available HIV RNA ≥50/400 copies/mL';

Week 48: The snapshot analysis is based on the last observed viral load data within the Week 48 window (day 309 up to and including day 350, Window 44-54 weeks, baseline = day 1).

Changes from baseline in CD4+ count:

The change from baseline in $CD4^+$ count and CD4% at a given time point is defined as:

CD4+/CD4% at a given time point - baseline CD4+/CD4%

Participants who discontinued will have their $CD4^+$ values after discontinuation imputed with their baseline value, thus resulting in a 0 change; For timepoints with intermittently missing data, last observation carried forward approach is applied (Non-Completer=Failure imputation, NC=F). Analysis results based on observed data only will also be presented.

5.2.2. Analysis Methods

Tabulations (numbers and proportions) per time point by dose and weight and overall for the categorical parameters; 95% CIs (Clopper-Pearson) for the virologic response and failure rates over time will be calculated.

Descriptive statistics (n, mean, standard error [SE], median, and range [min and max]) per time point and graphical display for the continuous parameters(log_{10} HIV-1 RNA and changes from baseline in log_{10} HIV-1 RNA and $CD4^+$ cell count and change from baseline) will be presented. Both observed value as well as imputed values using the NC=F imputation method will be displayed.

Patient profiles will be provided for viral load and CD4+ counts over time.

5.3. Other Efficacy Variables

5.3.1. Resistance

HIV-1 Viral Genotyping:

Inclusion of participants for resistance analysis will solely be based on the availability of post-baseline genotypic data within the treatment phase: ie, up to Week 48 and post Week 48 treatment extension.

The first and the last post-baseline time point within the treatment phase for which genotypic data are available will be analyzed and presented. Phenotypic data will be reported only if there is also genotypic data available for the corresponding time points.

Sequencing of HIV-1 protease, reverse transcriptase and integrase will be performed in real time on plasma for participants with (suspected) virologic failure (see definition above).

Reverse Transcriptase (RT) resistance associated mutations

- IAS-USA NRTI RAMs (n=22)[2]

M41L, A62V, K65E/N/R, D67N, 69ins, K70E/R, L74V, V75I, F77L, Y115F, F116Y, Q151M, M184I/V, L210W, T215F/Y, K219E/Q.

- Extended NNRTI RAMs (n=53) [2]

V90I, A98G, L100I, K101E/H/P/Q, K103H/N/S/T, V106A/I/M/T, V108I, E138A/G/K/Q/R, V179D/E/F/G/I/L/T, Y181C/I/V, Y188C/H/L, V189I, G190A/C/E/Q/S/T, H221Y, P225H, F227C/L/R, M230I/L, P236L, K238N/T, L243I, Y318F

- RPV RAMs (n=16)

K101E, K101P, E138A, E138G, E138K, E138R, E138Q, V179L, Y181C, Y181I, Y181V, Y188L, H221Y, F227C, M230I, M230L

Protease resistance associated mutations

- IAS-USA primary PI RAMs (n=24) [2]

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

- IAS-USA PI RAMs (n = 75) [2]

L10C/F/I/R/V, V11I, G16E, K20I/M/R/T/V, L24I, D30N, V32I, L33I/F/V, E34Q, M36I/L/V, K43T, M46I/L, I47A/V, G48V, I50L/V, F53L/Y, I54A/L/M/S/T/V, Q58E, D60E, I62V, L63P, I64L/M/V, H69K/R, A71I/L/T/V, G73A/C/S/T, T74P, L76V, V77I, V82A/F/I/L/S/T, N83D, I84V, I85V, N88D/S, L89I/M/V, L90M, I93L/M

Integrase resistance associated mutations (n=27):

- T66A/I/K, L74M, E92G/Q, T97A, G118R, F121Y, E138A/K/T, G140A/C/R/S, Y143C/H/R, S147G, Q148H/K/R, S153F/Y, N155H, R263K

Concordance/discordance with "Virologic Failure" as per FDA Snapshot approach (see section 5.2.1) will be assessed.

Results will be shown in different columns, unless explicitly specified differently in the Data Presentation Specifications (DPS):

- Non-VF: responder
- Non-VF: discontinued due to AE or other reason
- VF
- Overall

Results from viral genotyping in plasma will be tabulated and described, particularly for participants with virologic failure.

Individual mutations identified via viral genotyping will be reported relative to the HIV-1 WT reference sequence.

Retrospective evaluation of RAMs in PBMCs:

Peripheral Blood Mononuclear Cell (PBMC) sample will be taken to allow retrospective characterization of archived viral resistance, if needed. Inclusion of participants for archived resistance analysis is based on the availability of results obtained at screening or Week 48 or final/withdrawal visit.

Results from archival viral resistance from PBMC sample will be tabulated and described, particularly for participants with virologic failure.

6. SAFETY

All safety analyses will be based on the FAS

For all continuous safety variables, descriptive statistics will include the N, mean, SD, median, minimum, and maximum. Categorical variables will be summarized using frequency counts and percentages.

Safety data will be presented by dose and weight and overall for the treatment phase:

- 48-week initial treatment period: 48-week treatment period
- Post week 48 treatment extension period: Post Week 48 till end of study
- Treatment phase: both periods combined

6.1. Adverse Events (AE)

Adverse Event (AE): An AE is any untoward medical occurrence in a clinical study participant administered a medicinal (investigational or non-investigational) product.

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA 24.1 or latest).

Any AE occurring at or after the initial administration of RPV through the day of last dose is considered to be treatment-emergent. If the event occurs on the day of the initial administration of RPV, and either event time or time of administration are missing, 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 RPV 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 participants who experience at least 1 occurrence of the given event will be summarized by dose and weight group and overall.

Summary tables will be provided for all treatment-emergent:

- AEs
- SAEs
- AEs leading to discontinuation of RPV
- AEs leading to dose interruption of RPV
- AEs by severity
- AEs by relationship to RPV

In addition to the summary tables, listings will be provided for participants who had:

- SAEs
- AEs leading to discontinuation of RPV
- HIV-related AEs
- Stage 3-defining Opportunistic Illnesses in HIV infection (see ATTACHMENT 3: STAGE-3-DEFINING OPPORTUNISTIC ILLNESSES IN HIV INFECTION

A listing of participants who died during the study will be provided.

Overall AE summary tables by preferred term/System Organ Class for SAEs and pregnancies, AEs leading to discontinuation, AEs at least grade 3, HIV-related AEs, stage 3-defining Opportunistic Illnesses in HIV infection and AEs at least possibly related to RPV will be presented throughout the treatment phase only; any AEs in the Follow-up phase will be listed only.

Number of occurrences of an AE:
Number of recorded events of the same preferred term, during the trial phase. Combined events (ie, within the same phase) will be counted only once.

AE grading:
Reported AE parameters and grades are based on the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (see ATTACHMENT 1: DAIDS GRADING TABLE

AE duration.

For the calculation of duration of AEs, only AEs are considered with complete start and end date or for which the end date is imputed (see STEP 1 for imputation of end date).

Duration is calculated as:

End date – Start date +1

Onset day of AE:

- *after start of investigational medication* = first start date of the AE – first intake date of investigational medication + 1 day. In case of combined events, the onset day will be computed only once, and relative to the start date of the first event.
- *in the phase* = first start date of the AE – start date of the phase in which the AE emerges + 1 day. In case of combined events, the onset day will be computed only once, and relative to the start date of the first event.

Adverse Events of Interest (EOI):
Different events of interest will be investigated separately. A list of Events of Interest (EOI) is maintained at Janssen Infectious Diseases which is updated (if necessary) based on accumulating AE data from both RPV Adult Phase III studies. A list of EOI for analysis purposes will be provided prior to the database lock. The different classes of events of interest that should be investigated are the following:

- Skin events of interest: The skin events of interest will be defined based on the adverse event preferred terms and will be summarized using alternative groupings: 'Dermatitis Contact', 'Dermatitis / Eczema', 'Oedema', 'Rash', 'Rash Vesicular', 'Other'.
- Neuropsychiatric events of interest: Neuropsychiatric events of interest will be defined based on the adverse event preferred terms and will be summarized using alternative groupings: 'Nervous System Disorders', 'Psychiatric Disorders'. Under the 'Psychiatric Disorders' an extra row will be included, namely the combination of "ABNORMAL DREAMS" or "NIGHTMARES".
- Potential QT prolongation-related events: selection of preferred terms is based on a MedDRA standardized query for "Torsade de pointes/QT prolongation"
- Hepatic events of interest: Hepatic events of interest will be defined based on the adverse event preferred terms.
- Endocrinology events of interest: These are defined as all endocrinology events categorized under the system organ class 'ENDOCRINE DISORDERS' or all AEs categorized under the system organ class 'INVESTIGATIONS' related to any of the endocrine analytes measures (cortisol, 17-OH progesterone, aldosterone, dehydroepiandrosterone (DHEAS), androstenedione, testosterone) in the trial.
- AIDS defining Illnesses and Stage-3-defining Opportunistic Illnesses in HIV Infection: All adverse events classified as CDC Stage 3 and Stage-3-defining Opportunistic Illnesses.

6.2. Clinical Laboratory Tests

All clinical laboratory tests will be displayed for the participants included in the FAS. Results from central laboratory testing (Covance/Labcorp) will be included in the analysis; results from local laboratories will not be included in the analysis, only listed.

Observed and change from baseline to each scheduled time point will be summarized descriptively for laboratory tests and displayed by dose and weight group and overall.

The laboratory tests will be grouped as follows:

1) General biochemistry (albumin, blood urea nitrogen, calcium, calcium adjusted for albumin, chloride, phosphate, creatinine, potassium, sodium, uric acid, creatinine phosphokinase, …)
2) Pancreatic Parameters (pancreatic amylase, lipase)
3) Renal Parameters (serum creatinine, eGFR (creatinine), …)
4) Hepatic parameters (ALT, AST, gamma-GT, alkaline phosphatase, LDH, bilirubin (all types), total protein…)
5) Lipids and glucose (cholesterol, HDL cholesterol (HDL-C) (all types), LDL cholesterol (LDL-C) (all types), TC/HDL-C, insulin, glucose, triglycerides, …)
6) General hematology (Hematocrit, hemoglobin, red blood cell count, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC), platelet count, white blood cell count)
7) Hematology differential counts (Basophils, eosinophils, lymphocytes, monocytes, neutrophils (counts and %), …)
8) Endocrinology (Cortisol, 17-hydroxyprogesterone, dehydroepiandrosterone (DHEAS), androstenedione, testosterone, follicle stimulating hormone (FSH), luteinizing hormone (LH))

Toxicity grades:
Toxicity grades are determined according to the DAIDS grading list (see ATTACHMENT 1: DAIDS GRADING TABLE). In case no toxicity grades are defined for a test, the abnormalities (above/below normal range) are used. In determining toxicity grades, the following rules are applied:

- Laboratory values are rounded to the same number of decimals as the DAIDS grading, and the rounded value is used to allocate a grading to the value.
- There is no overruling of the DAIDS grades when the value is between the normal limits
- In case no numeric value is available, but only a verbatim term (eg, PTT>120) then the numeric value will be derived by determining the closest value to the cut-off value, taking into account the usual number of decimals for the particular parameter, in order to be able to allocate a grade to these observations.
- Note: as the grading scale for some parameters in the DAIDS grading table has some gaps (zones where no toxicity grade definition exists), laboratory results falling in these zones are allocated to the immediate worst-case grade.

Cross-tabulations for the worst toxicity grades versus baseline per laboratory test will be reported. Separate tabulations and listings will be provided for those participants who develop a grade 3 or 4 laboratory toxicity. For tests for which no DAIDS grading exists, a cross-tabulation versus baseline (with classes below/within/above normal range) will be performed.

Endocrine safety: Adrenocorticotropic hormone (ACTH) stimulation testing

Abnormal ACTH response:

The ACTH test result will be categorized into the following categories:
1) Maximum cortisol measurement (time points T0 and T60) ≥ 500 nmol/L
2) Maximum cortisol measurement (time points T0 and T60) ≥ 450 - < 500 nmol/L
3) Maximum cortisol measurement (time points T0 and T60) < 450 nmol/L

Cross-tabulations for on-treatment ACTH stimulation test abnormalities (defined as cortisol after ACTH stimulation < 500 nmol/L) will be reported for following timepoints: Week 48, worst on-treatment measurement till end of study.

Endocrine safety (cortisol and 17-hydroxyprogesterone) will be summarized per analysis time point for following measurements: T0, T60. In addition, abnormal basal cortisol (defined as <248 nmol/L) will be tabulated per analysis time point.

6.3. Vital Signs and Physical Examination Findings

Continuous vital sign parameters including height, weight, pulse, blood pressure (systolic and diastolic), and BMI will be summarized at each assessment time point. BMI will be calculated as weight (kg)/(height (m))^2, at each time point that body weight is measured.

Observed and change from baseline will be summarized by dose and weight group and overall. Descriptive statistics (mean, standard deviation, median, minimum and maximum) will be presented.

Incidence of markedly abnormal vital signs while on treatment, as defined Table 5, will be summarized for participants who had at least 1 postbaseline assessment for that vital sign.

Table 5 - Markedly Abnormal Vital Sign

Vital Sign	Criteria
Pulse	≥ 120 bpm for higher limit
	≤ 50 bpm for lower limit
Systolic blood pressure	Grade 1: >120 mmHg
	Grade 2: ≥95th to <99th percentile +5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)
	Grade 3: ≥99th percentile +5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)
Diastolic blood pressure	Grade 1: >80 mmHg
	Grade 2: ≥95th to <99th percentile +5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)
	Grade 3: ≥99th percentile +5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)

To classify vital sign measurements into abnormality codes, the following approach is used:
An absolute blood pressure measurement is translated into a blood pressure percentile (cf table provided in ATTACHMENT 2: BLOOD PRESSURE LEVELS BY AGE AND HEIGHT PERCENTILES) based on the participant's age and height percentile (= height-for-age percentiles at the time of the blood pressure measurement).

For calculation of height-for-age percentiles, see SAS programs available from http://www.who.int/childgrowth/software/en/ (up to 5 years of age) and http://www.who.int/growthref/tools/en/ (from 5 to 19 years of age).

Last-Observation-Carried-Forward (LOCF) imputation will be used for missing height percentiles. In case a participant's height percentile does not exactly match a value reported in attachment 2, calculated height-for-age percentiles are translated into values available in attachment 2, as follows:

Calculated height-for-age percentile	Height Percentile
1 - 7	5
8 - 17	10
18 - 37	25
38 - 62	50
63 - 82	75
83 - 92	90
93 - 100	95

Also, occurrence of orthostatic hypotension will be summarized, defined as:

supine SBP – standing SBP ≥ 20 mmHg
OR
supine DBP – standing DBP ≥ 10 mmHg

Physical Examination:

Physical examination findings will be summarized at each scheduled time point with full physical examination per body system by dose and weight group and overall.

Physical examination abnormalities will be listed.

Growth Examination:

Growth will be followed regularly and evaluated consistently using WHO standardized growth charts.

- Height (cm)
- Height-for-age (z-score and percentile)
- Weight (kg)
- Weight-for-age (z-score and percentile)
- BMI = weight (kg)/ (height (m))^2
- BMI-for-age (z-score and percentile)

Observed and change from baseline will be summarized for by dose and weight group and overall. Descriptive statistics (mean, SD, median, minimum and maximum) will be presented.

Tanner Stage:

Tanner stage (for pubic hair and genitalia/breasts) will be cross-tabulated versus baseline. In addition, in girls, the occurrence of first menses during treatment will also be cross-tabulated versus baseline, and the date of menarche will be listed.

6.4. Electrocardiogram

All ECG parameters will be displayed for the participants included in the FAS. No statistical testing will be performed. In addition, for QTcB/F pre-dose and post-dose at Baseline and at Week 4 will be analyzed as separate time points.

The ECG parameters that will be analyzed are heart rate, PR interval, RR interval, QRS interval, QT interval, QTcB and QTcF using the following correction methods: Bazett's formula (QTcB), Fridericia's formula (QTcF).

Bazett's formula: QTcB (ms) = $\frac{QT(ms)}{\sqrt{RR(ms)/1000}}$

Fridericia's formula: QTcF (ms) = $\frac{QT(ms)}{\sqrt[3]{RR(ms)/1000}}$

* If RR is missing, it will be derived from HR (see formula below) if this is parameter is available from the same ECG reading as the QT. HR from the Vital Signs dataset will not be used to calculate the corrected QT parameters.

$$RR(ms) = 1000 * \frac{60}{HR(bpm)}$$

QT corrections will be re-computed even if they are provided.

Observed and change from baseline to each scheduled time point will be descriptively summarized by dose and weight group and overall for the above ECG parameters.

A listing of clinically relevant ECG results will also be provided.

The number and percentage of participants within each of the categories defined below will be presented for the maximum postbaseline value (ie: the maximum ECG result over the study period) by dose and weight and overall.

Categories to assess QT prolongation:

QTc Interval: QTcB criteria are based on DAIDS 2017 (see the study protocol Addendum 2: DAIDS Table) and QTcF criteria copied from MOCHA/CRAYON protocol:

- Normal:
  QTcF: <460 ms
  QTcB: <450 ms
- Grade 1:
  QTcF: ≥460 to <480 ms
  QTcB: ≥450 to ≤470 ms
- Grade 2:
  QTcF: ≥480 to < 500 ms
  QTcB: >470 to ≤ 500 ms
- Grade 3:
  QTcF: ≥500 ms OR QTcF ≥480 ms AND QTcF > 60 ms greater than baseline
  QTcB: > 500 ms OR QTcB ≥ 60 ms greater than baseline
- Grade 4:
  QTcF/B: Life-threatening consequences: eg, Torsades de pointes, other serious ventricular dysrhythmias.

QTcF change from baseline:

- normal: <30 ms
- borderline: ≥30 to ≤60 ms
- abnormal high: >60 ms

QTcB change from baseline:

- normal: <30 ms
- borderline: ≥30 to ≤60 ms
- abnormal high: >60 ms

7. PHARMACOLOGY

7.1. Population Pharmacokinetics

Population pharmacokinetic parameters (AUC_{24h} and C_{0h}; based on sparse sampling) will be available for all participants.

Pharmacokinetic/Pharmacodynamic Relationships

PK and Efficacy
Scatterplot of individual PK parameters (AUC_{24h} and C_{0h}) by virologic response (plasma viral load <50/400 copies/mL) using FDA Snapshot (yes/no) at Week 48, will be created.

PK and Safety
Relationship between RPV pharmacokinetics (AUC_{24h} only) and the following AE groups / abnormalities will be explored graphically by means of scatterplots.

- Rash (yes/no) (The skin event of interest alternative grouping of 'Rash' will be used.)
- All neuropsychiatric events of interest combined (yes/no)
- Combined AEs in the Nervous System Disorders alternative grouping (yes/no)
- Combined AEs in the 'Psychiatric Disorders' SOC (yes/no)
- Combined AEs in the 'Gastrointestinal Disorders' SOC (yes/no)
- Combined AEs in the 'Blood and Lymphatic Disorders' SOC (yes/no)
- Combined AEs with preferred terms 'abnormal dreams', 'vivid dreams', 'nightmare' (yes/no)
- Dizziness (yes/no)
- Headache (yes/no)
- QTcF abnormalities (yes/no), both based on absolute values and changes from baseline (section 6.4)

Scatterplots of individual PK parameter values (AUC_{24h} only) by specific laboratory/ECG parameters (change from baseline), presented in the following table, will be shown.

Biochemistry	**Lipids**	**Hematology**	**Glucose metabolism**	**ECG**
ALT ([max])	HDL ([min])	Hemoglobin ([min])	Glucose ([max])	QTcF ([max])
AST ([max])	LDL ([max])	Hematocrit ([min])	Insulin ([min])	
Total bilirubin ([max])	Triglycerides ([max])		HOMA-IR ([max])	
Alkaline phosphatase ([max])	Total cholesterol ([max])			
Pancreatic amylase ([max])	Total cholesterol / HDL ([min])			
Lipase ([max])				
Creatinine ([max])				
eGFR (creatinine) ([min])				

Endocrine (Cortisol, 17-OH Progesterone)	
Cortisol	17-OH Progesterone
morning/T0 (non-ACTH) ([min])	morning/T0 (non-ACTH) ([max])

[min] or [max] indicates which value to use, ie, either the smallest or largest value respectively

7.2. Other Pharmacology Endpoints

Palatability:

The palatability of the 2.5 mg RPV tablet formulation will be assessed in a palatability questionnaire at Day 1 and Week-4 treatment period by documenting the participant's perception using a 5-point hedonic scale.

The number and percentage of participants within each of the categories, as well as cumulatively (from best to worst) will be presented by dose and weight group and overall.

REFERENCES

1. http://www.cdc.gov/growthcharts
2. Wensing AM, Calvez V, Ceccherine-Silberstein, et al. 2019 update of the drug resistance mutations in HIV-1. Top Antivir Med Sep/Oct 2019; 27(3):111-121
3. NPR-20060022-VRR_v7.0
4. Bennett DE, Camacho RJ, Otelea D, Kuritzkes DR, Fleury H, et al. 2009 Drug Resistance Mutations for Surveillance of Transmitted HIV-1 Drug-Resistance: 2009 Update. PLoS ONE 4(3): e4724. doi:10.1371/journal.pone.000472
5. H C Bazett: An analysis of the time-relations of electrocardiogram; Heart 1920; 7: 353 – 370.
6. L S Fridericia: Die systolendauer im elektrokardiogramm bei normalen menchen und bei herzkranken; Acta Med Scand 1920; 15: 335 – 642.

ATTACHMENTS

ATTACHMENT 1: DAIDS GRADING TABLE

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS, CORRECTED VERSION 2.1, PUBLISH DATE: JULY 2017

LABORATORY VALUES[m]				
CHEMISTRIES				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Acidosis	NA	pH ≥7.3 to <LLN	pH <7.3 without life-threatening consequences	pH <7.3 with life-threatening consequences
Albumin, Low (g/dL; *g/L*)	3.0 to <LLN *30 to <LLN*	≥2.0 to <3.0 *≥20 to <30*	<2.0 *<20*	NA
ALP, High	1.25 to <2.5×ULN	2.5 to <5.0×ULN	5.0 to <10.0×ULN	≥10.0×ULN
Alkalosis	NA	pH >ULN to ≤7.5	pH >7.5 without life-threatening consequences	pH >7.5 with life-threatening consequences
ALT or SGPT, High *Report only 1*	1.25 to <2.5×ULN	2.5 to <5.0×ULN	5.0 to <10.0×ULN	≥10.0×ULN
Amylase (Pancreatic) or Amylase (Total), High *Report only 1*	1.1 to <1.5×ULN	1.5 to <3.0×ULN	3.0 to <5.0×ULN	≥5.0×ULN
AST or SGOT, High *Report only 1*	1.25 to <2.5×ULN	2.5 to <5.0×ULN	5.0 to <10.0×ULN	≥10.0×ULN
Bicarbonate, Low (mEq/L; *mmol/L*)	16.0 to <LLN *16.0 to <LLN*	11.0 to <16.0 *11.0 to <16.0*	8.0 to <11.0 *8.0 to <11.0*	<8.0 *<8.0*
Bilirubin ***Direct Bilirubin[n], High*** *aged >28 days*	NA	NA	>ULN with other signs and symptoms of hepatotoxicity	>ULN with life-threatening consequences (eg, signs and symptoms of liver failure)
aged ≤28 days	ULN to ≤1 mg/dL	>1 to ≤1.5 mg/dL	>1.5 to ≤2 mg/dL	>2 mg/dL
Total Bilirubin, High *aged >28 days*	1.1 to <1.6×ULN	1.6 to <2.6×ULN	2.6 to <5.0×ULN	≥5.0×ULN
aged ≤28 days	NA	NA	NA	NA

mEq=milliequivalent, LLN=lower limit of normal, NA=not applicable, SGOT=serum glutamic-oxaloacetic transaminase, SGPT=serum glutamate-pyruvate transaminase

m Reminder: An asymptomatic abnormal laboratory finding without an accompanying AE should not be reported to DAIDS in an expedited time frame unless it meets protocol-specific reporting requirements.

n Direct bilirubin >1.5 mg/dL in a participant aged <28 days should be graded as grade 2, if <10% of the total bilirubin.

Calcium, High (mg/dL; *mmol/L*) *aged ≥7 days*	10.6 to <11.5 *2.65 to <2.88*	11.5 to <12.5 *2.88 to <3.13*	12.5 to <13.5 *3.13 to <3.38*	≥13.5 *≥3.38*
aged <7 days	11.5 to <12.4 *2.88 to <3.10*	12.4 to <12.9 *3.10 to <3.23*	12.9 to <13.5 *3.23 to <3.38*	≥13.5 *≥3.38*
Calcium (Ionized), High (mg/dL; *mmol/L*)	>ULN to <6.0 *>ULN to <1.5*	6.0 to <6.4 *1.5 to <1.6*	6.4 to <7.2 *1.6 to <1.8*	≥7.2 *≥1.8*
Calcium, Low (mg/dL; *mmol/L*) *aged ≥7 days*	7.8 to <8.4 *1.95 to <2.10*	7.0 to <7.8 *1.75 to <1.95*	6.1 to <7.0 *1.53 to <1.75*	<6.1 *<1.53*
aged <7 days	6.5 to <7.5 *1.63 to <1.88*	6.0 to <6.5 *1.50 to <1.63*	5.50 to <6.0 *1.38 to <1.50*	<5.50 *<1.38*
Calcium (Ionized), Low (mg/dL; *mmol/L*)	<LLN to 4.0 *<LLN to 1.0*	3.6 to <4.0 *0.9 to <1.0*	3.2 to <3.6 *0.8 to <0.9*	<3.2 *<0.8*
Cardiac Troponin I, High	NA	NA	NA	Levels consistent with myocardial infarction or unstable angina as defined by the local laboratory
Creatine Kinase, High	3 to <6×ULN	6 to <10×ULN	10 to <20×ULN	≥20×ULN
Creatinine, High *Report only 1°*	1.1 to 1.3×ULN	>1.3 to 1.8×ULN OR Increase to 1.3 to <1.5×participant's baseline	>1.8 to <3.5×ULN OR Increase to 1.5 to <2.0×participant's baseline	≥3.5×ULN OR Increase of ≥2.0×participant's baseline
Creatinine Clearance[p] or eGFR, Low *Report only 1°*	NA	<90 to 60 ml/min or ml/min/1.73 m^2 OR 10% to <30% decrease from participant's baseline	<60 to 30 ml/min or ml/min/1.73 m^2 OR 30% to <50% decrease from participant's baseline	<30 ml/min or ml/min/1.73 m^2 OR ≥50% decrease from participant's baseline or dialysis needed
Glucose (mg/dL; *mmol/L*) ***Fasting, High***	110 to 125 *6.11 to <6.95*	>125 to 250 *6.95 to <13.89*	>250 to 500 *13.89 to <27.75*	≥500 *≥27.75*
Nonfasting, High	116 to 160 *6.44 to <8.89*	>160 to 250 *8.89 to <13.89*	>250 to 500 *13.89 to <27.75*	≥500 *≥27.75*
Glucose, Low (mg/dL; *mmol/L*) *aged ≥1 month*	55 to 64 *3.05 to <3.55*	40 to <55 *2.22 to <3.05*	30 to <40 *1.67 to <2.22*	<30 *<1.67*
aged <1 month	50 to 54 *2.78 to <3.00*	40 to <50 *2.22 to <2.78*	30 to <40 *1.67 to <2.22*	<30 *<1.67*
Lactate, High	ULN to <2.0×ULN without acidosis	≥2.0×ULN without acidosis	Increased lactate with pH <7.3 without life-threatening consequences	Increased lactate with pH <7.3 with life-threatening consequences

LLN=lower limit of normal, NA=not applicable

o Reminder: Choose the method that selects for the higher grade.

p Use the applicable formula (ie, Cockroft-Gault in mL/min or Schwartz, modification of diet in renal disease study [MDRD], or chronic kidney disease epidemiology collaboration [CKD-Epi] in mL/min/1.73m^2). Sites should choose the method defined in their study and when not specified, use the method most relevant to the study population.

LABORATORY VALUES				
CHEMISTRIES				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Lipase, High	1.1 to <1.5×ULN	1.5 to <3.0×ULN	3.0 to <5.0×ULN	≥5.0×ULN
Lipid Disorders (mg/dL; *mmol/L*) ***Cholesterol, Fasting, High*** *aged ≥18 years*	200 to <240 *5.18 to <6.19*	240 to <300 *6.19 to <7.77*	≥300 *≥7.77*	NA
aged <18 years	170 to <200 *4.40 to <5.15*	200 to <300 *5.15 to <7.77*	≥300 *≥7.77*	NA
LDL, Fasting, High *aged ≥18 years*	130 to <160 *3.37 to <4.12*	160 to <190 *4.12 to <4.90*	≥190 *≥4.90*	NA
aged >2 to <18 years	110 to <130 *2.85 to <3.34*	130 to <190 *3.34 to <4.90*	≥190 *≥4.90*	NA
Triglycerides, Fasting, High	150 to 300 *1.71 to 3.42*	>300 to 500 *>3.42 to 5.7*	>500 to <1,000 *>5.7 to 11.4*	>1,000 *>11.4*
Magnesium[q], Low (mEq/L; *mmol/L*)	1.2 to <1.4 *0.60 to <0.70*	0.9 to <1.2 *0.45 to <0.60*	0.6 to <0.9 *0.30 to <0.45*	<0.6 *<0.30*
Phosphate, Low (mg/dL; *mmol/L*) *aged >14 years*	2.0 to <LLN *0.65 to <LLN*	1.4 to <2.0 *0.45 to <0.65*	1.0 to <1.4 *0.32 to <0.45*	<1.0 *<0.32*
aged 1 to 14 years	3.0 to <3.5 *0.97 to <1.13*	2.5 to <3.0 *0.81 to <0.97*	1.5 to <2.5 *0.48 to <0.81*	<1.5 *<0.48*
aged <1 year	3.5 to <4.5 *1.13 to <1.45*	2.5 to <3.5 *0.81 to <1.13*	1.5 to <2.5 *0.48 to <0.81*	<1.5 *<0.48*
Potassium, High (mEq/L; *mmol/L*)	5.6 to <6.0 *5.6 to <6.0*	6.0 to <6.5 *6.0 to <6.5*	6.5 to <7.0 *6.5 to <7.0*	≥7.0 *≥7.0*
Potassium, Low (mEq/L; *mmol/L*)	3.0 to <3.4 *3.0 to <3.4*	2.5 to <3.0 *2.5 to <3.0*	2.0 to <2.5 *2.0 to <2.5*	<2.0 *<2.0*
Sodium, High (mEq/L; *mmol/L*)	146 to <150 *146 to <150*	150 to <154 *150 to <154*	154 to <160 *154 to <160*	≥160 *≥160*
Sodium, Low (mEq/L; *mmol/L*)	130 to <135 *130 to <135*	125 to <130 *125 to <130*	121 to <125 *121 to <125*	≤120 *≤120*
Uric Acid, High (mg/dL; *mmol/L*)	7.5 to <10.0 *0.45 to <0.59*	10.0 to <12.0 *0.59 to <0.71*	12.0 to <15.0 *0.71 to <0.89*	≥15.0 *≥0.89*

LDL=low-density lipoprotein, LLN=lower limit of normal, mEq=milliequivalent, NA=not applicable

q To convert a magnesium value from mg/dL to mmol/L, laboratories should multiply by 0.4114.

Absolute $CD4^+$ Count, Low (cells/mm^3; *cells/L*) *aged >5 years (not HIV-infected)*	300 to <400 *0.300×10^9 to $<0.400\times10^9$*	200 to <300 *0.200×10^9 to $<0.300\times10^9$*	100 to <200 *0.100×10^9 to $<0.200\times10^9$*	<100 *$<0.100\times10^9$*
Absolute Lymphocyte Count, Low (cells/mm^3; *cells/L*) *aged >5 years (not HIV-infected)*	600 to <650 *0.600×10^9 to $<0.650\times10^9$*	500 to <600 *0.500×10^9 to $<0.600\times10^9$*	350 to <500 *0.350×10^9 to $<0.500\times10^9$*	<350 *$<0.350\times10^9$*
Absolute Neutrophil Count, Low (cells/mm^3; *cells/L*) *aged >7 days*	800 to 1,000 *0.800×10^9 to 1.000×10^9*	600 to 799 *0.600×10^9 to 0.799×10^9*	400 to 599 *0.400×10^9 to 0.599×10^9*	<400 *$<0.400\times10^9$*
aged 2 to 7 days	1,250 to 1,500 *1.250×10^9 to 1.500×10^9*	1,000 to 1,249 *1.000×10^9 to 1.249×10^9*	750 to 999 *0.750×10^9 to 0.999×10^9*	<750 *$<0.750\times10^9$*
aged ≤1 day	4,000 to 5,000 *4.000×10^9 to 5.000×10^9*	3,000 to 3,999 *3.000×10^9 to 3.999×10^9*	1,500 to 2,999 *1.500×10^9 to 2.999×10^9*	<1,500 *$<1.500\times10^9$*
Fibrinogen, Decreased (mg/dL; *g/L*)	100 to <200 *1.00 to <2.00* OR 0.75 to <1.00×LLN	75 to <100 *0.75 to <1.00* OR ≥0.50 to <0.75×LLN	50 to <75 *0.50 to <0.75* OR 0.25 to <0.50×LLN	<50 *<0.50* OR <0.25×LLN OR Associated with gross bleeding
Hemoglobin[r], Low (g/dL; *mmol/L*)[s] *aged ≥13 years (male only)*	10.0 to 10.9 *6.19 to 6.76*	9.0 to <10.0 *5.57 to <6.19*	7.0 to <9.0 *4.34 to <5.57*	<7.0 *<4.34*
aged ≥13 years (female only)	9.5 to 10.4 *5.88 to 6.48*	8.5 to <9.5 *5.25 to <5.88*	6.5 to <8.5 *4.03 to <5.25*	<6.5 *<4.03*
aged 57 days to <13 years (male and female)	9.5 to 10.4 *5.88 to 6.48*	8.5 to <9.5 *5.25 to <5.88*	6.5 to <8.5 *4.03 to <5.25*	<6.5 *<4.03*
aged 36 to 56 days (male and female)	8.5 to 9.6 *5.26 to 5.99*	7.0 to <8.5 *4.32 to <5.26*	6.0 to <7.0 *3.72 to <4.32*	<6.0 *<3.72*
aged 22 to 35 days (male and female)	9.5 to 11.0 *5.88 to 6.86*	8.0 to <9.5 *4.94 to <5.88*	6.7 to <8.0 *4.15 to <4.94*	<6.7 *<4.15*
aged 8 to ≤21 days (male and female)	11.0 to 13.0 *6.81 to 8.10*	9.0 to <11.0 *5.57 to <6.81*	8.0 to <9.0 *4.96 to <5.57*	<8.0 *<4.96*
aged ≤7 days (male and female)	13.0 to 14.0 *8.05 to 8.72*	10.0 to <13.0 *6.19 to <8.05*	9.0 to <10.0 *5.59 to <6.19*	<9.0 *<5.59*

LLN=lower limit of normal

r Male and female sex are defined as sex at birth. For transgender participants aged ≥13 years who have been on hormone therapy for more than 6 consecutive months, grade hemoglobin based on the gender with which they identify (ie, a transgender female should be graded using the female sex at birth hemoglobin laboratory values).

s The most commonly used conversion factor to convert g/dL to mmol/L is 0.6206. For grading hemoglobin results obtained by an analytic method with a conversion factor other than 0.6206, the result must be converted to g/dL using the appropriate conversion factor for the particular laboratory.

LABORATORY VALUES				
HEMATOLOGY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
INR, High (not on anticoagulation therapy)	1.1 to <1.5×ULN	1.5 to <2.0×ULN	2.0 to <3.0×ULN	≥3.0×ULN
Methemoglobin (% hemoglobin)	5.0% to <10.0%	10.0% to <15.0%	15.0% to <20.0%	≥20.0%
PTT, High (not on anticoagulation therapy)	1.1 to <1.66×ULN	1.66 to <2.33×ULN	2.33 to <3.00×ULN	≥3.00×ULN
Platelets, Decreased (cells/mm^3; *cells/L*)	100,000 to <125,000 *100.000×10^9 to <125.000×10^9*	50,000 to <100,000 *50.000×10^9 to <100.000×10^9*	25,000 to <50,000 *25.000×10^9 to <50.000×10^9*	<25,000 *<25.000×10^9*
PT, High (not on anticoagulation therapy)	1.1 to <1.25×ULN	1.25 to <1.50×ULN	1.50 to <3.00×ULN	≥3.00×ULN
WBC, Decreased (cells/mm^3; *cells/L*) *aged >7 days*	2,000 to 2,499 *2.000×10^9 to 2.499×10^9*	1,500 to 1,999 *1.500×10^9 to 1.999×10^9*	1,000 to 1,499 *1.000×10^9 to 1.499×10^9*	<1,000 *<1.000×10^9*
aged ≤7 days	5,500 to 6,999 *5.500×10^9 to 6.999×10^9*	4,000 to 5,499 *4.000×10^9 to 5.499×10^9*	2,500 to 3,999 *2.500×10^9 to 3.999×10^9*	<2,500 *<2.500×10^9*

INR=International Normalized Ratio, NA=not applicable, PT=prothrombin time, PTT=partial thromboplastin time

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

ATTACHMENT 2: BLOOD PRESSURE LEVELS BY AGE AND HEIGHT PERCENTILES

Blood Pressure Levels for Boys by Age and Height Percentile

Age (Year)	BP Percentile ↓	Systolic BP (mmHg) ← Percentile of Height →							Diastolic BP (mmHg) ← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	50th	80	81	83	85	87	88	89	34	35	36	37	38	39	39
	90th	94	95	97	99	100	102	103	49	50	51	52	53	53	54
	95th	98	99	101	103	104	106	106	54	54	55	56	57	58	58
	99th	105	106	108	110	112	113	114	61	62	63	64	65	66	66
2	50th	84	85	87	88	90	92	92	39	40	41	42	43	44	44
	90th	97	99	100	102	104	105	106	54	55	56	57	58	58	59
	95th	101	102	104	106	108	109	110	59	59	60	61	62	63	63
	99th	109	110	111	113	115	117	117	66	67	68	69	70	71	71
3	50th	86	87	89	91	93	94	95	44	44	45	46	47	48	48
	90th	100	101	103	105	107	108	109	59	59	60	61	62	63	63
	95th	104	105	107	109	110	112	113	63	63	64	65	66	67	67
	99th	111	112	114	116	118	119	120	71	71	72	73	74	75	75
4	50th	88	89	91	93	95	96	97	47	48	49	50	51	51	52
	90th	102	103	105	107	109	110	111	62	63	64	65	66	66	67
	95th	106	107	109	111	112	114	115	66	67	68	69	70	71	71
	99th	113	114	116	118	120	121	122	74	75	76	77	78	78	79
5	50th	90	91	93	95	96	98	98	50	51	52	53	54	55	55
	90th	104	105	106	108	110	111	112	65	66	67	68	69	69	70
	95th	108	109	110	112	114	115	116	69	70	71	72	73	74	74
	99th	115	116	118	120	121	123	123	77	78	79	80	81	81	82
6	50th	91	92	94	96	98	99	100	53	53	54	55	56	57	57
	90th	105	106	108	110	111	113	113	68	68	69	70	71	72	72
	95th	109	110	112	114	115	117	117	72	72	73	74	75	76	76
	99th	116	117	119	121	123	124	125	80	80	81	82	83	84	84
7	50th	92	94	95	97	99	100	101	55	55	56	57	58	59	59
	90th	106	107	109	111	113	114	115	70	70	71	72	73	74	74
	95th	110	111	113	115	117	118	119	74	74	75	76	77	78	78
	99th	117	118	120	122	124	125	126	82	82	83	84	85	86	86
8	50th	94	95	97	99	100	102	102	56	57	58	59	60	60	61
	90th	107	109	110	112	114	115	116	71	72	72	73	74	75	76
	95th	111	112	114	116	118	119	120	75	76	77	78	79	79	80
	99th	119	120	122	123	125	127	127	83	84	85	86	87	87	88
9	50th	95	96	98	100	102	103	104	57	58	59	60	61	61	62
	90th	109	110	112	114	115	117	118	72	73	74	75	76	76	77
	95th	113	114	116	118	119	121	121	76	77	78	79	80	81	81
	99th	120	121	123	125	127	128	129	84	85	86	87	88	88	89
10	50th	97	98	100	102	103	105	106	58	59	60	61	61	62	63
	90th	111	112	114	115	117	119	119	73	73	74	75	76	77	78
	95th	115	116	117	119	121	122	123	77	78	79	80	81	81	82
	99th	122	123	125	127	128	130	130	85	86	86	88	88	89	90

Blood Pressure Levels for Boys by Age and Height Percentile (Continued)

Age (Year)	BP Percentile ↓	Systolic BP (mmHg) ← Percentile of Height →							Diastolic BP (mmHg) ← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
11	50th	99	100	102	104	105	107	107	59	59	60	61	62	63	63
	90th	113	114	115	117	119	120	121	74	74	75	76	77	78	78
	95th	117	118	119	121	123	124	125	78	78	79	80	81	82	82
	99th	124	125	127	129	130	132	132	86	86	87	88	89	90	90
12	50th	101	102	104	106	108	109	110	59	60	61	62	63	63	64
	90th	115	116	118	120	121	123	123	74	75	75	76	77	78	79
	95th	119	120	122	123	125	127	127	78	79	80	81	82	82	83
	99th	126	127	129	131	133	134	135	86	87	88	89	90	90	91
13	50th	104	105	106	108	110	111	112	60	60	61	62	63	64	64
	90th	117	118	120	122	124	125	126	75	75	76	77	78	79	79
	95th	121	122	124	126	128	129	130	79	79	80	81	82	83	83
	99th	128	130	131	133	135	136	137	87	87	88	89	90	91	91
14	50th	106	107	109	111	113	114	115	60	61	62	63	64	65	65
	90th	120	121	123	125	126	128	128	75	76	77	78	79	79	80
	95th	124	125	127	128	130	132	132	80	80	81	82	83	84	84
	99th	131	132	134	136	138	139	140	87	88	89	90	91	92	92
15	50th	109	110	112	113	115	117	117	61	62	63	64	65	66	66
	90th	122	124	125	127	129	130	131	76	77	78	79	80	80	81
	95th	126	127	129	131	133	134	135	81	81	82	83	84	85	85
	99th	134	135	136	138	140	142	142	88	89	90	91	92	93	93
16	50th	111	112	114	116	118	119	120	63	63	64	65	66	67	67
	90th	125	126	128	130	131	133	134	78	78	79	80	81	82	82
	95th	129	130	132	134	135	137	137	82	83	83	84	85	86	87
	99th	136	137	139	141	143	144	145	90	90	91	92	93	94	94
17	50th	114	115	116	118	120	121	122	65	66	66	67	68	69	70
	90th	127	128	130	132	134	135	136	80	80	81	82	83	84	84
	95th	131	132	134	136	138	139	140	84	85	86	87	87	88	89
	99th	139	140	141	143	145	146	147	92	93	93	94	95	96	97

BP, blood pressure

* The 90th percentile is 1.28 SD, 95th percentile is 1.645 SD, and the 99th percentile is 2.326 SD over the mean.

For research purposes, the standard deviations in Appendix Table B–1 allow one to compute BP Z-scores and percentiles for boys with height percentiles given in Table 3 (i.e., the 5th,10th, 25th, 50th, 75th, 90th, and 95th percentiles). These height percentiles must be converted to height Z-scores given by (5% = -1.645; 10% = -1.28; 25% = -0.68; 50% = 0; 75% = 0.68; 90% = 1.28%; 95% = 1.645) and then computed according to the methodology in steps 2–4 described in Appendix B. For children with height percentiles other than these, follow steps 1–4 as described in Appendix B.

Blood Pressure Levels for Girls by Age and Height Percentile

Age (Year)	BP Percentile ↓	Systolic BP (mmHg) ← Percentile of Height →							Diastolic BP (mmHg) ← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	50th	83	84	85	86	88	89	90	38	39	39	40	41	41	42
	90th	97	97	98	100	101	102	103	52	53	53	54	55	55	56
	95th	100	101	102	104	105	106	107	56	57	57	58	59	59	60
	99th	108	108	109	111	112	113	114	64	64	65	65	66	67	67
2	50th	85	85	87	88	89	91	91	43	44	44	45	46	46	47
	90th	98	99	100	101	103	104	105	57	58	58	59	60	61	61
	95th	102	103	104	105	107	108	109	61	62	62	63	64	65	65
	99th	109	110	111	112	114	115	116	69	69	70	70	71	72	72
3	50th	86	87	88	89	91	92	93	47	48	48	49	50	50	51
	90th	100	100	102	103	104	106	106	61	62	62	63	64	64	65
	95th	104	104	105	107	108	109	110	65	66	66	67	68	68	69
	99th	111	111	113	114	115	116	117	73	73	74	74	75	76	76
4	50th	88	88	90	91	92	94	94	50	50	51	52	52	53	54
	90th	101	102	103	104	106	107	108	64	64	65	66	67	67	68
	95th	105	106	107	108	110	111	112	68	68	69	70	71	71	72
	99th	112	113	114	115	117	118	119	76	76	76	77	78	79	79
5	50th	89	90	91	93	94	95	96	52	53	53	54	55	55	56
	90th	103	103	105	106	107	109	109	66	67	67	68	69	69	70
	95th	107	107	108	110	111	112	113	70	71	71	72	73	73	74
	99th	114	114	116	117	118	120	120	78	78	79	79	80	81	81
6	50th	91	92	93	94	96	97	98	54	54	55	56	56	57	58
	90th	104	105	106	108	109	110	111	68	68	69	70	70	71	72
	95th	108	109	110	111	113	114	115	72	72	73	74	74	75	76
	99th	115	116	117	119	120	121	122	80	80	80	81	82	83	83
7	50th	93	93	95	96	97	99	99	55	56	56	57	58	58	59
	90th	106	107	108	109	111	112	113	69	70	70	71	72	72	73
	95th	110	111	112	113	115	116	116	73	74	74	75	76	76	77
	99th	117	118	119	120	122	123	124	81	81	82	82	83	84	84
8	50th	95	95	96	98	99	100	101	57	57	57	58	59	60	60
	90th	108	109	110	111	113	114	114	71	71	71	72	73	74	74
	95th	112	112	114	115	116	118	118	75	75	75	76	77	78	78
	99th	119	120	121	122	123	125	125	82	82	83	83	84	85	86
9	50th	96	97	98	100	101	102	103	58	58	58	59	60	61	61
	90th	110	110	112	113	114	116	116	72	72	72	73	74	75	75
	95th	114	114	115	117	118	119	120	76	76	76	77	78	79	79
	99th	121	121	123	124	125	127	127	83	83	84	84	85	86	87
10	50th	98	99	100	102	103	104	105	59	59	59	60	61	62	62
	90th	112	112	114	115	116	118	118	73	73	73	74	75	76	76
	95th	116	116	117	119	120	121	122	77	77	77	78	79	80	80
	99th	123	123	125	126	127	129	129	84	84	85	86	86	87	88

Blood Pressure Levels for Girls by Age and Height Percentile (Continued)

Age (Year)	BP Percentile ↓	Systolic BP (mmHg) ← Percentile of Height →							Diastolic BP (mmHg) ← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
11	50th	100	101	102	103	105	106	107	60	60	60	61	62	63	63
	90th	114	114	116	117	118	119	120	74	74	74	75	76	77	77
	95th	118	118	119	121	122	123	124	78	78	78	79	80	81	81
	99th	125	125	126	128	129	130	131	85	85	86	87	87	88	89
12	50th	102	103	104	105	107	108	109	61	61	61	62	63	64	64
	90th	116	116	117	119	120	121	122	75	75	75	76	77	78	78
	95th	119	120	121	123	124	125	126	79	79	79	80	81	82	82
	99th	127	127	128	130	131	132	133	86	86	87	88	88	89	90
13	50th	104	105	106	107	109	110	110	62	62	62	63	64	65	65
	90th	117	118	119	121	122	123	124	76	76	76	77	78	79	79
	95th	121	122	123	124	126	127	128	80	80	80	81	82	83	83
	99th	128	129	130	132	133	134	135	87	87	88	89	89	90	91
14	50th	106	106	107	109	110	111	112	63	63	63	64	65	66	66
	90th	119	120	121	122	124	125	125	77	77	77	78	79	80	80
	95th	123	123	125	126	127	129	129	81	81	81	82	83	84	84
	99th	130	131	132	133	135	136	136	88	88	89	90	90	91	92
15	50th	107	108	109	110	111	113	113	64	64	64	65	66	67	67
	90th	120	121	122	123	125	126	127	78	78	78	79	80	81	81
	95th	124	125	126	127	129	130	131	82	82	82	83	84	85	85
	99th	131	132	133	134	136	137	138	89	89	90	91	91	92	93
16	50th	108	108	110	111	112	114	114	64	64	65	66	66	67	68
	90th	121	122	123	124	126	127	128	78	78	79	80	81	81	82
	95th	125	126	127	128	130	131	132	82	82	83	84	85	85	86
	99th	132	133	134	135	137	138	139	90	90	90	91	92	93	93
17	50th	108	109	110	111	113	114	115	64	65	65	66	67	67	68
	90th	122	122	123	125	126	127	128	78	79	79	80	81	81	82
	95th	125	126	127	129	130	131	132	82	83	83	84	85	85	86
	99th	133	133	134	136	137	138	139	90	90	91	91	92	93	93

BP, blood pressure

* The 90th percentile is 1.28 SD, 95th percentile is 1.645 SD, and the 99th percentile is 2.326 SD over the mean.

For research purposes, the standard deviations in Appendix Table B–1 allow one to compute BP Z-scores and percentiles for girls with height percentiles given in Table 4 (i.e., the 5th,10th, 25th, 50th, 75th, 90th, and 95th percentiles). These height percentiles must be converted to height Z-scores given by (5% = -1.645; 10% = -1.28; 25% = -0.68; 50% = 0; 75% = 0.68; 90% = 1.28%; 95% = 1.645) and then computed according to the methodology in steps 2–4 described in Appendix B. For children with height percentiles other than these, follow steps 1–4 as described in Appendix B.

ATTACHMENT 3: STAGE-3-DEFINING OPPORTUNISTIC ILLNESSES IN HIV INFECTION

Bacterial infections, multiple or recurrent*
Candidiasis of bronchi, trachea, or lungs
Candidiasis of esophagus
Cervical cancer, invasive†
Coccidioidomycosis, disseminated or extrapulmonary
Cryptococcosis, extrapulmonary
Cryptosporidiosis, chronic intestinal (>1 month's duration)
Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age >1 month
Cytomegalovirus retinitis (with loss of vision)
Encephalopathy attributed to HIV§
Herpes simplex: chronic ulcers (>1 month's duration) or bronchitis, pneumonitis, or esophagitis (onset at age >1 month)
Histoplasmosis, disseminated or extrapulmonary
Isosporiasis, chronic intestinal (>1 month's duration)
Kaposi sarcoma
Lymphoma, Burkitt (or equivalent term)
Lymphoma, immunoblastic (or equivalent term)
Lymphoma, primary, of brain
Mycobacterium avium complex or *Mycobacterium kansasii*, disseminated or extrapulmonary
Mycobacterium tuberculosis of any site, pulmonary†, disseminated, or extrapulmonary
Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
Pneumocystis jirovecii (previously known as "*Pneumocystis carinii*") pneumonia
Pneumonia, recurrent†
Progressive multifocal leukoencephalopathy
Salmonella septicemia, recurrent
Toxoplasmosis of brain, onset at age >1 month
Wasting syndrome attributed to HIV§

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* Only among children aged <6 years.
† Only among adults, adolescents, and children aged ≥6 years.
§ Suggested diagnostic criteria for these illnesses, which might be particularly important for HIV encephalopathy and HIV wasting syndrome, are described in the following references:
CDC. 1994 Revised classification system for human immunodeficiency virus infection in children less than 13 years of age. MMWR 1994;43(No. RR-12).
CDC. 1993 Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR 1992;41(No. RR-17).